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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zeposia

International non-proprietary name: ozanimod

Procedure No. EMEA/H/C/004835/0000

Note

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

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List of abbreviations

4MSU	4-months safety update
9HPT	9-hole peg test
AE	Adverse event
ADH	Alcohol dehydrogenase
ADME	Absorption, distribution, metabolism, and excretion
ADRs	Adverse Drug Reactions
AESI	Adverse event of special interest
AKR	Aldo-keto reductase
ALC	Absolute lymphocyte count
ALDH	Aldehyde dehydrogenase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the plasma concentration time curve over 24 hours
AV	Atrioventricular
BCRP	Breast cancer resistance protein
BMI	Body mass index
CD	Crohn's disease
CDP	Confirmed disability progression
CDP-3M	Confirmed disability progression at 3 months
CDP-6M	Confirmed disability progression at 6 months
CFU	Colony Forming Unit
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum plasma concentration
CL/F	Apparent oral clearance
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CQAs	Critical Quality Attributes
CR	Copy-reference
CSR	Clinical study report
CTD	Common technical document
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
D_{LCO}	Diffusing capacity for carbon monoxide
DMT	Disease-modifying treatment

DoE	Design of Experiment
DSC	Differential Scanning Calorimetry
EAE	Experimental autoimmune encephalomyelitis
EC	European Commission
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
EDSS	Expanded disability status scale
EE	Ethinylestradiol
EFD	Embryo-foetal development
EMA	European Medicines Agency
Emax	Maximum effect
E-R	Exposure-response
ESRD	End-stage renal disease
EU	European Union
FEV1	Forced expiratory volume in 1 second
FDA	Food and Drug Administration
FS	Functional System
FTIR	Fourier transform infrared spectroscopy
FVC	Forced vital capacity
GC	Gas chromatography
GCP	Good Clinical Practice
GdE	Gadolinium-enhancing
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
GMP	Good manufacturing practices
HCl	Hydrochloride
HCP	healthcare professionals
HDPE	High density polyethylene
hERG	Human ether-à-go-go-related gene
HFIP	Hexafluoroisopropanol
HPLC	High-Performance Liquid Chromatography
HR	Heart rate
HR	Hazard Ratio
HSD	11β-hydroxysteroid dehydrogenase
IBD	Inflammatory bowel disease
IBD	International birth date
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IFN	Interferon
IIV	Interindividual variability
IM	Intramuscular

INN	International non-proprietary name
IPC	In-process control
IR	Incidence Rates
IVRS	Interactive Voice Response System
J2R	Jump-to-reference
JP	Japanese Pharmacopeia
LCLA	Low-Contrast Letter Acuity
LOCF	Last Observation Carried Forward
MAH	Marketing Authorisation Holder
MAIC	Matching Adjusted Indirect Comparison
MAO	Monoamine oxidase
MERP	Macular Edema Review Panel
MI	Myocardial Infarction
mITT	Modified Intention-To-Treat
MHRD	Maximum human recommended dose
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MSQOL-54	Multiple sclerosis quality of Life-54
NAS	New active substance
NE	Norethisterone
NMSC	Non-melanoma skin cancer
NMT	Not more than
NOAELs	No-observed-adverse-effect levels
NOEL	No observed effect level
NYHA	New York Heart Association
OCT	Optical coherence tomography
OLE	Open-label extension
OOS	Out of specifications
OZA	Ozanimod
PAR	Proven acceptable range
PASAT	Paced Auditory Serial Addition Test
PCTFE	Polychlorotrifluoroethylene
PD	Pharmacodynamics
PDCO	The Paediatric Committee
PDE	Permitted Daily Exposure
PFT	Pulmonary function test
Ph.Eur.	European Pharmacopeia
PlGF-2	Placental growth factor 2
PIP	Paediatric investigation plan
PK	Pharmacokinetics

PML	Progressive multifocal encephalopathy
PO	Oral or orally
PopPK	Population pharmacokinetics
PP	Per-protocol
PPND	Pre- and postnatal development
PRAC	Pharmacovigilance Risk Assessment Committee
PRES	Posterior reversible encephalopathy syndrome
PSUR	Periodic safety update report
PT	Preferred term
PVC	Polyvinyl chloride
PY	Person-years
QD	Once daily
QR	Quick Response
QRD	Quality Review of Documents
QTc	Corrected QT
RH	Relative humidity
RMP	Risk Management Plan
RMS	Relapsing multiple sclerosis
RPC1063	Company code name for investigational drug product
RRMS	Relapsing-remitting multiple sclerosis
SA	Scientific Advice
S1P	Sphingosine 1-phosphate receptor
$S1P_1$	Sphingosine 1-phosphate receptor subtype 1
$S1P_2$	Sphingosine 1-phosphate receptor subtype 2
$S1P_3$	Sphingosine 1-phosphate receptor subtype 3
$S1P_4$	Sphingosine 1-phosphate receptor subtype 4
$S1P_5$	Sphingosine 1-phosphate receptor subtype 5
SAE	Serious adverse events
SAG-N	Scientific advisory group neurology
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDEI	Sponsor-designated event of interest
SDMT	Symbol Digit Modalities Test
SEER	Surveillance, Epidemiology and End Results
SEM	Standard error of the mean
SIR	Standardized Incidence Rates
SmPC	Summary of Product Characteristics
SNRI	Serotonin–norepinephrine reuptake inhibitors
SPMS	Secondary progressive multiple sclerosis

SSRI	Selective serotonin reuptake inhibitors
SOC	System organ class
T25FW	Timed 25-foot walk
TAMC	Total Aerobic Microbial Count
TEAE	Treatment emergent adverse event
TIA	Transitory ischemic attack
Tmax	Time at which the maximum plasma concentration was observed
$T_{1/2}$	Terminal elimination half-life
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Yeast and Mold Count
UC	Ulcerative colitis
ULN	Upper limit of normal
USP	United States Pharmacopeia
USP/NF	United States Pharmacopeia/National Formulary
UV	Ultraviolet
Vc/F	Apparent volume of distribution in the central compartment
VZV	Varicella Zoster Virus
VEC	vascular endothelial cells
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Celgene Europe BV submitted on 6 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Zeposia, 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 18 May 2017

The Applicant applied for the following indication: the treatment of adult patients with relapsing remitting 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 test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0345/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0345/2017 was not yet completed as some measures were deferred. A PIP was agreed with the Paediatric Committee (PDCO) with a waiver for all subsets of the paediatric population from birth to less than 10 years of age.

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.

New active Substance status

The Applicant requested the active substance ozanimod hydrochloride 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 the following Scientific Advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
24 April 2015	EMEA/H/SA/2779/1/2014/SME/III	*André Elferink, Mario Miguel Rosa*
20 July 2017	MEA/H/SA/2779/1/FU/1/2017/I	*Sheila Killalea, Luca Pani*

The Scientific Advice (SA) pertained to the following quality, non-clinical, and clinical aspects:

EMEA/H/SA/2779/1/2014/SME/III regarding quality, non-clinical and clinical aspects.

- Overall, Committee for Medicinal Products for Human Use (CHMP) agreed with the chemical, pharmaceutical and biological development. However, CHMP specifically advised to propose a different GMP starting material, discuss potential genotoxic impurities, further elaborate the single drug substance registration, a close follow of the ICHQ8 and Ph Eur recommendations.
- Overall, CHMP agreed with the non-clinical pharmacology and safety development plan including immunotoxicity, carcinogenicity and peri/post-natal studies.
- Regarding clinical aspects, the study design of the pivotal studies was overall considered to follow the Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2). Specifically, the overall study design, primary endpoint (annualized relapse rate (ARR)), choice of active control, and the intention to evaluate disability by pooling the data of both pivotal studies were generally agreed. CHMP noted that disability should be the most important of the secondary endpoints that confirmed disability progression after 6 months (CDP-6M) was considered more reliable than confirmed disability progression after 3 months (CDP-3M). In this regard, CHMP noted that 12-month duration (used in Study RPC01-301) was rather short in order to show an effect on disability. Statistical methods (including imputation of missing data) used for analysis of the pooled confirmed disability progression (CDP) data and methods of blinding were also discussed. In the context of broadness of indication, it was advised, that the resulting data should allow also for evaluation of benefit risk in subjects with highly active disease. This issue was raised considering the intended population preferentially including low active patients and the potential effects of the molecule on the cardiac rhythm and conduction. CHMP recommended subgroup analysis (by region). Further topics of the SA concerned dose titration and the proposed cardiac monitoring for which CHMP overall agreed with the Applicant's position and the safety database for which some uncertainties were raised in relation to long-term safety outcomes.

EMEA/H/SA/2779/1/FU/1/2017/I centralized follow-up advice was provided on quality issues including stability data and dissolution method.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bruno Sepodes Co-Rapporteur: Martina Weise

The application was received by the EMA on	6 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	24 June 2019

The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 July 2019
The CHMP agreed on the consolidated List of Questions to be sent to the Applicant during the meeting on	25 July 2019
The Applicant submitted the responses to the CHMP consolidated List of Questions on	11 October 2019
The following Good Clinical Practice (GCP) inspection(s) 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 one clinical investigator in Belarus and another one in Russia between 22/07/2019 and 02/08/2019. The outcome of the inspection carried out was issued on.	31 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 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	12 December 2019
The Applicant submitted the responses to the CHMP List of Outstanding Issues on	12 February 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 March 2020
SAG was 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.	16 March 2020
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 Zeposia on	26 March 2020
A revised opinion was adopted by the CHMP in order to amend Annex II.D (the patient/care giver card key message statement on first dose monitoring is narrowed for patients with certain heart conditions)	9 April 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple sclerosis (MS) is a chronic immune-mediated and neurodegenerative disease of the central nervous system (CNS) characterized by inflammation, demyelination, neuro-axonal injury leading to irreversible deficits in physical and cognitive functions that impair quality of life.

Clinical trials of disease-modifying therapies (DMTs) have utilized measures to assess the impact of MS on physical and cognitive disability. Classically used outcome measures in Phase 3 MS trials are the ARR, the expanded disability status scale (EDSS), number or volume of hyperintense T2-weighted lesions and gadolinium-enhancing (GdE) T1 lesions shown by brain Magnetic Resonance Imaging (MRI). Newer, potentially valuable outcome measures capture disease aspects that are insufficiently captured by the more traditional outcome measures have been increasingly used or explored in MS trials and include the MS Functional Composite (MSFC) score, MS Quality of Life-54 questionnaire (MSQOL-54), and brain volume changes to assess earlier factors that may impaired quality of life. Specifically, tracking brain volume changes is an appealing approach as brain volume loss starts early in the disease course and continues throughout the patient's lifetime.

2.1.2. Epidemiology

The prevalence of MS is increasing and is currently estimated to affect 2.3 million individuals worldwide (Multiple Sclerosis International Foundation, 2013). In Europe, the median prevalence is 100 cases per 100,000 and the highest prevalence of MS occurs in countries with high latitude, including Sweden (188.9 per 100,000), Norway (203 per 100,000), and Denmark (232 per 100,000). The incidence of MS appears to increase.

The onset of MS typically occurs between the ages of 20 and 40 and predominantly affects women (2 to 3 times more frequently than men). In young and middle-aged adults, MS represents the leading cause of non-traumatic neurologic disability. People living with MS experience physical disability, fatigue, and cognitive impairment, which often happens early in the disease course, markedly reducing quality of life and ability to work or study. This may contribute to an increasing socio-economic burden on patients and their families.

Reduction of inflammatory burden (relapses and inflammatory CNS lesions) is the primary focus of therapy as inflammation leads to neurodegeneration in MS. There is no known strategy to prevent MS in the general population.

2.1.3. Aetiology and pathogenesis

While the exact aetiology of MS remains unknown, it is generally assumed that MS is mediated by an immune-mediated inflammatory process that is triggered by environmental factors superimposed on a genetic predisposition. The major contributors to this process are T and B lymphocytes from the adaptive immune system and macrophages and microglia from the innate 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, clinical signs and symptoms may rise due to demyelination and inflammation that impairs or interrupts nerve conduction. Afterwards, remaining permanent symptoms (sequelae) are due to neuro-axonal injury. Elements from both adaptive and innate immune systems are involved in any stage of MS although the contribution and the patterns of inflammation may change across phenotypes and individuals.

2.1.4. Clinical presentation, diagnosis

Relapsing-remitting MS (RRMS) is the most common form of MS, representing approximately 85% of patients at diagnosis. The course of RRMS is unpredictable, with variable periods of disease activity interspersed with periods of stability. According to earlier natural history studies, approximately 50% of patients with RRMS will, within the first 20 years after diagnosis, develop secondary progressive MS (SPMS), which is characterized by worsening disability independently of the presence or absence of relapses. Recent findings from cohorts of patients mostly treated with DMTs from early onset have found lower transition rates to SPMS. Additionally, primary progressive MS is the presenting form at diagnosis in approximately 15% of MS patients and is characterized by chronic worsening of disability early in the disease and in the absence of relapses. In MS, transitory disability in the acute phase of a relapse represents clinical dysfunction due to a focal inflammatory lesion and subsequent myelin loss that impaired nerve conduction. After the acute phase, permanent disability as clinical sequalae represents irreversible neuro-axonal injury due to focal inflammation. In MS, progression in neuronal disability is due to accumulation of neuro-axonal injury either due to focal inflammation or due to diffuse chronic neuroinflammation.

Typical symptoms include numbness and weakness in the legs leading to difficulty walking, vision loss, incoordination, cognitive dysfunction, fatigue and pain. These lesion-driven symptoms are also associated with considerable anxiety and distress for patients. In addition to the major physical, psychological, and social impacts to patients and their families, MS carries a significant financial burden for patients, their families, and institutions responsible for health care. The diagnosis of RRMS can be made on clinical basis alone, but MRI, cerebrospinal fluid, and/or electrophysiological findings can support, supplement, or even replace some of the clinical diagnostic criteria for MS. Given the complexities of diagnosing MS, the McDonald diagnostic criteria have been developed and continue to be revised to facilitate earlier diagnosis and initiation of treatment. These criteria have been used for nearly two decades and most recently updated in 2017. The McDonald diagnostic criteria are comprised of clinical observation, neurologic examination, brain and spinal cord MRI scans and cerebrospinal fluid examination.

2.1.5. Management

There is no cure available for MS. Therapies for MS include treatment for relapses (e.g. steroids), symptomatic treatments (e.g. drugs for stabilization of nerve conduction or dealing with pain) and those that alter the course of the disease (DMTs).

The goal of treating RRMS with DMTs is to modify the natural course of disease by reducing the rate of relapses and MRI focal inflammatory activity to delay disability worsening. The inability of transected axons to be repaired and the limited ability to remyelinate demyelinated segments supports the need of an early intervention to preserve CNS early in the disease course. Consequently, optimization of outcomes using an early intervention with highly effective DMTs is increasingly recognized as an important treatment strategy to reduce both long-term physical and cognitive disability, thereby improving the patient's overall quality of life.

There are several DMTs available for the treatment of MS with different mechanisms of action and differentiated efficacy and safety profiles. These include (1) the first-approved DMTs (IFN β-1a, IFN β-1b, glatiramer acetate), (2) oral therapies (fingolimod, dimethyl fumarate, teriflunomide, cladribine and siponimod), and (3) monoclonal antibodies (alemtuzumab, ocrelizumab, and natalizumab; daclizumab has been withdrawn early last year due to serious adverse events (SAE) and death).

The earliest approved injectable DMTs (IFN β-1a, IFN β-1b, and glatiramer acetate) have a well characterized efficacy and safety profile leading to their widespread use. The safety profile for the interferons includes depression and risk of suicide, hepatic injury, decreased peripheral blood count, anaphylaxis, and injection-site reactions. For glatiramer acetate, safety concerns include immediate post-injection reactions/necrosis and transient chest pain. Tolerability issues such as injection site reactions and/or flu-like symptoms for the interferons and lipoatrophy with GA may impact adherence with these agents. In the real-world setting, based on patient claims data in 2016, approximately two-thirds of subjects discontinued treatment with interferons after twelve months of therapy (Symphony Claims data, Celgene analysis on file, 2019).

The first approved oral nonselective sphingosine 1-phosphate receptor (S1P) receptor modulator was indicated for RRMS patients with highly active disease despite a previous DMT or for rapidly evolving, severe disease. The safety profile includes cardiac effects at initiation of treatment (bradyarrhythmia and atrioventricular [AV] block) and QT prolongation, infections including herpes and cryptococcus, progressive multifocal encephalopathy (PML), macular oedema, posterior reversible encephalopathy syndrome (PRES), respiratory effects, increased liver enzymes and blood pressure, risk of significant disability after stopping in the post marketing setting (rebound), cutaneous malignancies, and lymphoma. More recently, the first oral selective S1P receptor modulator has been approved for SPMS with active disease.

Dimethyl fumarate and teriflunomide are more recently approved oral agents that have demonstrated moderate efficacy in the treatment of RRMS. The safety profile of dimethyl fumarate includes anaphylaxis, PML, lymphopenia, liver injury, gastrointestinal adverse events (AEs), and flushing. The safety profile for teriflunomide includes hepatotoxicity, bone marrow suppression, peripheral neuropathy, increased blood pressure, interstitial lung disease, hypersensitivity and serious skin reactions and teratogenicity.

The most recently approved oral therapy, cladribine, is a highly effective oral agent indicated for RRMS patients with highly active disease. The safety profile includes prolonged lymphocyte count reduction, infections such as herpes, and potential reactivation of tuberculosis, HIV, and hepatitis B, malignancy and a requirement for contraception in women of childbearing potential and in men.

Natalizumab was the first monoclonal antibody DMT approved for highly active RRMS, is administered as an intravenous infusion. The safety profile includes PML, herpes encephalitis, meningitis and acute retinal necrosis, hepatotoxicity, and serious hypersensitivity reactions. More recent monoclonal antibodies include alemtuzumab and ocrelizumab. Alemtuzumab is a highly effective monoclonal therapy originally indicated for RRMS patients with active disease that is administered IV separated by 12 months, with safety follow up for 48 months after the last infusion. The safety profile of alemtuzumab includes infusion-related reactions, infections, autoimmune disorders including immune thrombocytopenia, nephropathies and thyroid disorders requiring frequent laboratory monitoring, stroke and increased risk of malignancy including melanoma requiring yearly skin exams. Following new reports of immune-mediated conditions and cardiac/vascular problems, a review of Lemtrada was initiated on 10 April 2019 at the request of EC, under Article 20 of Regulation (EC) No 726/2004. On 16 January 2020, EC issued a final legally binding decision to restrict the use of Lemtrada to adults with RRMS that is highly active despite a full and adequate course of treatment with at least one disease-modifying therapy or rapidly evolving severe disease defined by 2 or more disabling relapses in one year, and with 1 or more GdE

lesions on brain MRI or a significant increase in T2 lesion load compared to a recent MRI. Ocrelizumab, another highly effective monoclonal DMT administered IV, is also indicated for RRMS patients with active disease, as well as early primary progressive MS. The safety profile of ocrelizumab includes infusion-related reactions and infections including PML, herpes and hepatitis B reactivation; an increased risk for malignancies, including breast cancer, may exist.

With the availability of multiple treatment modalities, clinicians can choose from several medications with differing mechanisms of action, risk profiles, and monitoring requirements. The greater array of treatment options available enables clinicians to individualize treatment taking patient preferences, monitoring recommendations, drug- and individual-specific risk factors, and concerns regarding the long-term risk of MS-related disability and morbidity into consideration.

Despite the availability of several medications for the treatment of MS, there remains a need for an effective oral agent with a favourable benefit, safety and tolerability profiles. Ozanimod may offer an alternative of an effective therapy with acceptable safety and tolerability profile and a dose escalation regimen that does not require first dose observation.

2.2. About the product

Ozanimod hydrochloride (HCl) (also known as RPC1063) is a potent, orally bioavailable, S1P agonist, which binds with high affinity and selectively to S1P subtypes 1 ($S1P_1$) and 5 ($S1P_5$). Agonist activation of $S1P_1$ induces down-modulation of cell surface $S1P_1$ expression which results in lymphocyte retention in lymphoid tissues and therefore, peripheral lymphocyte counts are decreased in the circulation that is thought to ameliorate the pathological processes (focal inflammatory activity) associated with MS.

Ozanimod is being developed for the clinical treatment of patients with relapsing multiple sclerosis (RMS). The proposed maximum human recommended dose (MHRD) for the treatment of this condition is one milligram (1 mg) ozanimod HCl per day.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as hard gelatine, immediate-release capsules for oral administration containing 0.23, 0.46, or 0.92 mg of ozanimod. The product contains 0.25, 0.5 or 1 mg of the hydrochloride salt of the active substance respectively.

Other ingredients are:

Capsule content: microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, magnesium stearate

Capsule shell: gelatin, titanium dioxide (E171) yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172, 0.23 and 0.46 mg capsules only)

Printing ink: shellac (E904), iron oxide black (E172), propylene glycol (E1520), concentrated ammonia solution (E527), potassium hydroxide (E525)

The product is available in polyvinyl chloride (PVC) / polychlorotrifluoroethylene (PCTFE) / aluminium foil blisters as described in section 6.5 of the SmPC.

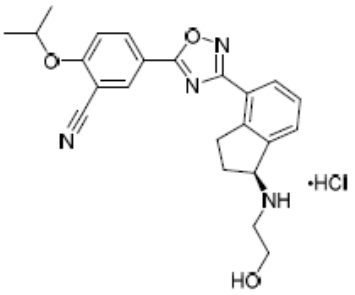
2.3.2. Active Substance

General information

The active substance ozanimod hydrochloride (HCl) is not described in the European Pharmacopoeia, pharmacopoeias of the EU member states or USP. No ASMF has been submitted. Full information on the active substance has been provided in the dossier.

The chemical name of ozanimod hydrochloride is 5-(3-{(1*S*)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1*H*-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile, monohydrochloride, corresponding to the molecular formula $C_{23}H_{24}N_4O_3$•HCl. It has a relative molecular mass of 440.92 g/mol and the following structure:

Figure 1: active substance structure



The structure of ozanimod HCl was inferred by the synthetic route and confirmed by Fourier transform infrared spectroscopy (FTIR), proton and carbon nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C NMR), UV spectroscopy, mass spectrometry, and elemental analysis. The chiral integrity of the downstream intermediates is confirmed by chiral HPLC. The solid-state properties were investigated by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

Ozanimod is a slightly hygroscopic white to off-white solid, with a logP of 3.28 and a pKa of 7.90. Its solubility in water depends on the pH. It has a melting point (by DSC) with an onset at 240 ºC.

Ozanimod exhibits stereoisomerism due to the presence of one chiral centre. The (*S*) configuration was confirmed for both RP101122 intermediate and the active substance by X-ray crystal structure determination. Enantiomeric purity is tested at release and during stability studies by chiral HPLC analysis.

A polymorph screening was conducted on ozanimod hydrochloride through competitive slurring studies Four forms were observed. Form 1 was the form selected for commercial use since it was found to be the most stable crystalline form. In addition, samples of ozanimod HCl from the stability program were characterized by XRPD. The XRPD of all samples are consistent with Form 1 and provided further evidence of the stability of Form 1 with no conversions to any other form in the solid state. Based on the stability data provided, it can be concluded that ozanimod HCl manufactured at the proposed manufacturing sites does not convert to another form even after 60 months at 25°C and 60% RH or 6 months under accelerated conditions (40°C / 75% RH).

The applicant claims that ozanimod is not authorized in the European Union (EU), and furthermore it is not a salt, complex, or isomer or mixture of isomers, or a derivative of an authorized substance and therefore it is a new active substance (NAS). To support his claim the applicant indicated that ozanimod activity is exerted by the ozanimod active substance and several active metabolites. It is stated that the

two major metabolites of ozanimod are CC9112273, and CC108403. Results from searches in various databases to support the NAS claim were presented.

it was concluded that ozanimod is not a salt, complex, or isomer or mixture of isomers, or a derivative of an authorized substance. Furthermore, ozanimod does not expose the patient to the same therapeutic moiety as any previously authorized active substance, and therefore it is concluded that it is a new active substance (NAS).

Manufacture, characterisation and process controls

Ozanimod HCl is synthesized in three main stages using commercially available well defined starting materials with acceptable specifications, one of them redefined during the marketing authorization application evaluation as requested by the CHMP. Relevant information on manufacturers, synthetic routes, specifications and impurity profiles has been included. An updated version of the CTD relevant sections regarding starting materials has been adequately presented resolving the previously raised major objection.

All holding times for intermediates have been supported by stability data.

A flow diagram and an adequately detailed narrative description of the manufacturing process, including criteria for all process parameters and IPCs, has been provided. Relevant process parameters and amounts of materials, reagents and solvents have been included in the process description with set points or ranges.

The introduction of the chiral centre was thoroughly discussed and evaluated. Adequate specifications have been set for isolated intermediates, starting materials and reagents. Experiments, including impurity fate and purge studies, have been adequately performed in order to gain additional process knowledge and understanding, as well as to justify the suitability of the control for starting materials, intermediates and the active substance. In general, the proposed methods used to control the starting materials and isolated intermediates have been properly described and validated in line with relevant ICH guidelines. Batch analyses have been provided for representative batches of starting materials confirming compliance with the proposed specifications.

Reprocessing has been adequately justified. The IPCs used to monitor and assess the process performance, the quality of the intermediates, and of the active substance are listed and are found to be adequate. Critical steps and the respective controls are identified.

A combination of one factor at a time (OFAT) experiments and multifactor statistical Design of Experiments (DoE) were used to understand and set proven acceptable ranges (PARs) for the studied parameters. Pilot and production scale batches along with scientific judgment regarding common variability were also used to establish PARs for process parameters of lower risk and/or less complex operations/factors. The established PARs combined with the critical process parameters CPPs described, the IPCs, and the control of materials comprise the overall control strategy.

A control strategy for critical quality attributes (CQAs) which resulted in the proposed specifications, was developed as the output of the quality risk management process. PARs established were adequately justified and ensure that the active substance produced complied with all required CQAs.

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. The applicant has presented an impurity discussion addressing all impurities possible from the starting materials, raw materials and subsequent synthesis. Hypothesized process impurities are also discussed. The starting

materials and raw materials are controlled by material specification. Process intermediates are controlled by material specification, IPC testing, and process design. Specified impurities are controlled in compliance to the ICH Q3A guideline. The impurity at a level greater than 0.15% has been suitably qualified.

The discussion on potential genotoxic impurities is adequate. Specified impurities and other structures hypothesized to have the potential for mutagenic concern, were evaluated in silico for potential mutagenicity using both rule-based and statistical-based tools in accordance with the ICH M7 Step 4 Guideline. All impurities were assigned into Control Class 5.

No significant changes to the manufacturing route were made during development. Any modifications were made to improve process efficiency but used the same reagents and yielded active substance with similar impurity profiles and no significant new impurities.

The active substance is packaged in double polyethylene bags. The bags are zip-tied and placed into tightly sealed high-density polyethylene (HDPE) drums. The container closure components comply with the EC directive 10/2011 and the Ph. Eur. monograph for polyethylene.

Specification

The active substance release specification includes tests for appearance, identification (FT-IR, HPLC), solid form (XRPD), chiral purity (chiral HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), residue on ignition (Ph. Eur.), water content (Ph. Eur.), free chloride (titration), particle size (Ph. Eur.) and microbial limits (Ph. Eur.).

The specification provides the necessary controls to ensure the suitability of the active substance for its intended use.

Specifications are well justified in view of current guidelines. Justification has been provided for each parameter.

Information on potential elemental impurities and the risk assessment performed in line with ICH Q3D Option 1 and assuming a maximum of 10g/day of active substance intake has been provided and considered satisfactory. Representative active substance batches were tested for relevant elemental impurities Levels were well below the 30% control threshold recommended in the ICH Q3D guideline so it is acceptable that elemental impurities are not directly controlled in the active substance release specification although a general residue on ignition test is included.

As indicated earlier, Form 1 is the only stable crystalline polymorph identified and studies conducted during development confirmed Form 1 on stability samples. Therefore, solid form will only be tested at release for the commercial active substance. Chiral purity data collected for release and stability demonstrates that ozanimod HCl remains in the (*S*)-isomer configuration. No racemization occurs over time and therefore the test is not required for stability testing.

The justification provided for the absence of water content control at stability, based on the non-hygroscopic nature and no changes in water content during stability is acceptable.

The proposed analytical procedures for identity, assay, related substances, chiral purity and residual solvents have been properly described and (non-compendial methods) validated in accordance with the ICH guidelines. The results from the validation studies showed the methods were suitable for their intended use. The stability indicating nature of the HPLC test method for determination of assay and related substances has been demonstrated by results of forced degradation studies. All compendial analytical procedures have been verified and shown to be suitable for testing ozanimod HCl active substance.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch data from 28 pilot to production scale batches have been provided. These included three stability batches as well as batches used during clinical development. All results were within the proposed limits and consistent from batch to batch.

Stability

Stability data from six pilot scale registration batches of active substance stored in a container closure system that simulates the commercial packaging configuration for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Supportive long term and accelerated stability data from representative active substance batches used for clinical development purposes or process validation, was also provided. Long term data is available for up to 60 months.

The following parameters were tested: appearance, polymorphic form, chiral purity, assay, related substances and water content. The analytical methods used were the same as for release and are stability indicating. In addition, chiral purity was monitored over time.

No changes or trends indicating degradation were observed for all samples under either long-term or accelerated conditions for the appearance, assay, water content, related substances or chiral purity parameters when the batches were stored in the proposed commercial packaging material. The polymorphic form remains unchanged over time and no racemization of the chiral centre occurs.

Forced degradation studies were performed on the active substance under acidic, basic, oxidative, and thermal stress conditions and the results obtained indicate that the HPLC method used for identification, assay and related substances is stability indicating.

Photostability studies were performed on active substance batches in line with ICH Q1B Option 2. The results obtained indicate that the active substance is not photosensitive.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. Based on these results, the re-test period for active substance stored in the container proposed for marketing with the storage condition has been accepted

2.3.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Ozanimod is presented as hard gelatin, immediate-release capsules for oral administration, containing 0.25, 0.5 and 1 mg ozanimod HCl, equivalent to 0.23, 0.46, or 0.92 mg of ozanimod free base. Size 4 (14.3 mm) capsules are used for all dosage strengths.

The 0.23 mg capsules consist of a light grey opaque cap and body, imprinted in black ink with "OZA" on the cap and "0.23 mg" on the body. The 0.46 mg capsules have an orange opaque cap and light grey opaque body, imprinted in black ink with "OZA" on the cap and "0.46 mg" on the body. The 0.92 mg capsules have an orange opaque cap and body, imprinted in black ink with "OZA" on the cap and "0.92 mg" on the body.

All excipients are well known pharmaceutical ingredients and, except the hard gelatin capsule shell and associated black inks, comply with compendial requirements. The composition and specification of the non-compendial excipients are presented and it is confirmed that the ingredients are pharmacopoeial grade or at least of foodstuff grade (colorants).

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.

The capsules are packaged into a polyvinylchloride/polychlorotrifluoroethylene (PVC/PCTFE) blister. The blister consists of a rigid PVC layer laminated to a PCTFE layer and is heat-sealed with a push through foil. Its components comply with Ph. Eur. and EC requirements.

The pharmaceutical development has been properly described through a minimal approach (without applying Quality by Design) but applying quality risk management concepts as per ICH Q8 (R2) and Q9 guidelines.

Batches of active substance with a range of particle size distributions were included in a multivariate study to evaluate the impact of particle size distribution on the dissolution behaviour of ozanimod HCl in the finished product.

During early development, a study to evaluate the compatibility of ozanimod HCl with potential excipients was performed. In this study, common solid dosage form excipients were combined with the active substance, either individually or in binary excipient mixtures. After storage the active substance itself, and the active substance/excipient mixtures were evaluated. All of the excipients utilized in the study were considered compatible with the active substance. The excipients selected for the finished product formulation are commonly used in direct blend capsule formulations and are utilized at levels common for their function in an immediate release product.

Risk assessment was used throughout the pharmaceutical development to identify risks in active substance, excipients and manufacturing process and to determine which studies were necessary to improve product and process understanding to develop a suitable control strategy for the finished product.

The dissolution method for ozanimod HCl capsules was developed through a course of experiments designed to identify conditions with sufficient discriminatory power.

The process development work to support Ozanimod HCl capsules has been performed Collectively, the data obtained and demonstrates robustness of the proposed commercial process.

The formulation and manufacturing development studies were adequately described.

Manufacture of the product and process controls

The manufacturing process was adequately described by the applicant. Ozanimod HCl capsules are manufactured using a conventional direct dry blending process followed by encapsulation, packaging and labelling. The process does not involve any compression of the blend during manufacturing. The process is a non-standard manufacturing process due to the low active substance content in the finished product (<0.3%).

Ranges for each process parameter are based on the data from process robustness studies. Bulk hold storage times have been established for final blend and bulk capsules. These were justified by appropriate stability studies and are considered acceptable.

The commercial manufacturing process for the 0.23 mg, 0.46 mg and 0.92 mg strengths has been adequately validated The validation consisted of three batches of each dosage strength utilizing the proposed commercial process and scale using active substance provided by the proposed commercial active substance supplier(s).

Although the development data indicate that the manufacturing process is well controlled, the capsule weight, as proposed by the applicant, was considered insufficient to ensure the uniformity of the dosage units, due to the low active substance content in the drug product (<0.3%). Therefore, the CHMP requested the addition of a content uniformity test as an IPC.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), uniformity of dosage units by content uniformity (Ph. Eur.), assay (HPLC), degradation products (HPLC), dissolution (HPLC), water content (Ph. Eur.) and microbial limits (Ph. Eur.).

The limits for impurities are within the qualification threshold recommended by ICH Q3B. The impurities present in the finished product are the same as those in the active substance. There are no new degradation products specific for the finished product.

Ozanimod HCl is a highly soluble active substance and the finished product was designed to be immediate release. Based on the reported results of clinical batches tightening of the dissolution limit following the principles described in the CHMP "Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action" (EMA/CHMP/CVMP/QWP/336031/2017) was requested during the MA review. The release and stability data collected demonstrate that the finished product formulation, manufacturing process, and stability do not have an impact on the chiral purity of the active ingredient. Therefore, chiral purity testing is not included in the finished product specification.

A risk assessment in line with ICH Q3D was conducted for ozanimod HCl capsules to identify potential elemental impurities that may be present in the finished product. The potential sources of elemental impurities in finished drug product are the manufacturing equipment and process, chemicals/utilities used in the process, the active substance and excipients, and the container-closure systems for both active substance and finished product. The assessment was performed for Class 1 (Hg, Cd, Pb, and As) and Class 2A (Ni, Co, and V) elements as recommended for oral dosage forms. Batches were tested for these elements and the results revealed that none of these elements were detected in the finished product apart from one which is a component of the active substance manufacturing equipment. The amount of this element present was well below 30% of the PDE recommended in the ICH Q3D guideline. In conclusion, no controls for elemental impurities in the finished product are required.

In view of recent nitrosamine discussions and considering ozanimod is a chemically synthesised active pharmaceutical ingredient, an evaluation of the risk of presence of nitrosamine impurities in both active substance and finished product was provided. No obvious risk factors for the generation or presence of nitrosamine impurities during the manufacturing process were identified. It was noted that nitrocellulose may be present in print primer in the aluminum push-through foils used for primary packaging, and amines may be present in the printing ink. From the overall risk assessment performed, it is concluded that there isn't a significant risk of nitrosamine contamination of Zeposia from the packaging materials.

However, given that nitrosamine formation between the amines in the active substance or printing ink and the nitrocellulose in the primer of aluminium push-through foil has been identified as a possible root cause for nitrosamine formation, even when the nitrocellulose is not in direct contact with the tablet or capsule (ref. EMA/CHMP/428592/2019 Rev. 2), the applicant is recommended to further evaluate this

potential root cause of nitrosamines and update his risk assessment accordingly as per the EMA note EMA/189634/2019".

Non-compendial analytical procedures are described in detail. The non-compendial analytical procedures have been adequately validated in accordance with the requirements of *ICH Q2 guideline: Validation of Analytical Procedures: Text and Methodology* which demonstrates their suitability for their intended use. The stability indicating nature of the HPLC method used for assay and degradation products has been demonstrated by means of forced degradation studies (thermal, thermal-humidity, oxidation, acid, base and photostability). Suitability of the microbial limit test for analysis of the finished product was provided.

The main reference standard used for testing the finished product is the ozanimod HCl reference standard. Other impurity reference standards are also used for testing the finished product. Satisfactory information regarding theses reference standards has been presented.

Batch analysis results for multiple commercial scale batches from commercial manufacturing sites as well as pilot and commercial scale batches from development sites confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification have been provided.

Stability of the product

Stability data from at least three commercial scale batches of finished product of each strength manufactured at each of the commercial sites stored for up to 36 months under long term (25ºC / 60% RH) conditions, and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Additional stability data from one 0.23 mg batch from each manufacturer stored at intermediate conditions (30°C / 65% RH) was also submitted. The batches of Zeposia are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supportive stability data from batches manufactured at other sites during development stored under long term and accelerated conditions were also presented. These studies represent the formulations and packaging configurations utilized in the clinical studies.

Samples were tested for appearance, chiral purity, assay, related substances, dissolution, water content, and microbial limits. The analytical procedures used are stability indicating.

No significant changes in the appearance of the finished product were noted under any of the conditions tested.

Assay values remained within the proposed acceptance criterion for all long term, intermediate and accelerated stability samples for the 0.46 mg and 0.92 mg strengths. However, out of specification (OOS) results were seen for a few batches of the 0.23 mg strength under accelerated conditions. Therefore, testing under intermediate conditions (30°C / 65% RH) was initiated for this strength and data up to 36 months have been provided. An out of specification assay result was observed for one batch after 24 months. However, all long-term results were within the specification. This justifies the proposed storage condition: "do not store above 25°C".

For the remaining tested parameters, the stability results comply with the proposed specifications for all three strengths under all conditions tested although some trends were observed.

A correlation between water content and product degradation, particularly at the low strength of 0.23 mg, was observed. Based on this correlation and the fact that the resultant degradation products are

monitored by a more sensitive HPLC technique, water content will not be performed on stability for commercial product.

Chiral purity values remained consistent during development and primary stability studies. Furthermore, the finished product formulation, manufacturing process, and storage condition do not have an impact on the chiral purity of the active ingredient. As a result, chiral purity testing will not be performed on the commercial product as discussed in the specification section.

The post-approval stability protocol and stability commitment are acceptable.

Photostability studies were conducted in accordance with ICH Q1B. The photostability study results revealed absence of significant changes for all samples exposed to light. Thus, the finished product is considered photostable. Forced degradation studies were performed in the context of validation of the HPLC method used for assay and degradation products which, as a result, is considered stability indicating. The results obtained indicate that the ozanimod HCl capsules are sensitive to most conditions tested, in particular oxidative conditions.

Based on available stability data, the proposed shelf-life of 36 months and storage condition "Do not store above 25°C" as stated in the SmPC (section 6.3) for all the three strengths is acceptable.

The start of shelf-life is set in accordance with CPMP/QWP/072/96 in that shelf-life begins with the date that the active ingredient is combined with other ingredients.

Adventitious agents

Valid TSE certificates of suitability for the gelatin used in the hard capsules have been provided. Magnesium stearate is derived from vegetable sources. No other excipients of human or animal origin are employed to manufacture ozanimod HCl capsules.

2.3.4. 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 major objection raised during the evaluation requesting the redefinition of the proposed starting material used for active substance synthesis was resolved. The applicant redefined it further back in the synthesis and provided further data. All other remaining concerns, including the risk assessment for the potential presence of nitrosamine impurities were also satisfactorily addressed. 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.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3.6. 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:

The applicant is recommended to further evaluate the potential formation of nitrosamines as a result of the use of nitrocellulose printing primer in the blister pack and to provide the result of an updated risk evaluation as per the EMA note EMA/189634/2019.

2.4. Non-clinical aspects

2.4.1. Introduction

Prior to the submission, the Applicant received SA (EMEA/H/SA/2779/1/2014/SME/III) and CHMP overall agreed with the non-clinical pharmacology and safety development plan including immunotoxicity, carcinogenicity and peri/post-natal studies.

The pivotal safety pharmacological core battery investigations on cardiovascular and respiratory function and all toxicology studies, except those with dose-range finding purpose, were conducted in compliance with GLP regulations.

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA P/0345/2017 on the agreement of a PIP. As part of the PIP, the two nonclinical studies included in the PIP, a 10-week juvenile rat toxicity study (study 2) and a 33-Day oral immunotoxicity study in juvenile rats (study 5), were completed and found to have been conducted in accordance with the PIP.

2.4.2. Pharmacology

Primary pharmacodynamic studies

Ozanimod hydrochloride (HCl) (also known as RPC1063) is a potent, orally bioavailable, S1P agonist, which binds with high affinity and selectively to $S1P_1$ and $S1P_5$ ($S1P_1$ and $S1P_5$) that demonstrated high affinity and selectivity for $S1P_1$ and $S1P_5$ receptors in various reporter, binding or activity assays using recombinant murine, rat, Cynomolgus monkey or human S1P receptor subtypes. The EC_{50} of ozanimod was 1.03 ± 0.16nM at human $S1P_1$ and about 10-fold lower at $S1P_5$ receptors (10.66 ± 0.29nM). Ozanimod showed no relevant interaction with $S1P_2$, $S1P_3$ and $S1P_4$ subtypes.

Ozanimod represents the main pharmacologically active component in animals, whereas two major metabolites CC112273 and CC1084037 predominate and persist in humans at significantly higher levels than in rodents and monkeys (>10% of human plasma Area under the concentration-time curve (AUC)). In contrast, the third main metabolite RP101124 did not unveil relevant pharmacological activity at any S1P receptor subtype, while all other major and minor metabolites generally share the affinity and selectivity profile at S1P receptors with ozanimod. In particular, the EC_{50} values of CC112273 and CC1084037 at human, murine, rat and monkey $S1P_1$ receptors were similar to ozanimod. In contrast, CC112273 showed 3-fold lower interaction with the human $S1P_5$ subtype than ozanimod, while CC1084037 revealed 3-fold higher affinity compared to its parent compound. Both major active metabolites showed 3- to 6-fold higher affinity for murine, rat and monkey $S1P_5$ receptors than ozanimod.

Prolonged $S1P_1$ interaction promoted internalisation and degradation of the receptors leading to a down-modulation of the signalling response. This modulation resulted in lymphocyte retention in lymphoid tissues and is thought to ameliorate the pathological processes associated with MS. $S1P_1$ expression in astrocytes may contribute to the severity of murine experimental autoimmune encephalomyelitis (EAE), an animal model of human MS. However, the activity at $S1P_5$ receptors must be different, because neither ozanimod, nor the non-selective S1P receptor agonist fingolimod triggered a similar down-

modulation up to the highest test concentration of 1 µM. $S1P_5$ is expressed on oligodendrocytes in the CNS and at all stages of their maturation. The myelination potential of these cells has been proposed to be modulated by $S1P_5$.

In the murine EAE model, efficacy for orally administered ozanimod or its active major and minor metabolites CC112273, RP101075, RP101988 and RP101442 was demonstrated as a general dose-dependent reduction of EAE disease scores. The amelioration of EAE symptoms was typically associated with decreased numbers of circulating lymphocytes (CD4+ and CD8+ T-cells and mature B-cells), which could hence serve as surrogate parameter to define the pharmacokinetics (PK)/pharmacodynamics (PD) relationship of ozanimod and its active metabolites in healthy mice, rats, dogs and monkeys. As all primary active metabolites are further converted into other active downstream compounds, the magnitude and duration of the lymphocyte reductions over time could be correlated with the total active drug concentration, which was estimated to amount to trough levels of ~2.7-6.1nM in both animals and humans at 24 h post dosing.

In a mouse model of demyelination induced by cuprizone and rapamycin, orally administered ozanimod had significantly attenuated the apoptosis of mature oligodendrocytes as indicated by lower myelin loss during the acute 6 weeks demyelination challenge but did not improve spontaneous remyelination by oligodendrocyte precursors in the hippocampus, cortex or the corpus callosum when dosed continuously over 12 weeks post-demyelinating challenge, although sustained reductions of peripheral lymphocytes were still evident.

Secondary pharmacodynamic studies

The potential for off-target interaction of ozanimod and metabolites was assessed in a CEREP® panel of at least 55 receptors, transporters, and ion channels. Adequate clinical margins were demonstrated for all identified receptor interactions. However, CC112273 was identified to effectively block MAO-B (IC_{50}=5.72nM) with >1000-fold selectivity over MAO-A, whereas ozanimod interfered with serotonin uptake *in vitro* (IC_{50}=1.74 µM). Still, ozanimod or CC112273 neither induced, nor exacerbated pre-existing serotonin syndrome in mice at 1.8 to 4.3-fold higher CC112273 plasma levels than determined in plasma of RRMS patients receiving the recommended clinical ozanimod therapy.

Safety pharmacology programme

Safety pharmacology studies evaluated neuromuscular, respiratory, and cardiovascular system interactions. Suitable clinical margins to the inhibition of Ikr currents mediated by the hERG channel were obtained with ozanimod and metabolites. Telemetered male monkeys administered up to 30 mg/kg ozanimod exhibited minor and transient increases in the PR interval, decreased diastolic blood pressure (DBP), and decreased heart rate (HR) at suitable multiples above the clinical exposure. Rat respiratory function was evaluated by plethysmography and initially identified only minor increases in respiratory rate and minor decreases in tidal volume in a non-Good laboratory practice (GLP) study, leaving the minute volume unchanged at the highest dose tested. In a subsequent GLP compliant study, however, daily oral ozanimod doses of 2 mg/kg and 30 mg/kg for 7 days remarkably increased lung weights of rats by 40 and 90 %, which was accompanied by progressively impaired respiration. These adverse findings were later confirmed in the toxicology program (see below).

Pharmacodynamic drug interactions

With respect to the specific mechanism of action of ozanimod at $S1P_1$ and $S1P_5$ receptors and the lack of relevant "off-target" affinities to other receptors, no pharmacodynamic drug interaction was studied.

2.4.3. Pharmacokinetics

The ADME (Absorption, distribution, metabolism, and excretion) characteristics of ozanimod and its main metabolites were investigated *in vitro* as well as in mice, rats, rabbits and Cynomolgus monkeys *in vivo* and further complemented by toxicokinetic determinations in these species.

Ozanimod is a highly permeable compound, with *in vitro* bidirectional permeability across Caco-2 monolayers indicating its principal intestinal absorption by passive diffusion. Accordingly, ozanimod was rapidly and dose-proportionally absorbed in all animal species with similar T_{max} in mice (1 h), rats and monkeys (4 h) and humans (T_{max}=6-8 h).

Following oral dosing, ozanimod was readily absorbed with oral bioavailability ranging from 40% to 60% in rat. In repeat-dose PK or toxicology studies in mice, rats, monkeys, and rabbits, systemic exposure of ozanimod and its metabolites remained unchanged and independent of dosing duration, consistent with their t½ in preclinical species.

Plasma protein binding of ozanimod in animal species used for toxicity testing was generally high and comparable with humans (approximately 98% or greater) with preference for lipoproteins, albumin and α_1-acid glycoprotein. Ozanimod readily distributed into cellular elements of blood (blood to plasma ratio 2 to 4). Ozanimod and its metabolites, except for RP101124 and RP101988, exhibited wide tissue distribution with highest levels in lungs, kidneys, liver, CNS, endocrine and exocrine glands, spleen, bone marrow and uveal tract of the eyes. Higher levels were additionally detected in pigmented compared to non-pigmented skin suggesting melanin-binding.

Ozanimod and its metabolites RP101988, RP101124, RP101075 and RP101442 crossed the placenta in rats and rabbits. About 22.5-34.4% of the maternal ozanimod dose was detected in plasma of GD18 rat foetuses, which further increases if the contribution of all active metabolites is additionally considered. Ozanimod was also excreted into the milk of lactating rats and particularly the RP101988 metabolite was confirmed at 24.5-fold higher levels than in maternal plasma. Although the foetal exposure of the major active human metabolites CC112273 and CC1084037 was not investigated, their placental and milk transfer can be expected given their structural and physico-chemical similarities with ozanimod.

Ozanimod was subject to extensive metabolism via multiple biotransformation pathways resulting in qualitatively comparable, but quantitatively different amounts of metabolites. It underwent primary metabolism via three distinct pathways: aldehyde dehydrogenase and alcohol dehydrogenase (ALDH/ADH) mediated oxidation of primary alcohol metabolite RP101988, CYP3A4 mediated dealkylation of methylene hydroxy function resulting in the formation of the indamine metabolite RP101075, and gut microbial mediated oxadiazole ring scission resulting in RP101124. Metabolite RP101075 was subject to N-acetylation resulting in RP101442. Nevertheless, RP101075 was principally metabolized by MAO-B to the indanone metabolite CC112273. CC112273 underwent further reversible metabolism with carbonyl reduction to form CC1084037 which in turn was rapidly converted back via oxidation by aldo-keto reductases and hydroxy steroid dehydrogenases to CC112273. No other down-stream metabolites of CC1084037 were identified, so the interconversion kinetics obviously favour formation of CC112273. CC112273 also undergoes CYP2C8 hydroxylation on the indanone ring to form RP112509. Thus, no single metabolic pathway or enzyme system predominates in the overall metabolism of ozanimod.

The exposures of the two major active (CC112273 and CC1084037) and the main inactive (RP101124) human metabolites were assessed using validated methods in repeat dose PK and/or toxicity studies. Exposures of these major metabolites increased approximately dose-proportionally following repeat dosing of ozanimod in animals and did not show accumulation or sex differences in exposures. Consistent with half-lives of ozanimod and its metabolites in nonclinical species, 14 day repeat dosing studies were sufficient to achieve steady-state for parent and metabolites. Although CC112273 and CC1084037 were also identified in nonclinical species, they were present at significantly higher levels in humans than in

rodents and rabbits. In monkeys, the exposure of CC112273 was equivalent to ozanimod, whereas CC1084037 was about 4-fold reduced. Interestingly, direct repeated oral or single intravenous administration of CC112273 or CC1084037 resulted in even lower and clearly less than dose-proportional systemic exposure in rodents and monkeys than following administration of ozanimod in these species. At elevated doses, the exposure of both major metabolites reached a plateau and did not outperform their levels at comparable ozanimod dosages. Due to the poor solubility of CC112273 and CC1084037, their systemic exposure could also not be increased by IV or SC administration. Accordingly, animals were unambiguously exposed to much lower levels of the disproportionate metabolites CC112273 and CC1084037 than humans. Enhanced clearance of CC112273 and CC1084037 obviously prevails in animals as evident by much shorter terminal elimination half-lives in rats ($t_{1/2}$ =8.8 to 31.8 h after ozanimod vs. 3.7 h after direct CC112273 p.o. dosing), mice (8 to 24 h after direct CC112273 p.o. dosing) and monkeys (11 h after ozanimod p.o. administration) compared to humans ($t_{1/2}$ ~10 days in humans).

In contrast, the exposure of the major inactive human metabolite RP101124 was 1.9-2.8-fold higher than ozanimod in rats and 2.3- to 4-fold lower in mice and monkeys. From the minor active metabolites representing <5 % of total drug-related AUC in humans, only RP101988 reached similar levels like ozanimod in rats and monkeys and was detected in 2-fold lower amounts in mice. Other minor metabolites did not reach appreciable exposures in animals.

In rats, the faecal route of excretion predominated accounting for elimination of approximately 83% of the administered radioactive dose within 48 h. Minor amounts of radioactive dose were excreted in urine (5% to 8% of dose). Evaluation in bile-duct cannulated rats revealed that the hepatobiliary elimination is the predominant excretory route for the absorbed fraction of [14C]-ozanimod. The excreted radioactivity was composed primarily of metabolites, with trace amounts of unchanged parent.

In pharmacokinetic interaction studies, CC112273 and CC1084037 and RP101075 selectively inhibited MAO-B with IC_{50} values of 5.7nM, 58nM and 56.13nM, respectively. RP101075 additionally showed moderate interference with MAO-A (IC_{50}=1322nM). Inhibition of MAO-B is adequately addressed in the section 5.2 of SmPC (Summary of Product Characteristics). Ozanimod was a weak inhibitor of P-gp (IC_{50}=8800nM) and Breast cancer resistance protein (BCRP) (IC_{50}=3500nM). CC112273, CC1084037, RP101075, RP101988 and RP101124 served as substrates for BCRP and both major active metabolites CC112273 and CC1084037 were BCRP inhibitors (IC_{50}=25.2 and 22.8nM, respectively), but at clinically relevant concentrations, the free maximum plasma concentration ($C_{max)}$ to IC_{50} ratio is expected to be <0.1; therefore, they are not expected to cause drug-drug interactions (DDI) with BCRP substrates. Neither ozanimod, nor its metabolites were inhibitors of efflux transporter MATE1 and MATE2-K, or uptake transporters OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 at clinically relevant concentrations. Moreover, ozanimod and its metabolites unveiled no significant induction or inhibitory potential of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6 and CYP3A4 enzymes. Furthermore, the two glucuronidated metabolites RP101124 and RP112402 did not inhibit UGT family members.

2.4.4. Toxicology

Single dose toxicity

No single dose toxicity studies were conducted. This is supported by the current guidelines.

Repeat dose toxicity

Repeated dose toxicity studies comprised studies with administration of ozanimod to mice, rats and Cynomolgus monkeys and studies with direct administration of metabolites CC112273, RP101075 and RP101442 to mice and/or rats. All studies employed the oral route of administration.

The main repeated dose toxicity studies have been conducted in Sprague Dawley rats and Cynomolgus monkeys with daily oral administration of ozanimod for up to 26 and 39 weeks, respectively. In each of these animal species, in addition to the GLP chronic toxicity studies, ozanimod was tested in GLP 28 days and 13 weeks duration studies, with all studies, except for the 13 weeks, including a recovery period. Overall, these investigations revealed comparable toxicity targets across species. However, no pronounced toxicities were observed even in dose range finding studies, hence, precluding the determination of maximum tolerated doses.

Chronic administration of ozanimod had similar effects in rats and Cynomolgus monkeys, with changes in haematological parameters (decrease in leucocytes, namely, T- but also B-lymphocytes) and lymphoid organs (decrease cellularity). In line with the role of $S1P_1$ receptor in maintaining endothelial barrier integrity within the lungs, ozanimod also dose-dependently induced prominent alterations in lungs of mice, rats and monkeys including juvenile animals (increase in weight and alveolar histiocytosis /accumulation of foamy macrophages). In both rats and monkeys, the severity of these lung toxicities did not deteriorate in long-term toxicity studies, but they were incompletely reversible after the 6 weeks recovery period and served to determine the no observed adverse effect level (NOAEL)s (0.2 and 0.1 mg/kg/day in rats and monkeys, respectively) in these investigations.

The Applicant's position that additional effects observed in shorter term studies in rats and Cynomolgus monkeys were attributed to stress or part of the background spectrum present in animals from different vendors and studies run in different locations was accepted as these effects were absent from the chronic toxicity studies. Similar doses levels were employed in the chronic and shorter-term studies in rats and different ozanimod batches were used in the chronic studies (Batch No. AJ506FP-11-001, purity of 99.5%) *versus* the 28 days and 13 weeks studies (Batch No. AJ501 FPRP-10-001, purity of 99.2%) in rats and Cynomolgus monkeys. Furthermore, in relation to those observed in the chronic toxicity studies with administration of ozanimod, no new toxicities were identified in studies conducted with direct administration of the metabolites CC112273, RP101075 or RP101442. Effects of ozanimod in the 28 days repeated dose toxicity study in CByB6F1 mice were also generally identical to findings observed in the chronic toxicity studies in rats and Cynomolgus monkeys.

Concerning safety margins/exposure multiples, the chronic toxicity studies included toxicokinetic analysis for ozanimod and its metabolites RP101075, RP101442, RP101988 and RP101124, where the first 3 are active metabolites (the 28 days and 13 weeks studies included toxicokinetic analysis for ozanimod and its metabolites RP101075 and RP101442 only). However, in humans, the major metabolites were identified after completion of the pivotal toxicity studies as CC112273, CC1084037 and RP101124, with the first two being pharmacologically active and, together with ozanimod, contributing to 94% of total active exposure of the drug in humans. Therefore, the systemic exposures of CC112273 and CC1084037 in the chronic toxicity studies had to be retrospectively estimated based on those determined in GLP compliant 14-days pharmacokinetic bridging studies conducted in Sprague Dawley rats and Cynomolgus monkeys (as well as in mice and rabbits). Based on measured or estimated exposures (AUC), at the chronic toxicity NOAEL, in rats, systemic exposures to ozanimod, the metabolites RP101124, CC112273 and CC1084037 and total active drug in humans (ozanimod+CC112273+CC1084037) were calculated to be 10.4-, 17.7-, 0.0446-, 0.0036- and 0.62-times, respectively, those expected in humans. In Cynomolgus monkeys, these multiples at the NOAEL were 3.73, 0.445, 0.316, 0.363 and 0.515, respectively. Due to the substantial pharmacokinetic differences between animals and humans delineated above, systemic exposure levels in animals to the disproportionate main active and persistent

human metabolites CC112273 and CC1084037 and even to total active drug at the NOAEL were, therefore, clearly lower than those expected in patients at the maximum recommended ozanimod dose. This information was added in section 5.3 of the SmPC.

Genotoxicity

The Applicant provided a characterisation of the genotoxic profile of ozanimod and most relevant metabolites. Some of the assays were conducted in a non-GLP setting but all relevant ones were conducted in compliance with GLP. The Applicant presented both *in vitro* and *in vivo* data.

All GLP-compliant bacterial reverse mutation assays (with or without metabolic activation) were negative for ozanimod, and metabolites RP110351, CC112273, CC1084037. Additionally, some non-GLP bacterial reverse mutation studies were performed with two minor metabolites (RP101075 and RP101442) and they were all negative.

Also, in a GLP-compliant mouse lymphoma assay ozanimod did not induce any biologically significant increase in the mutant frequency for the long treatment period (~24 hours) in the absence of metabolic activation, and for the short treatment period (~4 hours) either with or without metabolic activation.

In another GLP compliant study, the metabolite CC112273 was tested for the ability to induce structural chromosomal aberrations in human peripheral blood lymphocytes, with and without metabolic activation, and CC112273 was negative.

Also, the ability for CC1084037, and/or its metabolites, to induce micronuclei in TK6 cells in the presence and absence of an exogenous metabolic activation system was tested and here, CC1084037 was positive for the induction of micronuclei in the non-activated test system in the *in vitro* mammalian cell micronucleus test using TK6 cells. To further assess this *in vitro* TK6 result, an additional combined *in vivo* rat bone marrow micronucleus and hepatic Comet assay was conducted with CC1084037 and for ozanimod. The negative bone marrow micronucleus result and the negative hepatic Comet assay results for CC1084037 provided by the Applicant gave enough assurance of the absence of genotoxic activity and no additional tests were warranted according to the prevailing ICH S2(R1) guideline (EMA/CHMP/ICH/126642/2008).

Carcinogenicity

Once-daily (QD) oral administration of ozanimod to Tg.rasH2 mice at dose levels of 8, 25, and 80 mg/kg/day for 26 weeks identified a statistically significant increased incidence of hemangiosarcoma in males and females at all doses. Although the hemangiosarcoma incidence in the low dose group remained within laboratory background levels, the combined non-splenic haemangioma/hemangiosarcoma exceeded the historical control range. Therefore, considering the low dose as no observed effect level (NOEL) for hemangiosarcoma was regarded critical.

The driving mechanism for hemangiosarcoma development in mice may be stimulation of endothelial cells through $S1P_1$ (also known as the EDG1 receptor; Pognan et al., 2018). This receptor is abundant on vascular endothelial cells (VEC) and is important for endothelial cell migration, differentiation, and survival. In mice, $S1P_1$ agonism results in sustained production of placental growth factor 2 (PlGF-2) and subsequently, persistent VEC mitoses. In contrast, rat and human VEC do not release PlGF-2 or only transiently release PlGF-2. Sustained VEC stimulation and/or hemangiosarcoma formation are not observed in these species (Pognan et al., 2018). Although the hemangiosarcoma may not be relevant in other species than mice, a critical point in this study is the obviously minor exposure ratio for the disproportionate major active human metabolites CC112273 and CC1084037 at the low dose level with only insignificant 2.95- and 1.4-fold safety margins compared to human exposure at the proposed clinical

dose. The fact that the incidence of hemangiosarcoma was statistically increased at the low dose level in males was therefore reflected in section 5.3 of the SmPC.

In a 2-year carcinogenicity study in rats, ozanimod administered daily to at up to 2 mg/kg did not cause any test article-related neoplastic lesions. In fact, the NOAEL for toxicity could be generally considered satisfactory. The major drawback of this 2-year study is the insufficient exposure of the active human disproportionate metabolites CC112273 and CC1084037, which had not been identified as major metabolites at the time the study was conducted and, hence, their contribution to the active drug exposure was not part of the criteria for dose selection and the dose selection was based primarily on the parent compound ozanimod. This information was included in section 5.3 of the SmPC.

Reproduction Toxicity

Reproductive and development toxicity studies comprised studies on fertility and early embryonic development, embryo-foetal development (EFD), pre-/postnatal development (PPND) and studies with direct dosing of juvenile animals. Studies on embryo-foetal development were conducted in rats and rabbits, while all the others were conducted in rats only. Administration of ozanimod was investigated in all studies, except a pilot pre-/postnatal developmental toxicity study in rabbits, which tested the major human active metabolites CC112273. All studies used the oral route of administration.

Ozanimod impaired neither reproductive performance and fertility nor early embryonic development in rats. The exposure margin at the NOAEL of 30 mg/kg/day corresponds to 155-times the human exposure, when based on the total amount of active drug (ozanimod, CC112273 and CC1084037) determined in a bridging PK study at this dose level.

In the EFD study in rats, embryotoxicity was evident as significantly increased embryolethality at dosages above the NOAEL of 1 mg/kg/day, leaving less litters and pups for morphological examination in the high dose group. External malformations were noted in one low dose foetus (cyst extending from axilla to neck, classified as malformation in the study report), and 3 high dose foetuses out of 2 litters with anasarca. Another foetus from a separate litter showed a local oedema which was classified as anomaly. At visceral examination the same foetus also presented with cleft palate. Two other foetuses had bilaterally non descended testes. Anasarca is considered treatment-related due to the role of $S1P_1$ in vascular permeability. These findings coincide with data available for the $S1P_1$ knockout mouse, where germline knockout is embryonic lethal due the generalized haemorrhage (embryonic day 12.5 to 14.5). At the NOAEL determined in rats, a low safety margin (3.5-fold) compared to exposure of patients to total active drug (ozanimod, CC112273 and CC1084037) at the MHRD was obtained.

In rabbits, ozanimod similarly induced embryolethality (abortion, post-implantation loss) and teratogenic effects (malformed /absent blood vessels; malpositioned caudal vertebrae). However, in this species, malformations were already noted at the lowest dose level and consequently no NOAEL and no safety margin with respect to clinical exposure could be established.

In order to obtain higher exposures to the major active human metabolite CC112273, a DRF study with oral administration of the metabolite was conducted in rabbits. However, based upon the poor exposure using direct oral administration of CC112273, the decision was made not to perform a definitive embryo-foetal rabbit study.

In the PPND study in rats, adverse effects on pre-weaning body weights without any impact on developmental parameters were noted in the offspring of the high dose group. Across all groups, single instances of different macroscopic findings (e.g. malpositioned kidney, discoloration of lungs or liver, small aortic arch and persistent *truncus arteriosus*, umbilical hernia in the dose groups, and *situs inversus* in the control group) were evident either in stillborn or culled pups, or pups that died during the study.

Out of these findings special attention was drawn to the finding *"small aortic arch and the persistent truncus arteriosus"* noted in a female mid dose pup which died on study. It was obvious to consider these findings as treatment related due to the role of $S1P_1$ in vascular development during embryogenesis, and as similar findings had been observed in rabbit foetuses following treatment with ozanimod during organogenesis. However, malformations of the great vessels were not observed in any of the rat foetuses following exposure during organogenesis in the embryo-foetal development study. Consequently, these findings were judged of uncertain relationship to the test article.

After weaning, behavioural parameters were not negatively influenced in any dose group, except motor activity on postnatal day 35. Male offspring demonstrated a dose-dependent decrease in the number of rearings and high dose females showed a significant increase in the number of fine movements and the total distance. Interestingly, basic movement, mean fine movement and mean total distance were also significantly increased in female pups at a higher dose (10 mg/kg/day) in the pivotal 10 weeks juvenile toxicity study when tested at the same age (postnatal day 35). The relevance of these finding for humans is unclear and should be discussed in the context of a future application for a paediatric indication.

These data are reflected in section 5.3 of SmPC.

Local Tolerance

Ozanimod is being developed as a medical product administered by the oral route. The absence of local tolerance studies is agreed in line with recommendations of CHMP/EMA Guideline on non-clinical local tolerance testing of medicinal products (effective 1 May 2016).

Other toxicity studies

Ozanimod and its major active human metabolites CC112273 and CC1084037 maximally absorb around 280 nm followed by a minor decline at 320 nm, while the absorbance of the inactive major metabolite RP101124 peaks at 301 nm. At 290 or 301 nm, the corresponding Molar Extinction Coefficients of all four compounds were clearly above the threshold level of 1000 $l \cdot mol^{-1} \cdot cm^{-1}$ of the pertinent ICH S10 guideline (EMA/CHMP/ICH/752211/2012). Since ozanimod accumulates in the uveal tract of the eyes for more than 21 days and presumably binds to melanin-containing structures, the lack of a phototoxic potential was confirmed for ozanimod and its primary metabolites RP101075 and RP101988 in GLP compliant neutral red uptake phototoxicity assays in Balb/c 3T3 mouse fibroblasts irradiated with UVA light (320 and 400 nm).

Immunotoxicity assessment revealed the expected pharmacological action of decreased T- and B-lymphocyte counts and an inhibitory effect on primary and secondary T-dependent IgM and IgG antibody responses. Examination of ozanimod in rat juvenile toxicity studies identified the same effects as in adult rats (i.e., decreased peripheral blood lymphocytes, increased lung weights, and increased alveolar macrophages) as reflected in section 5.3 of the SmPC.

The qualification of impurities present in the ozanimod drug substance was based on analysis of the ozanimod lot administered to the rat and monkey in the GLP-compliant nonclinical studies (rat 26-week and monkey 39 week). These studies identified NOAELs of 0.2 mg/kg/day in the rat and 0.1 mg/kg/day in the monkey. The human equivalent dose was calculated based on the FDA Guidance for Industry (Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005) and assumed a 60-kg human body weight. The safety factor was derived as the ratio between the qualified levels of each impurity and the content in the MHRD of 1 mg ozanimod HCl (0.92 mg ozanimod).

Based on the results of repeated dose toxicology studies, RP-101948 was qualified at a level of 0.18% in the rat and monkey. The rat and monkey toxicology lot impurity percentage cover a human exposure limit of 3.48 µg/day for RP101948 corresponding to a relative amount of 0.348% in the MHRD. The specification for the impurity content of RP-101948 is 0.3%, resulting in maximum specified dose of 3 µg RP-101948 at the MHRD of 1 mg ozanimod HCl. The qualified impurity level has a safety factor of 1.16 (3.48 µg exposure limit/3 µg maximum specified dose) and is well below the 1 mg/day limit of the ICH M7(R1) guideline (see Note 1 of EMA/CHMP/ICH/83812/2013).

2.4.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment was submitted in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2*).

The log Kow of ozanimod HCl was experimentally determined under GLP conditions at pH 4, 7 and 9 following the shake flask method in accordance with the OECD 107 guideline. The resulting logKow was 1.1, 3.0 and 4.4 at pH 4, 7 and 9, respectively, and thus the Applicant's position that a PBT assessment was not required was agreed by the CHMP (**Table 1**).

The $PEC_{surfacewater}$ in phase I taking into consideration the member state with the highest prevalence of RRMS in Europe and the maximum daily dose of 0.92 mg/day was found to be below the action limit of 0.01 µg/L. Therefore, a phase II assessment was not required (**Table 1**).

Table 1: Summary of main study results

Substance (INN/Invented Name): Ozanimod hydrochloride			
CAS-number (if available): 1618636-37-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.1 at pH 4 3.0 at pH 7 4.4 at pH 9	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater	0.001	µg/L	> 0.01 threshold (N)

2.4.6. Discussion on non-clinical aspects

Ozanimod hydrochloride (HCl) (also known as RPC1063) is a potent, orally bioavailable, S1P agonist, which binds with high affinity and selectively to $S1P_1$ and $S1P_5$. Agonist activation of $S1P_1$ induces down-modulation of cell surface $S1P_1$ expression which results in lymphocyte retention in lymphoid tissues that is thought to ameliorate the pathological processes associated with MS.

Ozanimod is being developed for the clinical treatment of patients with RRMS. The proposed MHRD for the treatment of this condition is one milligram (1 mg) ozanimod HCl per day.

All relevant non-clinical aspects were presented and discussed above. From the point of view of non-clinical pharmacodynamics, no specific concerns arose, and the position of the Applicant was generally endorsed.

In terms of non-clinical pharmacokinetics, one specific concern needed further discussion. Following multiple dosing in humans, the majority of active drug in circulation is CC112273 (73%), followed by CC1084037 (15%) and ozanimod (6%). Although CC112273 and CC1084037 were present in nonclinical species, they were present at significantly higher levels in humans than in rodents and rabbits. It was acknowledged that systemic delivery of metabolites to improve the exposures was not feasible due to poor solubility of CC112273 and CC1084037 in vehicles suitable for IV or SC administration, and that higher CC112273 and CC1084037 exposures were obtained via administration of the parent compound, ozanimod. However, from the data originally provided by the Applicant, it was not clear that, in all species, human major metabolites (CC112273, CC1084037, and RP101124) attained sufficient exposures for adequate characterization of its *in vivo* pharmacology and toxicity. In response to this concern, the Applicant stated that "*major active metabolites are structurally similar to ozanimod with comparable activity and selectivity, and the combined total active drug exposures (ozanimod+CC112273+CC1084037) demonstrate sufficient exposures for adequate characterization of toxicity*". This response was considered not acceptable. The use of combined total active drug exposures may be acceptable for the primary pharmacodynamic effect, considering the similar activity and selectivity for human $S1P_1$ and $S1P_5$ and also similar activity for rat and Cynomolgus monkey $S1P_1$ and $S1P_5$, but structural similarity did not provide reassurance on the safety profile of a drug. In fact, the mean steady-state AUC_{0-t}/AUC_{0-24} of CC112273 was nearly comparable to ozanimod in monkeys, but 1.5- to 2-fold lower in rabbits, ≥8.5-fold lower in rats and ≥13.4-fold lower in mice. The exposure of CC1084037 was even ≥189.5-fold lower in rats, ≥19.5-fold lower in mice and ≥3.2-fold lower in monkeys. This contradicts the predominance and persistence of CC112273 and CC1084037 in humans, which represent the majority of the human drug-related AUC (66% and 13%, respectively), and can be attributed to the enhanced clearance of CC112273 and CC1084037 in animals compared to humans ($t_{1/2}$ ~19–22 h in animals vs. ~10 days in humans). Consequently, clinically relevant exposure levels (AUC_{0-t}/AUC_{0-24}) of CC112273 CC1084037 were not attained at the NOAEL in the toxicology program of ozanimod and not at even higher dosages in the 2-year carcinogenicity study in rats as well as the embryo-fetal development studies in rats and rabbits. The Applicant was requested to address the clinical implications of the inadequate coverage of CC112273 and CC1084037 levels in the above-mentioned studies by amendments of sections 4.4 and 4.6 of the SmPC concerning the embryo-foetal risks and section 4.4 of the SmPC concerning carcinogenic risks (immunosuppressive effects and cutaneous neoplasms).

As noticed earlier in the safety pharmacology study on respiratory function, ozanimod dose-dependently induced pronounced oedema and histiocytosis in the lungs of mice, rats and monkeys, which manifested in increased organ weights in these species. The premature death of three rats, which presented with multiple oedema/haemorrhage in the chronic toxicity study might have been additionally impacted by this lung toxicity. While changes in haematological parameters and lymphoid organs, observed in the same studies, were clearly related to the intended pharmacological activity of ozanimod/its active metabolites, the same did not appear to apply to the changes in lungs. Comparable adverse lung findings had been earlier reported for S1P modulators in rats, dogs and monkeys and were mechanistically related to the breakdown of the endothelial barrier in the lungs by $S1P_1$ receptor modulation (Shea et al., 2010; Oo et al., 2011). In view of the lack of any safety margins concerning exposure of the major active metabolites CC112273 and CC1084037 in animals with regard to therapeutic ozanimod administration in humans, the Applicant implemented a warning regarding clinical respiratory effects of ozanimod demanding its cautious use in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (COPD) in line with the currently approved SmPC of another S1P modulator and reported lung toxicities in non-clinical studies as included in section 5.3 of the SmPC.

In relation to the pharmacological relevance of the animal models, *in vitro* pharmacological studies showed that ozanimod and its major active metabolites CC112273 and CC1084037 share similar activity at human, murine and rat $S1P_1$ receptors, while the affinity of CC112273 for human and murine $S1P_5$

was 3-fold lower and that of CC1084037 about 3-fold higher compared to ozanimod. In line with the >94% identity in the amino acid sequence of human and monkey S1P receptors, the Applicant also confirmed the comparable affinity and selectivity of ozanimod at $S1P_1$ and $S1P_5$ receptors of Cynomolgus monkeys as observed in humans. Likewise, ozanimod, CC112273 and CC1084037 demonstrated similar binding profiles to $S1P_5$ receptors of rats as earlier determined in mice.

No relevant genotoxic potential of ozanimod and its major metabolites was apparent when tested in accordance with the ICH S2(R1) guideline (EMA/CHMP/ICH/126642/2008). With respect to the carcinogenicity studies of ozanimod, the insufficient exposure to the two human active metabolites CC112273 and CC1084037 was considered as a major drawback and reflected for the 2-year study in rats in section 5.3 of the SmPC. Likewise, the statistically increased incidence of haemangiosarcoma at the low dose level in males of the 26 weeks carcinogenicity study in transgenic Tg rasH2 mice was detailed in section 5.3 of the SmPC.

Concerning data on reproductive toxicity, the Applicant clarified that a definitive EFD study in rabbits with direct oral administration of the metabolite CC112273 was not conducted. The Applicant also agreed that a NOAEL could not be set regarding EFD in rabbits (i.e. the NOAEL was below the lowest tested dose of 0.2 mg/kg/day ozanimod). Finally, the Applicant agreed that vascular findings in rats and rabbits were consistent with expected $S1P_1$ pharmacology and that teratogenic effects occurred at total agonist exposures that were at or near the clinical dose. However, the Applicant considered the great vessel malformation observed in one dead pup of the mid dose group in the PPND study of uncertain relationship to the drug substance, due to the absence of any major vessels changes or cardiac abnormalities in the treated pups in the EFD study. These concerns were therefore considered resolved and these safety findings were satisfactorily reflected in sections 4.4, 4.6 and 5.3 of the SmPC.

Given the established role of the $S1P_1$ receptor in vasculogenesis (Ben Shoham *et al*., 2012; Pyne and Pyne, 2017), five cases of abnormal foetal development among 66 pregnancies with *in utero* exposure to fingolimod (Karlsson *et al*., 2014) and the embryo lethality and teratogenicity in both rats and rabbits administered ozanimod in the EFD studies, it was reasonable to assume that ozanimod could cause foetal harm when used in pregnant women. As a consequence, an absolute contraindication for the use of ozanimod during pregnancy and in women of childbearing potential not using effective contraception was included in section 4.3 as requested. Also, in line with other S1P modulators, the same risk minimisation measures were implemented in sections 4.4 and 4.6 of the SmPC regarding the risk for teratogenicity**.**

Postnatal development was not affected by maternal treatment with ozanimod except for some effects noted in motor activity parameters. After weaning, behavioural parameters were not negatively influenced in any dose group, except motor activity on postnatal day 35. Male offspring demonstrated a dose-dependent decrease in the number of rearings and high dose females showed a significant increase in the number of fine movements and the total distance. The relevance of these findings for humans is unclear but they were not considered adverse in the study report. Nevertheless, basic movement, mean fine movement and mean total distance were also significantly increased in female pups at a higher dose (10 mg/kg/day) in the 10 weeks juvenile toxicity study when tested at the same age (postnatal day 35). This should be discussed in detail at the time a paediatric indication is applied for. The juvenile parts of the nonclinical overview as well as of the documentation have to be revised prior to any extension of the currently proposed indication due to major inconsistencies identified.

The absence of a phototoxic potential was confirmed for ozanimod and its primary metabolites RP101075 and RP101988 in 3T3 NRU *in vitro* assays. However, the fibroblasts in these assays were irradiated with UVA light (320 and 400 nm). Given the absorption maxima of ozanimod, CC112273, CC1084037 and RP101124 (~290 and 301 nm, respectively), it is unfortunate that the more appropriate UVB range (280-315 nm) was not additionally tested to strengthen the validity of the assay results. Nonetheless, the

Applicant elucidated that the specific methodological recommendations of the pertinent OECD guideline 432 for appropriate irradiation conditions had been followed.

In view of the carboxylic acid functional group, the Applicant considered the main inactive human metabolite RP101124 additionally more hydrophilic than ozanimod, which should limit its tissue distribution including light-exposed structures. The Applicant further claimed that the benzoic acid moiety of RP101124 is similarly contained within its parent compound rendering specific phototoxicity of the metabolite unnecessary in line with the ICH S10 guideline (EMA/CHMP/ICH/752211/2012). As an additional argument, benzoic acid, a common pH adjustor and preservative within cosmetic products comprising also suntan lotions, lacks a phototoxic potential. Further confidence is gained by the much lower absorption of RP101124 in the range of natural sunlight compared to ozanimod, CC112273 and CC1084037. It was therefore agreed, that no dedicated phototoxicity test was required for RP101124.

Despite the lack of skin tumours in the toxicology program of ozanimod, increased cutaneous neoplasms have meanwhile been identified in MS patients treated with other S1P receptor modulators prompting recent amendments of their SmPC. With respect to the established role of the $S1P_1$ receptor in tumorigenesis (Yamaguchi *et al*., 2003; Pyne and Pyne, 2010; Kishimoto *et al*., 2011; Reimann *et al*., 2015), the lack of experience from long-term clinical ozanimod therapy and the generally wide tissue distribution of ozanimod including the eyes and skin, the potential risk for skin neoplasms has been included as a warning in section 4.4 of the SmPC has meanwhile implemented for other S1P modulators (see EMA/688187/2015, EMA/82227145/2017 and also clinical evaluation).

Finally, the Applicant verified the log Kow of ozanimod HCl and the Applicant's position that a PBT assessment was not required was agreed by the CHMP.

2.4.7. Conclusion on the non-clinical aspects

The findings in the chronic toxicology, carcinogenicity, and reproductive toxicology studies appeared to be target mediated effects of $S1P_1$ agonists. These include peripheral blood lymphopenia, increased lung weights and mononuclear alveolar infiltrates, species-specific hemangiosarcoma in mice, and great vessel abnormalities during foetal development. Overall, the data presented in this nonclinical package were regarded acceptable for marketing authorization of ozanimod, although the safe clinical administration of ozanimod could not be reliably concluded due to substantial pharmacokinetic differences between all animal species and humans leading to insufficient exposure to the major disproportionate active human metabolites CC112273 and CC1084037 in toxicology studies. Thus, adequate risk minimisation measures in accordance with other S1P modulators were implemented.

2.5. Clinical aspects

2.5.1. Introduction

The Applicant Celgene Europe BV applied for marketing authorisation for Zeposia pursuing the indication of the treatment of adult patients with RRMS. The proposed MHRD for the treatment of this condition is one milligram (1 mg) ozanimod HCl per day.

Prior to the submission, the Applicant received SA (EMEA/H/SA/2779/1/2014/SME/III) and the study design, choice of the population and efficacy end-points (ARR, CDP) and population was discussed together with questions about dose titration and safety (cardiac monitoring and long-term safety outcomes). Overall, the study design of the pivotal studies was overall considered to follow the Guideline

on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2).

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA P/0345/2017 on the agreement of a PIP. At the time of submission of the application, the PIP P/0345/2017 was not yet completed as some measures were deferred. A PIP was agreed with PDCO with a waiver for all subsets of the paediatric population from birth to less than 10 years of age. As part of the PIP, the study on extrapolation, modelling and simulation included in PIP, namely Study 4: Development of a population PK/PD model to support the choice of dose in the safety and efficacy study in children from 10 to less than 18 years of age with relapsing multiple sclerosis was completed and found to have been conducted in accordance with the PIP. This study aims to set the dose for the study 3 clinical study which is the "double-blind, double-dummy, randomised, active-controlled trial to evaluate safety and efficacy of ozanimod compared to interferon β-1a in children from 10 to less than 18 years of age with relapsing multiple sclerosis (RPC01-304)" which was not submitted as part of this application.

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.

- Tabular overview of clinical studies

The clinical pharmacology of ozanimod has been characterized in 16 Phase 1 clinical pharmacology studies (**Table 2**). Sparse PK samples were also collected in 3 Phase 2 and 3 studies in patients with RMS for population PK and exposure-response (E-R) analyses.

Table 2: Summary of studies contributing to characterize the clinical pharmacology profile of ozanimod

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPCS 001 (SAD/MAD); A Phase 1, Single-center, Randomized, Double-blind, Placebo-controlled, Ascending, Single- and Multiple-dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of Orally Administered RPC1063 in Healthy Adult Volunteers	5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	Safety; tolerability; PK; PD	Single-center, randomized, double-blind, placebo-controlled, ascending, single- and multiple-dose	Ozanimod, placebo; Capsules: 0.1 mg and 1 mg or placebo Part A: Single dose 0.3 mg, 1 mg, 2 mg, or 3 mg or placebo Part B: Once daily 0.3 mg, 1 mg, or 2 mg or placebo for 7 days Part C: Once daily 0.3 mg, 1 mg, or 1.5 mg or placebo for 28 days Part D: Once daily ozanimod or placebo. Ozanimod dose escalation for 7 days (Days 1 to 3 at 0.3 mg, Days 4 to 5 at 0.6 mg, Days 6 to 7 at 1 mg), then fixed dosing (2 mg) for 3 days starting Day 8; Route: oral	Ozanimod (total): 68 Placebo: 24 (4 subjects received both during the study); **Sex:** Total ozanimod: Male: 37 (54.4%) Female: 31 (45.6%) Total placebo: Male: 12 (50.0%) Female: 12 (50.0%) **Age (yrs):** Total ozanimod: Mean (SD): 36.7 (10.78) Min, Max: 19, 55 Total placebo: Mean (SD): 33.6 (9.79) Min, Max: 20, 53 **Race:** Total ozanimod: White: 47 (69.1%) Black: 11 (16.2%) Asian: 1 (1.5%) Other: 9 (13.2%) Total placebo: White: 22 (91.7%) Black: 2 (8.3%) Asian 0 (0%) Other 0 (0%)	Healthy male and female	Completed; Full + Amendment + Summary of Changes + SR Erratum

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1901 (Food Effect); A Randomized, Three-period, Crossover Study of the Effect of Food on the Pharmacokinetics of a Single Oral Dose of RPC1063 in Healthy Adult Subjects	5.3.3.4 Extrinsic Factor PK Study Reports	PK; safety; tolerability	Open-label, randomized, 3-period, 6-sequence, crossover study of a single dose of ozanimod under 1 fasted and 2 fed conditions	Ozanimod; Capsules: 1 mg Single dose 1 mg on Days 1, 8, and 15; Route: oral	Ozanimod 1 mg: 24; **Sex:** Male: 10 (41.7%) Female: 14 (58.3%) **Age (yrs):** Mean (SD): 34.8 (10.21) Min, Max: 18, 55 **Race:** White: 17 (70.8%) Black: 6 (25.0%) Asian: 1 (4.2%)	Healthy male and female	Completed; Full

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1902 (DDI with CYP3A/P-gp Modulators); A Phase 1, Open-label Study to Evaluate the Effects of a Strong Cytochrome P450 3A and P-glycoprotein Inhibitor (Itraconazole) and Inducer (Rifampin) on the Single-dose Pharmacokinetics of RPC1063 in Healthy Adult Subjects	5.3.3.4 Extrinsic Factor PK Study Reports	PK; safety; tolerability	Single-center, open-label, 2-period, 1-sequence crossover in parallel groups	Ozanimod, itraconazole, rifampin; Capsules: 0.25 or 1 mg ozanimod, 100 mg itraconazole, 300 mg rifampin Group 1: Treatment A: Single dose 0.25 mg ozanimod, Day 1 Treatment B: Itraconazole 200 mg daily, Days 8-10 Treatment C: Itraconazole 200 mg and ozanimod 0.25 mg on Day 11, then itraconazole 200 mg daily, Days 12-16 Group 2: Treatment D: Single dose 1 mg ozanimod, Day 1 Treatment E: Rifampin 600 mg daily, Days 8-13 Treatment F: Rifampin 600 mg and ozanimod 1 mg coadministration, Day 14; Route: oral	Ozanimod 0.25 mg: 18 Ozanimod 1 mg: 18 Itraconazole 200 mg: 17 Rifampin 600 mg: 17; **Sex:** Male: 21 (58.3%) Female: 15 (41.7%) **Age (yrs):** Mean (SD): 37.2 (9.81) Min, Max: 19, 55 **Race:** White: 22 (61.1%) Black: 12 (33.3%) Asian: 1 (2.8%) Other: 1 (2.8%)	Healthy male and female	Completed; Full + Summary of Changes+ CSR Erratum

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1903 (DDI with P-gp/BCRP Inhibitor); A Phase 1, Open-label Study to Evaluate the Effect of Cyclosporine, a Strong Inhibitor of Both P-glycoprotein and Breast Cancer Resistance Protein, on the Single-dose Pharmacokinetics of RPC1063 in Healthy Adult Subjects	5.3.3.4 Extrinsic Factor PK Study Reports	PK	Single-center, open-label, fixed-sequence, 2-period, crossover	Ozanimod, cyclosporine; Capsules: 0.25 mg ozanimod, 100 mg cyclosporine Sequential: Treatment A: Single dose 0.25 mg ozanimod, then 7-day washout period Treatment B: Single dose of each 0.25 mg ozanimod and cyclosporine 600 mg; Route: oral	Ozanimod 0.25 mg: 18 Cyclosporine 600 mg: 18; **Sex:** Male: 11 (61.1%) Female: 7 (38.9%) **Age (yrs):** Mean (SD): 34.3 (8.74) Min, Max: 20, 47 **Race:** White: 11 (61.1%) Black: 7 (38.9%) Asian: 0 (0%) Other: 0 (0%)	Healthy male and female	Completed; Full + Summary of Changes+ CSR Erratum
RPC01-1904 (Hepatic Impairment); A Phase 1, Open-label Study to Characterize the Pharmacokinetics and Safety of a Single Oral Dose of RPC1063 in Subjects with Hepatic Impairment	5.3.3.3 Intrinsic Factor PK Study Reports	PK; safety	Open-label, parallel-group	Ozanimod; Capsule: 0.25 mg Single dose: 0.25 mg; Route: oral	Ozanimod 0.25 mg: 31; **Sex:** Male: 25 (80.6%) Female: 6 (19.4%) **Age (yrs):** Mean (SD): 57.4 (5.87) Min, Max: 44, 67 **Race:** White: 24 (77.4%) Black: 5 (16.1%) Asian: 0 (0%) Other: 2 (6.5%)	Moderate or mild hepatic impairment or normal hepatic function	Completed; Full (Amendment)+ CSR Erratum

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1905 (Japanese PK Bridging); A Phase 1 Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of RPC1063 in Healthy Adult Japanese and Caucasian Subjects	5.3.3.3 Intrinsic Factor PK Study Reports	PK; PD; safety, tolerability	Randomized single-blind, placebo-controlled, parallel cohort	Ozanimod, placebo; Capsules: Ozanimod 0.25, 0.5, 1 mg, or placebo Group 1: Part 1: Single dose ozanimod (0.25 mg, 0.5 mg, or 1 mg) or placebo on Day 1 Group 2: Part 2: Once daily dosing of ozanimod in escalating doses (0.25 mg on Days 1-4, Days 5-7: 0.5 mg, Days 8-12: 1 mg) or placebo on Days 1-12; Route: oral	Ozanimod 0.25 mg single dose : 12 Ozanimod 0.5 mg: single dose: 13 Ozanimod 1 mg single dose: 12 Ozanimod 1 mg QD (including dose escalation): 16 Placebo: 16 **Part 1 only:** **Caucasian:** **Sex:** Male: 12 (48.0%) Female: 13 (52.0%) **Age (yrs):** Mean (SD): 35.9 (10.38) Min, Max: 21, 53 **Race:** White: 25 (100%) **Japanese:** **Sex:** Male: 12 (50.0%) Female: 12 (50.0%) **Age (yrs):** Mean (SD): 37.0 (7.38) Min, Max: 22, 48 **Race:** Asian: 24 (100%)	Healthy male and female	Completed; Full + Summary of Changes+ CSR Erratum

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1906 (Renal Impairment); A Phase 1, Open-label Study to Characterize the Pharmacokinetics and Safety of a Single Oral Dose of Ozanimod in Subjects with End Stage Renal Disease	5.3.3.3 Intrinsic Factor PK Study Reports	PK; safety	Open-label, single-dose Additional design information: Subjects with normal renal function will be matched by body weight (± 20%) and age (± 10 years) to subjects with end stage renal disease (ESRD).	Ozanimod; Capsule: 0.25 mg Single dose; Route: oral	Ozanimod 0.25 mg: 16 **Sex:** Male: 14 (87.5%) Female: 2 (12.5%) **Age (yrs):** Mean (SD): 53.8 (13.70) Min, Max: 22, 70 **Race:** White: 12 (75.0%) Black: 4 (25.0%) Asian: 0 (0%) Other: 0 (0%)	Non-Asian male and female with ESRD and age-matched subjects with normal renal function	Completed; Full + CSR Erratum,

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1907 (DDI Oral Contraceptive); A Phase 1 Study to Characterize the Effects of Ozanimod on the Pharmacokinetics of an Oral Contraceptive Containing Ethinyl Estradiol and Norethindrone in Healthy Adult Females	5.3.3.4 Extrinsic Factor PK Study Reports	PK effects of ozanimod on oral contraceptive; PK of ozanimod for oral contraceptive coadministration	Randomized, open-label, 2-period crossover	Ozanimod, Nortrel®; Capsules: 0.25 mg, 1 mg ozanimod Tablets: EE 35 µg and NE 1 mg Randomized 1:1 to treatment sequence AB or BA. Treatments A and B separated by 14-day washout. Treatment A: Single dose of oral contraceptive containing EE 35 µg and NE 1 mg. Treatment B: Once daily dosing of ozanimod 0.25 mg on Days 1-4, 0.5 mg on Days 5-7, and 1 mg on Days 8-13. On Day 12, ozanimod is coadministered with a single dose of oral contraceptive containing EE 35 µg and NE 1 mg; Route: oral	Ozanimod 0.25 mg: 24 Ethinyl estradiol 35 µg/ norethindrone 1 mg: 21; **Sex:** Male: 0 Female: 24 (100%) **Age (yrs):** Mean (SD): 42.7 (13.08) Min, Max: 18, 60 **Race:** White: 18 (75.0%) Black: 5 (20.8%) Asian: 0 (0%) Other: 1 (4.2%)	Healthy female	Completed; Full + Summary of Changes+ CSR Erratum

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1908 (DDI with BB/CCB); A Phase 1 Study to Characterize the Pharmacokinetic and Pharmacodynamic Interaction Between Ozanimod and Propranolol or Diltiazem in Healthy Adults	5.3.3.4 Extrinsic Factor PK Study Reports	Cardiac effects; safety; PK	Double-blind, randomized, placebo-controlled, crossover	Ozanimod, propranolol, diltiazem; Capsules: 0.25 mg ozanimod, 80 mg propranolol, 240 mg diltiazem Group 1: Randomized to sequences ABC, ACB, BAC, BCA, CAB, or CBA Group 2: Randomized to sequences DEF, DFE, EDF, EFD, FDE, or FED Washout period of 7-10 days between treatments A: Propranolol placebo once daily Days 1-5. On Day 5, single dose of ozanimod 0.25 mg after propranolol placebo B: Propranolol 80 mg once daily Days 1-5. On Day 5, a single dose of ozanimod placebo after propranolol C: Propranolol 80 mg once daily Days 1-5. On Day 5, a single dose of ozanimod 0.25 mg after propranolol D: Diltiazem placebo once daily Days 1-5. On Day 5, a single dose of ozanimod 0.25 mg after diltiazem placebo E: Diltiazem 240 mg once daily Days 1-5. On Day 5, a single dose of ozanimod placebo after diltiazem. F: Diltiazem 240 mg once daily Days 1-5. On Day 5, a single dose of ozanimod 0.25 mg after diltiazem; Route: oral	Ozanimod 0.25 mg: 36 Propranolol 80 mg: 18 Propranolol placebo: 18 Diltiazem 240 mg: 17 Diltiazem placebo: 18; **Group 1 (Propranolol):** **Sex:** Male: 11 (61.1%) Female: 7 (38.9%) **Age (yrs):** Mean (SD): 44.0 (7.22) Min, Max: 31, 55 **Race:** White: 9 (50.0%) Black: 7 (38.9%) Other: 2 (11.1%) **Group 2 (Diltiazem):** **Sex:** Male: 13 (72.2%) Female: 5 (27.8%) **Age (yrs):** Mean (SD): 37.6 (10.3) Min, Max: 19, 55 **Race:** White: 6 (33.3%) Black: 10 (55.6%) Other: 2 (11.1%)	Healthy male and female	Completed; Full

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1909 (Mass Balance); A Phase 1, Single-center, Single-dose Oral Excretion Balance Study of [^{14}C]-RPC1063 in Healthy Male Adults	5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	Elimination and mass balance recovery; metabolite profiling; identify chemical structures of metabolites; PK	Open-label, nonrandomized, single oral dose	[^{14}C]-RPC1063; Solution: 10 mL Single dose 10 mL of [^{14}C] RPC1063 solution (0.1 mg/mL), containing not more than 1.3 MBq (37 µCi) ^{14}C; Route: oral	[^{14}C]-RPC1063: 6; **Sex:** Male: 6 (100%) Female: 0 **Age (yrs):** Mean (SD): 40.3 (11.45) Min, Max: 31, 63 **Race:** White: 6 (100%)	Healthy male	Completed; Full
RPC01-102 (TQT); A Phase 1, Double-blind, Randomized, Placebo- and Positive-controlled, Parallel-group, Nested Crossover, Thorough QT/QTc Study to Evaluate the Effect of Therapeutic and Supratherapeutic Multiple Doses of RPC1063 on Cardiac Repolarization in Healthy Male and Female Subjects	5.3.4.1 Healthy Subject PD and PK/PD Study Reports	QTc interval; assay sensitivity; PK; safety; tolerability	Double-blind, randomized, placebo- and positive-controlled, parallel-group, nested crossover	Ozanimod, placebo; Ozanimod capsules: 0.25 mg, 1 mg, placebo Moxifloxacin tablet: 400 mg, placebo Once daily then single dose: Group 1: Ozanimod escalation (0.25 mg for 4 days, 0.5 mg for 3 days, 1 mg for 3 days, then 2 mg for 4 days). Single dose moxifloxacin placebo Days 2 and 17. Group 2a/b: Ozanimod placebo for 14 days. Single dose moxifloxacin 400 mg or moxifloxacin placebo on Days 2 and 17; Route: oral	Ozanimod (total): 62 Combined placebo: 62 **Sex:** Male: 72 (58.1%) Female: 52 (41.9%) **Age (yrs):** Mean (SD): 32.0 (7.50) Min, Max: 18, 45 **Race:** White: 88 (71.0%) Black: 32 (25.8%) Asian: 3 (2.4%) Other: 1 (0.8%)	Healthy male and female	Completed; Full + Summary of Changes + Memo

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1001 (RMS Intensive PK/PD); A Phase 1, Multicenter, Randomized, 12-week, Open-label Study to Evaluate the Multiple Dose Pharmacokinetics and Pharmacodynamics of RPC1063 in Patients with Relapsing Multiple Sclerosis	5.3.4.2 Patient PD and PK/PD Study Reports	PK; PD	Randomized, open-label, multiple-dose and multiple-site, parallel-group, 12-week	Ozanimod; Capsules: 0.25 mg, 0.5 mg, 1 mg Once daily 0.5 mg or 1 mg for 12 weeks (with 7-day dose escalation); Route: oral	Ozanimod 0.25 mg: 24 Ozanimod 0.5 mg: 24 Ozanimod 1 mg: 11 **Sex:** Male: 7 (29.2%) Female: 17 (70.8%) **Age (yrs):** Mean (SD): 38.8 (8.36) Min, Max: 23, 51 **Race:** White: 18 (75.0%) Black: 5 (20.8%) Asian: 1 (4.2%)	Patients with RMS	Completed; Full+ CSR Erratum

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1910 (Cardiac Effects after Missed Doses); A Randomized, Double-blind, Placebo-controlled, Adaptive, Phase 1 Study to Characterize the Cardiac Effects of Ozanimod Re-initiation after Different Drug Washout Intervals	5.3.4.1 Healthy Subject PD and PK/PD Study Reports	Cardiac effects - re-initiation after different washout intervals	Randomized, double-blind, placebo-controlled, adaptive	Ozanimod, placebo; **Period 1**: 0.25 mg (1 capsule of ozanimod HCl 0.25 mg or placebo) QD (approximately every 24 hours) on Days 1 through 4, 0.5 mg (1 capsule of ozanimod HCl 0.5 mg or placebo) QD on Days 5 through 7, and 1 mg (1 capsule of ozanimod HCl 1 mg or placebo) QD on Days 8 through 28 **Period 2**: A single dose of 1 mg (1 capsule of ozanimod HCl 1 mg or placebo) Route: oral	**Ozanimod (total): 56** **Combined placebo: 18** **(3-day Washout Group:** Sex: Male: 10 (62.5%) Female: 6 (37.5%) Age (yrs): Mean (SD): 37.2 (8.97) Min, Max: 19, 51 Race: White: 13 (81.3% Black: 3 (18.8%) **7-day Washout Group:** Sex: Male: 9 (50.0%); Female: 9(50.0%) Age (yrs): Mean (SD): 32.3 (7.93) Min, Max: 19, 48 Race: White: 8 (44.4% Black: 10 (55.6%) **14-day Washout Group:** Sex: Male: 8 (50.0%); Female: 8 (50.0%) Age (yrs): Mean (SD): 39.0 (10.60) Min, Max: 19, 52 Race: White: 10 (62.5% Black: 5 (31.3%) **Combined Placebo) Group:** Sex: Male: 10 (55.6%); Female: 9 (44.4%) Age (yrs): Mean (SD): 36.2 (8.85) Min, Max: 26, 55 Race: White:13 (72.2%; Black: 5 (27.8%)	Healthy male and female	Completed; Full+ HR Post-Hoc Analysis

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1911 (Multiple-dose PK in Japanese and Caucasians); A Phase 1 Study to Characterize the Pharmacokinetics and Pharmacodynamics of Ozanimod Following Administration of Different Multiple-dose Regimens in Healthy Adult Caucasian and Japanese Subjects	5.3.3.3 Intrinsic Factor PK Study Reports	PK, PD in Caucasian and Japanese	Randomized, double-blind, placebo-controlled multiple-dose	Ozanimod, placebo; Subjects in each part were randomly assigned 2:2:2:1 to receive 1 of the 4 treatment arms: Ozanimod HCL 0.5 mg QD or placebo QD for 28 days (including the initial 7-day dose escalation) Ozanimod HCL 1 mg QD or placebo QD for 28 days (including the initial 7-day dose escalation) Ozanimod HCL 2 mg QD or placebo QD for 28 days (including the initial 7-day dose escalation) Placebo QD for 28 days Route: oral	Caucasian: 42 Japanese: 39 **Overall Demographics:** **Part A – Caucasians** Sex: Male: 30 (71.4%) Female: 12 (28.6%) Age (yrs): Mean (SD):38.5 (9.48) Min, Max:21, 53 Race: White: 42 (100%) **Part B – Japanese** Sex: Male: 34 (87.2%) Female: 5 (12.8%) Age (yrs): Mean (SD):32.8 (7.79) Min, Max:20, 50 Race: Asian: 39 (100%)	Healthy male and female	Completed; Full

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1912 (DDI with CYP2C8/3A modulators); A Phase 1, Randomized, Parallel-group, Open-label Study to Evaluate the Effect of the Modulators of the Cytochrome P450 (CYP) 2C8 and/or 3A on the Single-dose Pharmacokinetics of Ozanimod and CC112273 in Healthy Adult Subjects	5.3.3.4 Extrinsic Factor PK Study Reports	Evaluate the effect of the following index inhibitors or inducers of CYP2C8 and/or CYP3A on the single-dose PK of ozanimod and its active metabolites CC112273 and CC1084037 in healthy adult subjects: gemfibrozil (strong inhibitor of CYP2C8), rifampin (moderate inducer of CYP2C8 and strong inducer of CYP3A), and itraconazole (strong inhibitor of CYP3A).	A Phase 1, Randomized, Parallel-group, Open-label Study to Evaluate the Effect of the Modulators of the Cytochrome P450 (CYP) 2C8 and/or 3A on the Single-dose Pharmacokinetics of Ozanimod and CC112273 in Healthy Adult Subject.	Part 1 (Potential increase in CC112273 exposure with CYP2C8 inhibitor): Treatment Group A (reference): A single dose of ozanimod 0.5 mg on Day 1. Treatment Group B (test): Gemfibrozil 600 mg twice daily (BID) on Days 1 through 17. On Day 4, a single dose of ozanimod 0.5 mg will be coadministered with the morning dose of gemfibrozil Part 2 (Potential decrease in CC112273 exposure with CYP3A inhibitor or CYP2C8/3A inducer): Treatment Group C (reference): A single dose of ozanimod 1 mg on Day 1. Treatment Group D (test): Itraconazole 200 mg once daily (QD) on Days 1 through 17. On Day 4, a single dose of ozanimod 1 mg will be coadministered with itraconazole. Treatment Group E (test): Rifampin 600 mg QD on Days 1 through 21. On Day 8, a single dose of ozanimod 1 mg will be coadministered with rifampin. Route: oral	Overall Demographics: **Sex:** Male: 57 (57%) Female: 43 (43%) **Age (yrs):** Mean (SD): 34.5 (9.55) Min, Max: 18, 55 **Race:** Native American or Alaskan Native: 1 (1%) Asian: 4 (4%) Black: 43 (43%) White: 50 (50%) Other: 2 (2%)	Healthy male and female	Completed; Full

Study Number; Study Title	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects; Overall Demographics	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
RPC01-1914 (DDI with pseudoephedrine); A Phase 1, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of Ozanimod on Blood Pressure and Heart Rate Response to Pseudoephedrine in Healthy Adult Subjects	5.3.3.4 Extrinsic Factor PK Study Reports	To evaluate the effect of ozanimod after repeated dosing on systolic blood pressure response to a single-dose administration of pseudo-ephedrine in healthy adult subjects.	A Phase 1, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of Ozanimod on Blood Pressure and Heart Rate Response to Pseudo-ephedrine in Healthy Adult Subjects	Days 1 to 4: 0.25 mg ozanimod or placebo daily Days 5 to 7: 0.5 mg ozanimod or placebo daily Days 8 to 10: 1 mg ozanimod or placebo daily Days 11 to 29: 2 mg ozanimod or placebo daily Day 30: 2 mg ozanimod or placebo, co-administered with pseudoephedrine 60 mg	Ozanimod (total): 28 Placebo: 26 Overall Demographics: **Placebo:** **Sex:** Male: 15 (57.7%) Female: 11 (42.3%) **Age (yrs):** Mean (SD): 36.7 (10.75) Min, Max: 19, 54 **Race:** Asian: 1 (3.8%) Black: 10 (38.5%) White: 14 (53.8%) Other: 1 (3.8%) **Ozanimod:** **Sex:** Male: 16 (57.1%) Female: 12 (42.9%) **Age (yrs):** Mean (SD): 38.3 (12.01) Min, Max: 19, 55 **Race:** Black: 12 (42.9%) White: 13 (46.4%) Other: 3 (10.7%)	Healthy male and female	Completed; Full

2.5.2. Pharmacokinetics

Methods

The overall assay performance (accuracy, precision) of quality control standards (ozanimod) complied with acceptance limits recommended in the appropriate guideline. The metabolites CC112273 and CC1084037 and their contribution to the active moiety have been elucidated lately in the clinical development. CC112273 has been investigated in 8 studies, including PK after multiple dosing and in renal and hepatic impaired population. Data of CC1084037 have been provided only for two studies.

The incurred sample reanalysis of RP101075 showed ISR failures during sample analysis which were attributable to the low concentrations of RP101075 (<10pg/mL) in the study samples relative to the range of the assay. In samples where the concentration of RP101075 was above 40pg/mL, the passing rate for ISRs met the criteria. Moreover, RP101075 is a minor metabolite with demonstrated coverage in preclinical toxicology species and is not a key determinant for understanding exposure-efficacy relationship.

Long term stability data have been updated in the bioanalytical reports, e.g. in study RPC01-1906, for analyte RP112273, long term-stability has been updated for 392 days at -70°C (the maximum sample storage time was 382 days at -70°C).

Absorption

In vitro and *in vivo* data enabled to characterize the absorption of ozanimod after oral administration.

In a validated Caco-2 monolayer system, ozanimod, at concentrations ranging from 0.0989 µM (approximately 1% of the 1 mg clinical dose strength in 250 mL) to approximately 9.89 µM (100%), has demonstrated equal or greater permeability relative to minoxidil, classifying ozanimod as a highly cell permeable molecule. In addition, stability of ozanimod was also demonstrated in SGF and SIF matrices. Therefore, ozanimod has been classified as highly permeable and its permeability and absorption is unlikely to be limited by efflux transporters.

Following oral administration, the median time to maximum plasma concentration (T_{max}) of ozanimod was approximately 6 to 8 hours (RPCS 001 [SAD/MAD], RPC01-1904 [Hepatic Impairment], RPC01-1906 [Renal Impairment], and RPC01-1901 [Food Effect]). The median T_{max} of CC112273 and CC1084037 were approximately 10 hours, and 16 hours, respectively.

Moreover, food (high- and low-fat meals) intake did not alter exposure of ozanimod, RP101988, and RP101075 (RPC01-1901 [Food Effect]). However, the delayed median T_{max} observed for the high fat meal when compared to fasting and low-fat conditions might be caused by a delayed gastric emptying, as a physiological condition after a high fat stimulus. While data on CC112273 and CC1084037 were not available, food is not expected to have an effect on the metabolism or elimination of metabolites since food only affects the absorption of the parent drug (e.g., delay gastric emptying, change gastrointestinal pH, and physically or chemically interact with a dosage form). In fact, regarding metabolites RP101988 and RP101075, results from the study show no influence of both high fat and low-fat meals in the exposure of metabolites. Delayed T_{max} is due to a delayed absorption of ozanimod. Based on food interaction study, ozanimod can be administered with or without food, as described in the SmPC.

Following multiple dose administration of ozanimod, the median T_{max} of ozanimod, CC112273 and CC1084037 was approximately 8 to 10 hours, 10 to 12 hours, and 4 to 24 hours, respectively.

The observed high variability in CC1084037 mean T_{max} was not due to the analytical method nor to study design, but to normal fluctuations in steady state.

Based on mass balance study, the Applicant estimated a fraction absorbed of approximately 65%. This estimate was derived from the recovered radioactivity in urine 26% and from the recovered radioactivity in feces for RP112480, RP112479 and RP101988 metabolites, which together account for 14.77% of the radioactive dose. Combining the radioactive dose excreted in urine and hepatic metabolites excreted in feces indicated that at least 65% the recovered dose was absorbed (40.77% ÷ 63% of the recovered dose). Upon request, the low recovery on total radioactivity (63%) was justified by the Applicant to the long $t_{1/2}$ of metabolites CC112273 and CC1084037 and to the loss of ^{14}C-label as carbon dioxide ($^{14}CO_2$) in the expired air, due to anaerobic microbial reductive metabolism, which were not covered on mass balance study. This justification was found to be plausible by CHMP. Oral bioavailability is however not possible to be predicted from mass balance study. Based on results from this study, the profile for the cumulative recovery of total radioactivity, as total radioactive compounds concentration, were approximately 10 times higher than the sum of measured radioactive compounds, which was found to be due to metabolite CC112273. After long term validation, samples from study RPC01-1909 were analysed for this active metabolite and the results showed graphically a similar log-linear terminal phase for metabolite CC112273, in comparison to total radioactivity. Therefore, the prolonged $t_{1/2}$ observed on total radioactivity profile was hypothesised to be due to the prolonged $t_{1/2}$ of metabolite CC112273.

The absolute and/or relative bioavailability of ozanimod was not estimated in appropriate pharmacokinetic studies.

Considering that the registration/commercial drug product (Formulation 3) uses the same quantitative and chemical formulation as the clinical drug product, no bioequivalence study was performed to bridge results from the clinical drug product to the registration/commercial drug product.

Distribution

Plasma protein binding of ozanimod and its metabolites (discrete) was assessed *in vitro* by equilibrium dialysis in animal and human plasma

According study results, ozanimod plasma protein binding was high and ranged from 82.6% to 98.7%. In general, all the active metabolites of ozanimod are highly protein bound with extent binding comparable to ozanimod and the binding was similar across the species tested.

Based on mass balance study and other pharmacokinetic studies, the estimated apparent volume of distribution (V/F) is very high (>5000L). Despite no intravenous data is available, it is hypnotized that high volume of distribution is due to physicochemical properties of the molecule and not due to the low bioavailability. A high volume of distribution was also observed in preclinical species**.**

From the PK studies it can be concluded that V/F do not variate from single to multiple dose and from healthy to patient populations.

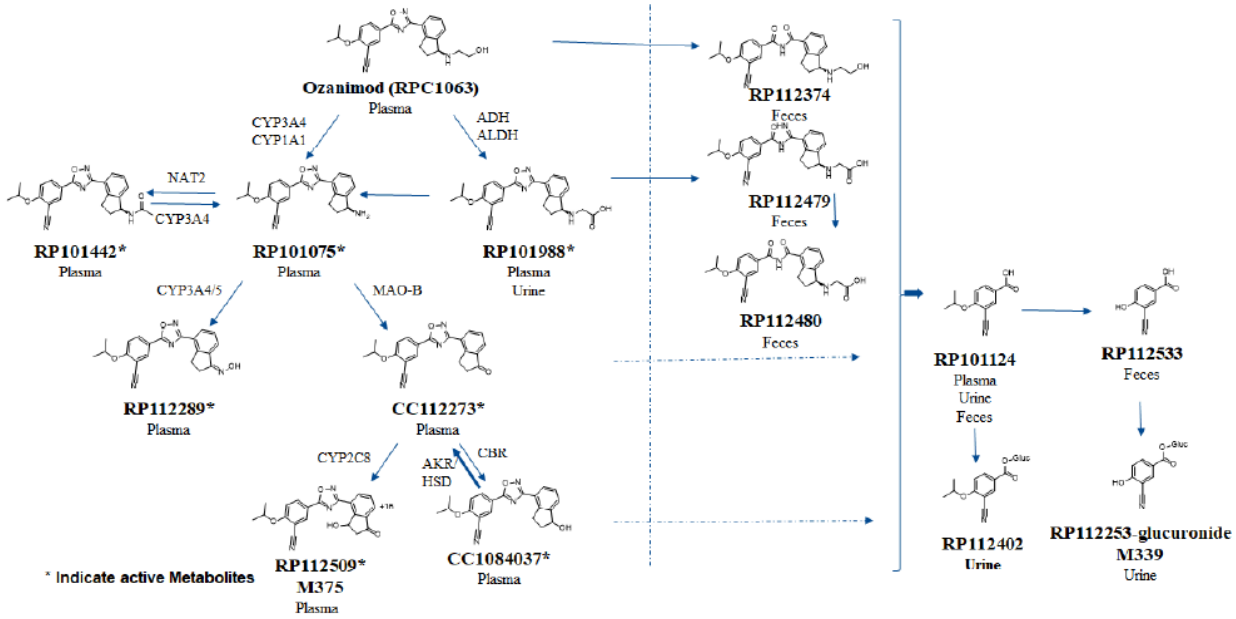
Elimination

Metabolism

In vitro and *in vivo* metabolism studies have been conducted in various species to characterize the metabolism of ozanimod. [^{14}C]-ozanimod radiolabel at two distinct positions of the molecule: 5' (carbon between oxygen and nitrogen of oxadiazole ring) and 3' (carbon between the two nitrogens of the oxadiazole ring) was used to investigate metabolic profiles.

Figure 2 represents the proposed metabolic pathway of ozanimod.

Figure 2: the proposed metabolic pathway of ozanimod



Abbreviations: ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenases; CBR = carbonyl reductase; CYP = cytochrome P450; MAO-B = monoamine oxidase B; NAT2 = N-acetyltransferase-2; AKR=aldo-keto reductases; HSD = hydroxy steroid dehydrogenase.
Source: Metabolite identification data from RPC01-1909

Ozanimod is extensively metabolized in humans to form a number of circulating active metabolites and one circulating inactive metabolite RP101124. Multiple enzyme systems play an important role in the metabolism of ozanimod and no single enzyme system predominates the overall metabolism of ozanimod. The oxidative pathway to formation of carboxylate metabolite RP101988 is mediated by ALDH/ADH while formation of RP101075 by dealkylation is predominantly carried out by cytochrome P450 CYP-3A4. RP101075 is N-acetylated by N-acetyltransferase-2 to form RP101442 or deaminated by MAO-B to form the major metabolite CC112273.

CC112273 is either reduced to form CC1084037 or undergoes CYP2C8 mediated oxidation to form RP101509. CC1084037 is oxidized rapidly to form CC112273 by aldo-keto reductase (AKR) 1C1/1C2, and/or 3β- and 11β-hydroxysteroid dehydrogenase (HSD). The oxido-reduction interconversion between CC112273 and CC1084037 favours CC112273 and there are no direct metabolites of CC1084037 other than its metabolism to CC112273 and subsequent elimination via that pathway. Gut microbial flora play an important role, *in vivo*, via anaerobic reductive metabolism of the oxadiazole ring system in the formation of many inactive metabolites which constitute a predominant portion of the excreted dose via urine and feces.

CC1084037 is a direct and inter-converting metabolite of CC112273 and there is no known genetic polymorphism on the activity of the enzymes involved in the inter-conversion of these metabolites (CBR, AKR, and HSD).

Following multiple dosing of ozanimod in healthy subjects, ozanimod, CC112273, CC1084037 and RP101124 each represents approximately 5%, 66%, 13%, and 10% of circulating total drug related (active + inactive) exposure, respectively. Ozanimod, CC112273, and CC1084037 each represents approximately 6%, 73%, and 15% of circulating total active drug exposure, respectively. Together, ozanimod, CC112273, and CC1084037 contribute to approximately 94% of circulating total active drug

exposure. The other active metabolites together contribute to the remaining 6% of circulating total active drug exposure.

Several synonyms have been used for different metabolites during the clinical development. Of special importance when evaluating the metabolism is the fact that major active metabolite CC112273 and CC1084037 were discovered rather late in the clinical development, when several studies in the clinical pharmacology program were already completed. The Applicant analysed CC112273 in seven Phase 1 studies. Samples were used that were in the established 17-month long-term stability for CC112273. The overwhelming majority of samples were analysed prospectively and only 12.8% of total Phase 1 samples were retrospectively analysed for CC112273. It is unlikely the retrospective analysis had a significant impact on the overall PK analysis. For CC1084037, no retrospective analysis was performed. For metabolite RR112509, there was basically no data provided.

Aspects of the metabolic pathway were clarified by the Applicant. No new major or minor pathways have been identified since the initial application. Inactive metabolites found in feces are expected to come from unabsorbed parent drug as well as active metabolites, that are excreted via bile. Inactivation of ozanimod and its active metabolites occur after biliary excretion by microbial gut flora. The inactive metabolite RP101124 found in plasma is expected to be absorbed from the gut after being formed by microbial flora. Moreover, RP101988 can also be cleared through bile in addition to renal clearance and therefore no significant accumulation is expected in patients with end-stage renal disease (ESRD).

Based on *in vivo* studies, the Applicant appropriately characterized the pharmacokinetics of the main ozanimod metabolites CC112273, CC1084037, RP101988, RP101075 and RP101124.

Monoamine oxidase B (MAO-B) plays a key role in the formation of major active metabolite CC112273 and subsequently CC1084037. Different activity of MAO-B could have a significant impact on CC112273, and subsequently CC1084037, exposure. Moreover, data from patients who smoke indicates that a lower activity of MAO-B due to smoking may have an impact on CC112273 exposure. The clinical relevance of this is yet unknown. However, based on scientific literature review, a clinically significant influence on metabolite exposure by known polymorphisms of MAO-B is highly unlikely. Additionally, a lack of association between CC112273 and AE of interest (ie, ALT/AST elevation) was observed, as well as a lack of correlation between platelet MAO-B activity and plasma CC112273 concentrations. Measurement of MAO-B activity is not expected to anticipate or understand the safety and efficacy of ozanimod.

Excretion

Based on the urine recoveries as the percent of the administered total radioactivity in the human mass balance study (RPC01-1909 [Mass Balance]), the mean fraction of the administered dose excreted in the urine (%CumAe) was less than 0.2% for ozanimod and RP101075 and less than 3% for RP101988, indicating that renal clearance is not an important excretion pathway for ozanimod or its active metabolites RP101988 and RP101075. The major inactive metabolite recovered in the urine is RP112402, and the major inactive metabolites recovered in the feces are RP112533 and RP112480.

Ozanimod, CC112273, and RP101075 concentrations in urine were negligible (ie, below threshold for identification), and RP101988 is the only intact oxadiazole recovered in urine with approximately 4% of the radioactive dose, indicating that renal clearance is not an important excretion pathway for ozanimod or its active metabolites.

Moreover, based on the available data, it was agreed that there is no evidence for biliary excretion and entero-hepatic recirculation.

Total elimination

The average apparent oral clearance (CL/F) for ozanimod was 3200 mL/min (192 L/h) (RPC01-1909 [Mass Balance]). The mean terminal elimination half-life (T½) values for ozanimod were approximately

19 to 22 hours (RPC01-1901 [Food Effect], RPC01-1909 [Mass Balance], RPC01-1910 [Cardiac Effects after Missed Doses], RPC01-1001 [RMS Intensive PK/PD], and RPC01-1912 [DDI with CYP2C8/3A Modulators]).

Steady-state concentrations for ozanimod were reached within 5 to 7 days of QD administration of ozanimod [RPCS 001 [SAD/MAD], RPC01-1905 [Japanese PK Bridging], and RPC01-1910 [Cardiac Effects after Missed Doses]). At steady state, approximately 2-fold drug accumulation for ozanimod was observed.

Metabolites CC112273 and CC1084037 exhibited similar mean $t_{1/2}$ of approximately 10 days following single oral doses in healthy subjects (RPC01-1912 [DDI with CYP2C8/3A Modulators]). The estimated mean T½ of CC112273 was approximately 11 days in RRMS patients following multiple dosing. The model-based mean time to steady state for CC112273 was approximately 45 days and with the estimated mean accumulation ratio of approximately 16. Steady state attainment and accumulation ratio for CC1084037 are expected to be similar to CC112273 since both metabolites exhibited similar mean T½ (RPC01-1912 [DDI with CYP2C8/3A Modulators]).

Dose proportionality and time dependencies

Dose proportionality

Ozanimod demonstrated dose-proportional increases in C_{max} and AUC following a single dose over the dose range of 0.25 to 3 mg in healthy subjects across clinical pharmacology studies. The active metabolites CC112273 and CC1084037 also exhibited dose-proportional increases in C_{max} and AUC following a single dose over the investigated dose range of 0.25 to 1 mg (for CC112273) and 0.5 to 1 mg (for CC1084037). Exposure (C_{max} and AUC) for CC112273 and CC1084037 were highly correlated with or without extrinsic factors (ie, interacting drugs).

Ozanimod demonstrated dose-proportional increases in C_{max} and AUC following multiple QD doses over the dose range of 0.3 to 2 mg across clinical pharmacology studies. The major active metabolite CC112273 also exhibited dose-proportional increases in C_{max} and AUC following multiple QD doses over the dose range of 0.5 to 1 mg across clinical pharmacology studies. Exposure (C_{max} and $AUC_{0\text{-last}}$) for CC112273 and CC1084037 were highly correlated.

Time dependency

The T½ for ozanimod and CC112273 were similar after a single dose or repeated doses. The mean T½ value for ozanimod were approximately 18 to 22 hours after single doses or approximately 22 hours after multiple doses. The mean T½ for CC112273 was approximately 10 days after single doses and was approximately 11 days after chronic dosing. Both CC112273 and CC1084037 exhibited similar T½ after single doses and are expected to have similar T½ after chronic dosing.

After reaching steady state, PK parameters for ozanimod did not change with time following chronic dosing. The trough concentrations of CC112273 at steady state were also consistent, and results of population PK analysis of CC112273 suggested no systematic changes with time in PK parameters for metabolite formation and disposition.

Intra- and inter-individual variability

Between-subject variability (%CV) in C_{max} and area under the concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24}$) for ozanimod, CC112237 and CC1084037 following 28-day dosing were similar (≤ 35%).

In RMS patients, the inter-subject variability (%CV) was estimated for ozanimod CL/F as 23.5% and for CC112273 CL/F, apparent volume of distribution in the central compartment (Vc/F) and formation rate constant as 74.5%, 25.9% and 37.2%, respectively.

Based on food effect study data, intra-subject variability of ozanimod was estimated to be low (8-16%).

Target population

The Applicant appropriately characterized the pharmacokinetics of ozanimod and its metabolites (except RP112273) in RMS patients.

The PK of ozanimod were not significantly different between healthy subjects and RMS patients. However, for CC112273, CL/F was found to be higher in RMS patients compared to healthy subjects, resulting in an AUC that was higher by approximately 40% in healthy subjects compared to that in RMS patients receiving the same ozanimod dose. Such PK differences for the metabolite with a long T½ were likely attributed, in part, to the limitation on ozanimod dosing duration in healthy subjects (≤28 days).

Special populations

Hepatic Impairment

The PK of ozanimod and CC112273 were evaluated in subjects with mild or moderate hepatic impairment (Child Pugh class A or B, respectively) and compared to matched subjects with normal hepatic function (RPC01-1904 [Hepatic Impairment]). The PK of ozanimod and metabolites were not evaluated in subjects with severe hepatic impairment.

Following a single oral dose administration of ozanimod 0.25 mg, total (bound + unbound) systemic exposures (ie, $AUC_{0\text{-last}}$) for ozanimod and CC112273 in subjects with mild hepatic impairment were approximately 11% lower and 31% lower, respectively, compared to subjects with normal hepatic function. Total (bound + unbound) systemic exposures (ie, $AUC_{0\text{-last}}$) for ozanimod and CC112273 in subjects with moderate hepatic impairment were approximately 27% higher and 33% lower, respectively, compared to subjects with normal hepatic function. Fraction of drug unbound for ozanimod and CC112273 were similar between all groups.

The differences in systemic exposures were considered as not clinically meaningful. While CC1084037 was not evaluated, results on CC112273 was applicable for CC1084037 since CC1084037 is a direct and inter-converting metabolite of CC112273.

No dosage adjustment is recommended in subjects with mild or moderate hepatic impairment.

Renal Impairment

The PK of ozanimod and the major active metabolite CC112273 were evaluated in subjects with ESRD and compared to matched subjects with normal renal function (RPC01-1906 [Renal Impairment]). Following a single oral dose administration of 0.25 mg ozanimod, systemic exposure ($AUC_{0\text{-last}}$) for ozanimod and CC112273 in ESRD subjects were approximately 27% higher and 23% lower, respectively, compared to subjects with normal renal function. These differences were not considered clinically meaningful. While CC1084037 was not evaluated, results on CC112273 was applicable for CC1084037 since CC1084037 is a direct and inter-converting metabolite of CC112273.

No dosage adjustment is recommended in subjects with impaired renal function.

Paediatric population

Ozanimod was not assessed for paediatric patients.

Intrinsic factors

Gender

While population PK of ozanimod was not affected by gender, CC112273 steady-state exposure (AUC) was lower in males than in females. The effect of gender on CC112273 systemic exposure was not deemed clinically meaningful.

Race

The effect of race (Japanese) was evaluated in two Phase 1 studies, RPC01-1905 (Japanese PK Bridging) and RPC01-1911 (Multiple-dose PK in Japanese and Caucasians). Study RPC01-1905 did not evaluate CC112273 while study RPC01 1911 included CC112273 in PK assessments. While CC1084037 was not evaluated in these studies, results on CC112273 were applicable for CC1084037 since CC1084037 is a direct and inter-converting metabolite of CC112273 and there was no known genetic polymorphism on the activity of the enzymes involved in the inter-conversion of these metabolites (CBR, AKR, and HSD).

In both studies, no clinically meaningful differences in the PK of ozanimod were observed between Japanese and Caucasian subjects for the multiple-dose regimens of ozanimod 0.5, 1, and 2 mg QD. In study RPC01-1911, no clinically meaningful differences in PK of ozanimod and CC112273 and PD were observed between Japanese and Caucasian subjects for multiple-dose regimens of ozanimod 0.5 or 1 mg QD.

No dosage adjustment is recommended in Japanese subjects receiving the multiple-dose regimens of ozanimod 0.5 or 1 mg QD.

Body Weight

Body weight was studied as a covariate on ozanimod and main metabolites through population pharmacokinetics (PopPK) analysis. It was concluded that body weight had no effect on ozanimod safety or efficacy and therefore the effect of body weight on systemic exposures of ozanimod and CC112273 was not deemed clinically meaningful.

No dosage adjustment is recommended based on body weight.

Age

Age was studied, on the range of 18-55 years in RMS patients, as a covariate on ozanimod and main metabolites, through popPK analysis. It was concluded that age did not appear to have a significant impact on either safety or efficacy parameters and therefore, the effect of age on ozanimod systemic exposure was not deemed clinically meaningful.

No dose adjustment is recommended based on age in adult patients. Ozanimod was not evaluated in elderly patients (>55 years).

Extrinsic factors

Smoking status

A significant effect of smoking on exposure of CC112273 (a metabolism responsible for 73% of overall drug activity) was found. Overall the metabolites exposure was reduced up to 50% in smokers compared to non-smokers. At request, the Applicant provided *ad hoc subgroup* analyses showing no sign of clinically significant differences on efficacy or safety between current smokers and non-current smokers (including never smoked, and former smokers) at baseline.

Interactions

Based on the *in vitro* data results regarding ozanimod metabolism and metabolic pathways and interactions with transporters, the Applicant appropriately characterized *in vivo* all the expected possible DDI, with ozanimod as victim and as perpetrator.

All the obtained results support the proposed wording for section 4.5 in the SmPC and the warning statement on section 4.4 about Concomitant medicinal products

Inhibitors of the BCRP

An inhibitor of the BCRP (ciclosporin) doubled the exposure (AUC) of the minor active metabolites may subsequently lead to a similar increase in the major active metabolites and increase the risk of adverse reactions. The coadministration of BCRP inhibitors (e.g. ciclosporin and eltrombopag) with ozanimod is not recommended (see section 4.4).

Effect of inhibitors of CYP2C8 on ozanimod

The coadministration of gemfibrozil (a strong inhibitor of CYP2C8) 600 mg twice daily at steady state and a single dose of ozanimod 0.46 mg increased exposure (AUC) of the major active metabolites by approximately 47% to 69%. Caution should be exercised for concomitant use of ozanimod with strong CYP2C8 inhibitors (e.g. gemfibrozil, clopidogrel).

Effect of inducers of CYP2C8 on ozanimod

The coadministration of rifampin (a strong inducer of CYP3A and P-gp, and a moderate inducer of CYP2C8) 600 mg QD at steady state and a single dose of ozanimod 0.92 mg reduced exposure (AUC) of major active metabolites by approximately 60% via CYP2C8 induction which may result in reduced clinical response. The coadministration of CYP2C8 inducers (i.e., rifampin) with ozanimod is not recommended (see section 4.4).

Effect of inhibitors of monoamine oxidase (MAO) on ozanimod

The potential for clinical interaction with MAO inhibitors has not been studied. However, the coadministration with MAO-B inhibitors may decrease exposure of the major active metabolites and may result in reduced clinical response. The coadministration of MAO inhibitors (e.g., selegiline, phenelzine) with ozanimod is not recommended (see section 4.4).

Effect of inhibitor of CYP3A on ozanimod

The coadministration of itraconazole (a strong inhibitor of CYP3A and P-gp) 200 mg QD at steady-state and a single dose of Zeposia 0.92 mg resulted in no clinically meaningful changes in exposure of ozanimod, CC112273 and CC1084037. In line with SmPC guidelines, the absence of DDI was not included in section 4.5

Effects of ozanimod on other drugs

In vitro, ozanimod and metabolites did not inhibit nor induce activities of CYPs at clinically relevant concentrations. Therefore, ozanimod coadministration is not expected to alter systemic exposure of CYP substrates. *In vitro*, CC112273 and CC1084037 inhibited BCRP with an IC_{50} of 25nM and 23nM, respectively, however they should have no potential to inhibit BCRP *in vivo*. *In vitro*, CC112273 and CC1084037 inhibited MAO-B with more than 1000-fold selectivity over MAO-A. However, the use of ozanimod is not expected to interact *in vivo* with serotonergic and adrenergic agents.

Effects of ozanimod on oral contraceptives

The coadministration of Zeposia 0.92 mg QD and a single dose of oral contraceptive containing ethinylestradiol (EE) 35 mcg and norethisterone (NE) 1 mg resulted in no change in EE or NE exposure. Dosing duration of ozanimod was not long enough to attain steady state for the major active metabolites; however, CC112273 and CC1084037 had no *in vitro* effect on CYP enzymes and therefore are not expected to have any effect on EE and NE exposure.

Effects of ozanimod on MAO activity

In vitro, CC112273 and CC1084037 inhibited MAO-B with more than 1000-fold selectivity over MAO-A. In a clinical study with ozanimod, CC112273 and CC1084037 had no inhibition effect on human platelet MAO-B activity.

Population PK analyses

Methods

Table 3: Reported population analyses

Report Number	Report Title
CLG-Certara-RMS-358-1	Population pharmacokinetic modelling analyses of ozanimod and its two active metabolites RP101988 and RP101075 following oral administration of ozanimod HCL
CLG-Certara-RMS-358-2	E-R analyses of ozanimod in patients with relapsing multiple sclerosis
RPC-01-CP-2017-03	Simulation of pharmacokinetics of ozanimod in paediatric population aged 10 years up to < 18 years for treatment of relapsing multiple sclerosis
Clegene-A2PG-0003	Population pharmacokinetic analyses of ozanimod and its active metabolite, CC112273, in healthy subjects and patients with relapsing multiple sclerosis
Celgene-A2PG-0004	Population E-R analyses for ozanimod´s major active metabolite CC112273 following oral administration of ozanimod to healthy subjects and patients with relapsing multiple sclerosis

Report CLG-Certara-RMS-358-1: Data from four Phase 1, one Phase 2, and two Phase 3 clinical studies in healthy volunteers and RMS patients were used for this analysis. PopPK analysis was performed using NONMEM version 7.3 and PsN version 4.2.0. Data exploration, model diagnostics, graph and table creation and data management were performed using R version 3.3.1. Model development was performed sequentially (structural model, random effects model, full model, tentative final model, model evaluation /validation and final model). For covariate analysis, a stepwise forward inclusion (p=0.01) and backward elimination (p=0.001, ΔOFV – 10.84 points) procedure was performed.

Report Clegene-A2PG-0003: Data from five phase 1 studies in RMS patients (RPC011001), patients with hepatic impairment (RPC011904), patients with end stage renal disease (RPC011906), healthy volunteers (RPC011910, RPC011911) were and two phase 3 studies in RMS patients (Study RPC01-201B and Study RPC01-301) were used for this analysis. Population PK analysis was performed using NONMEM software (Version 7.3), data post-processing was done using SAS, SPlus or R. Graphical analysis was performed using SPlus and/or R. Model development was performed sequentially (structural model, random effects model, full model, tentative final model, model evaluation /validation and final model). Once a suitable base model was finalized, all pre-specified covariates were included simultaneously in a full model. A covariate reduction procedure was performed. Covariate analysis was performed using the backward elimination procedure (ΔOFV < 10.8, p<0.001).

Intra- and inter-individual variability

Report CLG-Certara-RMS-358-1: For ozanimod interindividual variability (IIV) was low to moderate for CL/F, Vc/F, Vp/F, Ka, and D0 (12.2 to 33.1 %CV). Different population values for CL/F were identified for studies RPCS001 and RPC01-102 (CL/F=246 L/h) compared to the remaining studies (CL/F=166 L/h). Further, body weight and age were identified as covariates explaining some variability in CL/F.

For the metabolite RP101988, IIV was low for CL/Ffm, Vp/Ffm, and Kam (6.8 to 13.1 %CV). Covariates identified were body weight and age on CL/Ffm, and study (RPCS001, RPC01-102, and RPC01-1905) on CL/Ffm.

For the metabolite RP101075, IIV for CL/Ffm was 25.2 %CV and for F1fm 35.4 %CV. Different effects on CL/Ffm were found for study RPC01-1905, and studies RPCS001 and RPC01-102. In addition, age on CL/Ffm and sex on F1fm were identified.

Report Clegene-A2PG-0003: For the active metabolite CC112273 IIV were moderate (V2/F=37.2 %CV and K12 = 37.2 %CV) to high (CL/F=74.5 %CV). The following covariates were found on CL/F: sex, smoking status, mild or moderate hepatic impairment, body weight, total bilirubin, patient status (RMS patients). Furthermore, sex, mild or moderate hepatic impairment and body weight were found on V2/F and K12.

CC112273 exposure (AUC0-τ,ss) is predicted to be about 35% lower in males compared to females and may be related to higher MAO-B activity in females leading to increased formation of CC112273. Further, CC112273 AUC0-τ,ss is predicted to be about 52% lower in current smokers compared to non-smokers, possibly due to lower MAO-B activity in smokers compared with non-smokers. A population difference (healthy volunteers vs. RMS patients) in CC112273 CL/F was observed with exposures approximately 40 % higher in healthy volunteers compared to RMS patients. Subjects with mild or moderate hepatic impairment had lower exposure of CC112273 compared to subjects with normal hepatic function, which may be explained by the potential for reduced conversion of ozanimod to CC112273.

Pharmacokinetics in target population

Report CLG-Certara-RMS-358-1: The model building data set included 8,936 quantifiable ozanimod concentrations from 1,262 subjects, 8,280 quantifiable RP101988 concentrations from 1,234 subjects and 8,024 quantifiable RP101075 concentrations from 1234 subjects. The external evaluation data set (Study RPC01-201B) included 2,294 quantifiable ozanimod concentrations from 831 subjects, 294 quantifiable ozanimod RP101988 concentrations from 832 subjects and 2,272 quantifiable RP101075 concentrations from 829 subjects.

Of the model building data set, 184 healthy volunteers contributed 4,551, 3,959, 3,847 quantifiable concentrations for ozanimod, RP101988 and RP101075, respectively, and 1,083 patients with RMS contributed 4,385, 4,321 and 4,177 quantifiable concentrations for ozanimod, RP101988 and RP101075, respectively.

The final population PK model for ozanimod was a 2-compartment model with zero- and first-order absorption processes with IIV on CL/F, Vc/F, Vp/F, Ka and D0. Covariates were identified for body weight on CL/F, age on CL/F, and study (RPCS001 and RPC01-102) on CL/F.

The PK model for RP101988 and RP101075 was a two-compartment open model with combined zero- and first-order absorption processes, similar to that for ozanimod.

Using the final PK model, ozanimod CL/F and metabolite CL/Ffm were used to calculate AUC_{ss} based on the free base amount of ozanimod (adjusted from ozanimod HCl doses by multiply 0.92). For studies RPC01-201B and Study RPC01-301 the mean model based predicted exposure at steady-state were 6340

ng*h/L (4593 to 8683 ng*h/L) and 6210 ng*h/L (4209 to 8550 ng*h/L) for 1 mg, respectively. For 0.5 mg AUC_{SS} were 3214 ng*h/L (2384 to 4265 ng*h/L) and 3150 ng*h/L (2190 to 4216 ng*h/L), respectively. Based on the requested plot comparing the model predicted vs. the observed minimal concentrations and a table showing the model predicted exposures for the 1 mg QD dosing in phase 3 RMS patients, the final model appeared to under-predict higher, and over-predict the lower concentrations.

Report Clegene-A2PG-0003: A total of 1687 of 1898 volunteers contributed to the PK analysis of CC112273. Overall, the percentage of BLQ was 5.9 %. For the combined (ozanimod and C112273) PK analysis, a total of 12499 ozanimod PK samples from1915 volunteers were included.

The final base model was a two-compartment model with first-order formation rate, lag time for formation and first-order elimination. IIV was estimated for CL/F, V2/F and formation rate constant (K12).

Covariates remaining in the final PK model were sex, current smoker, hepatic impairment, body weight, baseline total bilirubin level and RMS patient on CL/F; sex, hepatic impairment and body weight on V2/F; and sex, hepatic impairment and body weight on K12.

Using the final population PK model for CC112273, individual parameters estimates were used to simulate CC112273 concentrations for all subjects in the Phase 3 studies (Study RPC01-201B and Study RPC01-301) that were included in the population PK analysis (N=1,492). The dosing regimen was 0.92 mg QD ozanimod for 1000 days. PK profiles were simulated with frequent sampling to allow for calculation of $C_{min,ss}$, $C_{max,ss}$ and AUC0-τ,ss (using the trapezoidal rule) on the final day of dosing. Model-predicted CC112273 PK parameters are summarized in Table 4 for RMS patients in Study RPC01-201B and Study RPC01-301 that had ozanimod dose escalated to 0.92 mg (N=754).

Table 4: Summary of the Model Predicted Steady State PK Parameters for CC112273 in patients with RMS Following Ozanimod 0.92 mg QD

Parameter	Mean[a]	Median[a]	90% Prediction Interval[a]
$AUC_{0\text{-}\tau,ss}$ (pmol·hr/L)	237588	186691	(38813, 603393)
$C_{min,ss}$ (pmol/L)	9616	7497	(1394, 24828)
$C_{max,ss}$ (pmol/L)	10071	7937	(1781, 25321)

[a] N=754 RMS patients in Study RPC01-201B and Study RPC01-301 that had ozanimod dose escalated to 0.92mg. PK=pharmacokinetic; RMS=relapsing multiple sclerosis; QD=once daily, $AUC0_{\tau,ss}$ =steady state area under the plasma drug concentration-time curve over the 24-hour dosing interval; $C_{min,ss}$ =steady state minimum plasma drug concentration; $C_{max,ss}$=steady state maximum plasma drug concentration=hour.

Using the final population PK model for CC112273, simulations were performed to estimate the time to steady state, accumulation ratio and effective half-life (t1/2,eff) of CC112273 for each of the patients in Phase 3 studies (Study RPC01-201B and Study RPC01-301) that were included in the population PK analysis (N=1,492). **Table 5** summarizes the time to steady state (assuming that 90% of the asymptotic CC112273 concentration calculated at Day 1000 is equivalent to steady state conditions), accumulation ratio and T½ eff for individual patients.

Table 5: Summary of the Model-Predicted to Steady State. Accumulation Ration and Effective Half-life of CC112273 in patients with RMS Following Ozanimod 0.92 mg QD

Parameter	Mean	CV%[d]	Min	Max	Median	5th Percentile	95th Percentile
Time to Steady State[a] (days)	44.8	45.4	16	274	40	22	69
R_{acc}[b]	16.2	101	1.6	173	11.2	3.56	49.0
$t_{1/2,eff}$[c] (days)	10.9	104	0.7	119	7.43	2.10	21.5

a Calculated as the first day a subject reaches 90% of the asymptote in the simulated concentration-time profile
b Racc = AUC0-τ ,D1000 / AUC0-τ ,D1
c $T1/2,eff = \tau \cdot \ln(2) / \ln(Racc / Racc^{-1})$, where τ = 1 day
d CV% = (SD/mean)*100
QD = once daily; CV% = percent coefficient of variation; Racc = accumulation ratio; t1/2,eff = effective halflife;
AUC0-τ ,D1000ss = steady state area under the plasma drug concentration-time curve over the 24-hour dosing interval on Day 1000; AUC0-τ ,D1 = area under the plasma drug concentration-time curve over the 24-hour dosing interval on Day 1 (D1); SD = standard deviation
Note: Summary statistics are based on simulations using N=1492 subjects in the Phase 3 studies (RPC01-201B and RPC01-301) that were included in the population PK analysis

In addition, a combined ozanimod and CC112273 PK model was developed sequentially, however, it the model was discontinued at the stage of a working full model. A discrepancy between the two base models and the combined model was observed on the estimation of the apparent volume of distribution in the central compartment (Vc/F), reflecting the lack of data supporting for the combined PK model to estimate Vc/F for ozanimod and CC112273 separately.

Special populations

Impaired renal function

No significant effect of renal function (creatinine clearance) on ozanimod or its three main metabolites RP101988, RP1010735, and CC112273 was identified in the population PK analyses as reported in CLG-Certara-RMS-358-1 and Clegene-A2PG-0003. According to the Applicant position, no dose adjustment is needed in patients with renal impairment. Nevertheless, since the number of patients with ESRD contributing to the analysis was small (n=8), the results should be interpreted with caution.

Impaired hepatic function

Hepatic function on clearance was evaluated in report CLG-Certara-RMS-358-1 using alanine transaminase (ALT), aspartate transaminase (AST), serum bilirubin and serum albumin. None of these parameters was retained in the final PK models for ozanimod, RP101988, or RP1010735. As reported in Clegene-A2PG-0003, hepatic impairment had statistically significant effect on CC112273 CL/F (158 % increase), V2/F (64.1 % decrease) and K12 (63.1 % slower formation of CC112273). CC112273 exposure was lower in volunteers with hepatic impairment. However, the lower exposure seemed not to be clinical meaningful and therefore dose adjustments for these patients are not considered necessary according to the Applicant´s position. Nevertheless, since only 15 volunteers classified as mild or moderate hepatic impairment were included as a combined covariate category in the population PK model development for CC112273, the results should be interpreted with caution.

Gender

Sex was a significant covariate on the Fraction of metabolite amount available to enter the central compartment (F1fm) for the metabolite RP101075 (report CLG-Certara-RMS-358-1). CC112273 exposure (AUC0-τ,ss) is predicted to be 35% lower in males compared to females which may be related to lower MAO-B activity in males. Given this relatively small difference in CC11273 exposure between males and females, coupled with the lack of any clinically meaningful difference in efficacy parameters of ozanimod 1 mg, it was concluded that no dose adjustments for male patients are warranted. Accordingly, the subsection regarding gender was removed from section 5.2 of the SmPC.

Race

Race was not a significant covariate in the two population PK analyses CLG-Certara-RMS-358-1 and Clegene-A2PG-0003.

Weight

Body weight was a statistically significant covariate on CL/F and CL/Ffm of ozanimod and RP101988, respectively (Report CLG-Certara-RMS-358-1). Further, body weight was a statistically significant covariate on CL/F, V2/F, and K12 in the population PK analysis of CC112273 (Report Clegene-A2PG-0003). However, body weight seemed to have a minimal effect (10% or less) on CC112273 exposure. Therefore, given the stable steady-state exposure of the most predominant active metabolite CC112273 across body weight quartiles, coupled with the lack of any clinically meaningful differences in efficacy and safety parameters across body weight quartiles, no dose adjustment for body weight is recommended.

Elderly

Age was a significant covariate on the clearance of ozanimod, RP101988, and RP101075 (Report CLG-Certara-RMS-358-1). However, Ozanimod $AUC_{\tau,ss}$ was distributed to similar extents, with essentially the same interquartile ranges, among the age quartiles in each dose group. For CC112273, age was not identified as a significant covariate on any of the parameters. Consequently, it is concluded that no dose adjustment is necessary based on age over the investigated range of 18-55 years.

Children

A simulation of the PK of ozanimod in paediatrics aged 10 years up to <18 years for the treatment of RMS was performed and is documented in Report RPC-01-CP-2017-03. The primary objective of this simulation was to predict the ozanimod doses in paediatrics with RMS aged 10 years up to <18 years which would provide similar exposure to the proposed therapeutic dose of 1 mg in adults with RMS. For population PK analysis the previously developed PK model as reported in CLG-Certara-RMS-358-1 was used.

2.5.3. Pharmacodynamics

The pharmacological rational for the use of Ozanimod was adequately supported by bibliography and the clinical pharmacodynamics is supported by data produced by the Applicant, namely in 16 Phase 1 clinical pharmacology studies. PK samples were also collected in Phase 2 study and Phase 3 studies in patients with RMS for population PK and E-R analyses.

Mechanism of action

Ozanimod HCl is a S1P receptor modulator, which binds with high affinity and selectively to $S1P_1$ and $S1P_5$. Ozanimod is 10-fold more selective for $S1P_1$ relative to $S1P_5$ and has little activity on the other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$).

Ozanimod causes internalization of $S1P_1$ and retention of lymphocytes in the lymphoid tissues, as evidenced by a dose-dependent reduction in peripheral lymphocyte count and therefore ameliorating the pathological processes through inhibition of lymphocyte migration into the CNS.

Ozanimod is extensively metabolized in humans to form a number of circulating active metabolites including two major active metabolites, CC112273 and CC1084037, and one circulating inactive metabolite RP101124. Following multiple dose administration of ozanimod in healthy subjects, approximately 94% of circulating total active drug exposure is represented by ozanimod (6%),

CC112273 (73%), and CC1084037 (15%). The remaining 6% of circulating total active drug exposure is represented by other minor active metabolites.

The relevance of the differences in human S1P selectivity between ozanimod and other S1P modulators and their implications for pharmacodynamics was supported by a literature review on the differential effects exhibited by fingolimod and ozanimod on the four S1P receptors in question ($S1P_1$, $S1P_3$, $S1P_4$, $S1P_5$). At this moment, scientific and clinical data appear to support the balance between mainly beneficial effects from $S1P_1$/$S1P_5$ modulation and mainly adverse effects from the $S1P_3$/$S1P_4$ receptors. Specifically, evidence appears to suggest that $S1P_1$ agonism might be more related to an acute effect in bradycardia induction compared to a $S1P_3$-mediated chronic effect chronic on heart rate and conductivity. This might explain, at least in part, the different effect profile of ozanimod in heart conductivity compared to fingolimod. The lesser bradycardic effect in therapy initiation of ozanimod might be related to a combination of the dose-escalation protocol with the modulation of $S1P_1$ rather than $S1P_3$.

Primary PD is based mainly in *in vitro* non-clinical data and an *in vivo* non-clinical and clinical relations with the main biomarker for primary PD, the Absolute Lymphocyte Count (ALC) reduction.

One of the main outcomes regarding this biomarker came from Study RPC01-1001 where RMS subjects received ozanimod 0.5 mg or 1 mg QD for 12 weeks, in which the mean reductions in ALC from baseline were approximately 50% and 70% for the 0.5 mg and 1 mg dose groups, respectively.

Primary and Secondary pharmacology

Primary Pharmacology

The ALC reduction from baseline in study RPC01-201 (phase 3) was 45-55% while ALC reduction was 50-70% in RPC01-1001 (phase 1). At request, the Applicant analysed the relevance of these differences which were found to be not significant due to 3 main reasons: i) the reduced number of patients in RPC01-1001 (Phase 1 trial) might have overestimated the relevance of the ALC reduction observed when compared to the much larger patient sample in the other trials; ii) the higher baseline values for ALC in patients included in RPC01-1001 increased the probability of achieving higher reduction percentages when compared to the other trials; iii) the absence of differences in PK profiles for ozanimod and metabolites between both studies.

RPC01-1911 investigated a supratherapeutic dose of 2 mg in Japanese and Caucasian subjects. No significant increases above the clinical dose of 1 mg were found further supporting that the dose of 1 mg is in the plateau area of the dose-response relationship. Of note, there was a clear difference in ALC reduction between Japanese and Caucasians on day 28 in the 2 mg group (67% vs. 57%). This might have been due to higher CC112273 exposure in Japanese, but the ALC reduction in Caucasians was also noticeably weaker than in the FIH study (65% and 68% for 1 mg and 1.5 mg respectively). The Applicant provided further data that demonstrated that the differences observed were due to the differences in the reporting Day (Day 28 for 2 mg vs. Day 29 for 1 mg and 1.5 mg) and statistical measures (mean value for 2 mg vs. median values for 1 mg and 1.5 mg). This data also showed that ALC reduction appeared to reach the plateau effect at 1 mg.

Following multiple dosing for 28 days in healthy subjects, recovery of ALC into the normal range ($\geq 1 \times 10^9$/L), but not necessarily to baseline, occurred approximately 3 to 8 days after the last dose. However, recovery of ALC into the normal range was not evident within 7±2 days after the last dose in RMS patients following multiple dosing for 12 weeks. Based on the Kaplan-Meier estimate using data from controlled and uncontrolled RMS studies (Pool B), the median time to recovery of ALC to the normal range ($\geq 1 \times 10^9$/L) was 30 days after treatment discontinuation in the ozanimod 1 mg treatment group.

Ozanimod, like S1P modulators, leads to a decrease in ALC and therefore increases the risk for development of diseases that are related to an immunocompromised state. Therefore, considering an analogy to S1P modulators SmPC, the inclusion of immunodeficient state (immunodeficiency syndromes, patients with increased risk for opportunistic infections, immunocompromised patients including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis) and active malignancies as contraindications in section 4.3 was agreed by the Applicant upon request.

Given the relevance of ALC as biomarker for ozanimod efficacy and safety issues, further characterization of the effects of ozanimod on ALC reduction was found to be necessary in Section 4.4 of the SmPC, and a reference to suspension of ozanimod therapy in case of an ALC<$0.2x10^9$/L was added, along with the limit for reintroduction.

Secondary Pharmacology

Previous data on S1P receptor modulators supports a potential for heart rate (HR) reduction leading to potentially dangerous bradycardia. Also, there was a potential for QT interval prolongation, with severe cardiac arrhythmias (Torsade de Pointes) as a consequence. Several studies regarding the effects of ozanimod on cardiac conductivity were performed in order to characterize these effects.

The implementation of a dose-escalation protocol in the beginning of therapy appeared to attenuate the effects on HR observed at higher doses of ozanimod treatment.

Briefly, introducing a gradual dose escalation of ozanimod over several days with the starting dose of 0.25 mg or 0.3 mg for 4 days (Days 1 to 4) followed by 0.5 mg for 3 days (Days 5 to 7) helped to mitigate in the first-dose HR effect in healthy subjects. During dose escalation (0.25 mg Day 1 to Day 4, and 0.5 mg Day 5 to Day 7) preceding the 1 mg maintenance dose period (Day 8 to Day 28), healthy subjects in both placebo and ozanimod groups demonstrated HR reductions. The CFP_{min} HR (0 to 12 hours) ranged from -9.45 to -7.79 bpm for the placebo group and -11.9 to -8.70 bpm for the ozanimod group. Predose HR values on Day 5 (0.5 mg) and Day 8 (1 mg) for ozanimod were approximately 5 bpm lower than on Day 1 (0.25 mg). The CFP_{min} HR (0-12 hours) values for ozanimod were similar between Days 5 and 8, which were less than on Day 1 by approximately 3 bpm. No effect on HR was evident on Day 28 at the maintenance dose of 1 mg. The median time to HR_{Nadir} (0 to 12 hours) was similar between ozanimod (4.0 hours) and placebo (3.0 to 4.0 hours). Analyses of HR-time profiles and concentration-HR effect suggested that desensitization of the $S1P_1$ receptor had started occurring by dose escalation Day 5. Dosing re-initiation of ozanimod at a 1 mg maintenance dose following drug discontinuation of up to 14 consecutive days was not associated with meaningful changes in HR.

However, caution must be observed in the interpretation of these results. Although bradycardic events are attenuated with the dose-escalation protocol, they are not abolished and some patients experienced bradycardic events, in the dose-escalation period and beyond (>1%). Bradycardia is still considered as a "Common" Adverse Reaction in section 4.8 of the SmPC since the incidence of this adverse reaction was found to be marginally superior to 1/100. Moreover, the Applicant further characterized bradyarrhythmia in the warning section 4.4 of SmPC.

Indeed, the overall incidence of bradycardic events (ie, preferred terms (PTs) of bradycardia or sinus bradycardia) over the course of the treatment period in the controlled Phase 3 studies (Pool A1) was 1.4% (12/882) in the ozanimod 1 mg treatment group. The differences in bradycardic events were mainly driven by differences in Day 1 and that subsequent to Day 1, the incidence of bradycardia was similar across the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups. These observations appeared to be consistent with the dose escalation period along with the putative mechanism for the bradycardic effect of ozanimod. Upon request, the Applicant further elaborated on the pharmacodynamic profile of ozanimod compared to non-selective S1P modulators and also explained the mechanistic

rational in the apparent reduced bradycardic effect, either related to the dose-escalation protocol or to the sub-receptor profile. Activity at $S1P_1$ is associated with first dose sinus bradycardia via activation of $S1P_1$-dependent inwardly-rectifying potassium channels on cardiac myocytes. Following activation by ozanimod and/or active metabolites, $S1P_1$ is internalized which effectively removes the ability of $S1P_1$ to mediate bradycardia. Ozanimod dose escalation regimen gradually increases pharmacokinetic exposure of ozanimod and its active metabolites and together with more gradual internalization of $S1P_1$, is believed to underlie ozanimod's reduced bradycardic effect relative to other S1P modulators in the absence of dose escalation. While $S1P_1$ is quickly internalized and no longer contributes to bradycardia, it is not known what the clinical effects of chronic modulation of $S1P_2$ and $S1P_3$ are on the cardiovascular system. This information was added to section 5.1 of SmPC as requested by CHMP.

Regarding the study of QT interval prolongation, a thorough QT (TQT) study conducted to assess whether exposure to therapeutic (1 mg) or supratherapeutic (2 mg) doses of ozanimod in healthy subjects increased the corrected QT (QTc) interval compared to placebo found no evidence of QTc prolongation as demonstrated by the upper boundary of the 95% one-sided confidence interval (CI) that was below the 10 ms threshold for both ozanimod 1 and 2 mg QD.

This initial Phase I study was not sufficient to fully characterize the QT interval prolongation of ozanimod due to insufficient duration of treatment leading to insufficient exposure to the major metabolites.

Concentration-QTc modelling analyses were performed to evaluate the effects of ozanimod, CC112273 with and without CC1084037 on the QTc interval using concentration data and extensive ECG data from two Phase 1 studies, and they did not reveal clinically relevant potential effect of ozanimod treatment on QT prolongation.

A study intended to characterize the cardiac effects of initiating ozanimod treatment in healthy adult subjects receiving steady-state propranolol or diltiazem did not result in any additional clinically meaningful changes in HR or interval from the beginning of the P wave to the beginning of the QRS complex (PR interval) compared to either drug alone. Although ozanimod appears to reveal no clinically relevant potential of QT interval prolongation, a relationship exists between therapies with bradycardic medicines and an increased risk of QT prolongation in patients taking QT prolonging medicines. As further clarified in section 4.5 of SmPC, patients on other bradycardic medicinal products and on antiarrhythmic medicinal products (which have been associated with cases of torsade's de pointes in patients with bradycardia) were not studied with ozanimod.

Pharmacodynamic interactions

Although the Applicant has studied the potential interactions of ozanimod with some classes of antihypertensive medications associated with heart rate decrease (propranolol and diltiazem), a number of other medicines with different mechanism of action could potentially have a synergistic effect that might also be of some concern. Study RPC01-1908 (DDI with beta blocker/calcium channel blocker) was conducted to characterize the cardiac effects of initiating ozanimod treatment in healthy adult subjects receiving steady-state propranolol or diltiazem and did not result in any additional clinically meaningful changes in HR or QT interval.

However, studies with propranolol and diltiazem only covered classes II and IV of the antiarrhythmic medicines, and several other antiarrhythmic medicines treat cardiovascular diseases that were not contemplated in the "4.3 Contraindication" section of the SmPC (arrhythmias such as atrial fibrillation, atrial flutter and ventricular tachycardia are a few examples). Several Na+ channel blockers and K+ channel blockers have various indication for treatment of arrhythmias and other cardiovascular diseases and can lead to reduced HR: amiodarone and digoxin, for example, are able to prolong QT interval and lead to bradycardia. Ivabradine is a heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker If current and is indicated for the symptomatic treatment of chronic stable

angina pectoris and treatment of chronic heart failure NYHA II to IV class. The proposed ozanimod SmPC only contraindicates ozanimod in Class III/IV heart failure.

Although bradycardic events were attenuated with the dose-escalation protocol, they were not abolished and some patients experienced bradycardic events, in the dose-escalation period and beyond, some of them considered serious and requiring emergent treatment and concomitant administration of ozanimod with known bradycardic medicines might lead to a synergist effect that was not covered by the studies performed. The absence of clinical studies regarding the safety of patients taking other bradycardic medicines (amiodarone, digoxin, ivabradine, for instance) in steady-state conditions detailed in section 4.5 section of SmPC, like those performed with propranolol and diltiazem led to addition of sentences regarding risk minimization measures stated in section 4.4 of the SmPC, mainly related to first dose monitoring and the seeking of cardiologist advice in patients with pre-existing cardiovascular diseases. Addition of pre-existing cardiovascular diseases in the 4.3 contraindications section was also performed.

Besides the reference to vaccination in the section 4.4 of the SmPC, cross-reference to potential interactions with ozanimod in section 4.5 was also performed: "During and for up to 3 months after treatment with ozanimod, vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should, therefore, be avoided during and for up to 3 months after treatment with ozanimod (see section 4.4)".

As ozanimod increases the risk for development of diseases that are related to an immunocompromised state, the potential interaction with anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies was also included in section 4.5 of SmPC as follows: "Anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies should not be coadministered due to the risk of additive immune system effects (see sections 4.3 and 4.4)".

Pharmacodynamic genetic differences

No specific pharmacodynamic study was performed to access genetic differences regarding the primary pharmacodynamic effect of ozanimod in S1P receptors.

At request, the Applicant made a review of the scientific literature regarding the differences in S1P receptor expression patterns that might depend on genetic differences. That review was mainly focused on genetic variations of receptors $S1P_1$ and $S1P_5$, the ones modulated by ozanimod, although the non-clinical studies were performed with fingolimod. Although some non-clinical and clinical studies have addressed specific mutations on S1P receptors, it was agreed there is not sufficient and/or consistent information to take conclusions regarding their clinical relevance in the therapy with S1P modulators. Some inter-subject variabilities regarding efficacy and safety of S1P modulators might be related to differences in receptor expression and depending on the receptor's sub-type expression that could become a relevant marker of efficacy/safety in the treatment of those patients. However, the CHMP also agreed that more information is needed regarding genetic variants for that to potentially influence the efficacy and safety of ozanimod and other S1P modulators.

Exposure-effect relationship

E-R analyses for PD biomarker (ALC), efficacy (ARR), and safety (hepatic enzymes elevation) were performed for both parent ozanimod and its major active metabolite CC112273 to further support the B/R assessments for ozanimod. Although E-R analysis did not include CC1084037, E-R data on CC112273 inform critical assessments related to ozanimod dosing, including the need for dosing adjustments for intrinsic or extrinsic factors.

1. Report CLG-Certara-RMS-358-2: E-R relationships of interest for ALC, ARR, HR, and liver aminotransferase (ALT/AST) were characterised for ozanimod.

Exposure-ARR analyses: The response metrics were ALC_{ss}, defined as the mean of values after 3 months of ozanimod HCl treatment, and patient-level ARR or the number of confirmed relapses during treatment. Patient-level relapse data was available from 2,659 RMS patients in studies RPC01-201B and RPC01-301. The dataset included 1,732 patients with both ozanimod AUC_{SS}, ALC_{SS} and relapse data. ALC_{SS} and relapse data from 885 patients receiving IFN β-1a were also included in the ALV_{SS}-ARR analysis.

Exposure-ALC model: The response metric was either the minimum value of or the maximum percent (%) change from baseline in ALC binned at the time points of 3, 6- and 12-months during treatment. The analysis data set included 1,843, 1,858 and 1,807 values for the maximum % change from baseline in ALC (or the minimum value of ALC with matched baseline) at 3, 6 and 12-month time points, respectively, from patients with RMS in studies RPC01-201A, RPC01-201B and RPC01-301. Exploratory graphical analysis revealed that increasing ozanimod AUC_{SS} were associated with a saturable decrease in ALC_{SS}. Median maximum change from ALC baseline at 3, 6, and 12 months were -47%, -50%, and -50%, respectively for the 0.5 mg QD dosage. For the 1 mg QD dosage, the maximum changes were -60%, -62%, and -63%. The relationship between AUC_{SS} and the maximum change from baseline ALC at 3, 6, and 12 months were described with a sigmoidal Emax (maximum effect) model ($f(AUC_{SSi}) = Emax * AUC_{SS}^{h} / EC_{50}^{h} + AUC_{SS}^{h}$). The typical maximum decrease from baseline was – 25.2% (at 3 months), – 26.8% (at 6 months), and – 26.6% (at 12 months). The E-R analysis using steady state ALC as the response metric estimated the parameters of baseline ALC and Emax consistently with the longitudinal PK-PD model. Accordingly, this model was used to draw the conclusion on the relationship for ozanimod AUC and ALC at steady state.

In addition, a longitudinal PK-PD model for ALC was developed. The analysis data set comprised 2,722 ALC values from 226 healthy volunteers in studies RPCS001, RPC01-102, RPC01-1905 and 13621 ALC values from 1,915 patients with RMS in studies RPC01-201A, RPC01-201B, RPC01-301 and RPC01-1001. A subset of 42 healthy subjects assigned to placebo treatment contributed 574 ALC values to the analysis data set. ALC data were described using an indirect response model with inhibitory effect of ozanimod on ALC production. The maximum effect of ozanimod concentration on ALC reduction is about 62.6% (Emax=0.626, 16.5%CV).

Exposure-HR analyses: The analysis data set included 158 supine HR measurements with matched baseline from healthy volunteers in studies RPCS001 and RPC01-102 (of which 26 subjects in study RPCS001 received placebo) and 1898 supine HR measurements from patients with RMS in studies RPC01-201A, RPC01-201B and RPC01-301. Graphical exploration revealed that HR decreased in magnitude with increasing C_{max1} in healthy volunteers treated with ozanimod. The minimum HR on day 1 was described using an inhibitory E_{max} model as a function of C_{max1} for healthy volunteers only. The minimum HR was considered independent of C_{max1} for RMS patients because, due to the different doses administered to healthy volunteers compared to RMS patients, the C_{max1} distribution was wider in healthy volunteers. The narrow distribution for ozanimod C_{max1} only resulted in a linear model with a slope of -0.052, which was not significantly different from 0 (p-value of 0.0853). Additionally, the effect on heart rate in healthy volunteers receiving placebo was greater than in healthy volunteers receiving 0.25 – 0.5 mg of ozanimod (13.6% vs. 5.2%). Variability in %-change in HR from baseline was considerably high (about -40% to ≥20%). Moreover, the placebo responses were not consistent and thus comparable between the two studies (about -35% to 0% in study RPCS001 vs. -10 to 20% in study RPC01-102).

For RMS patients, the minimum HR was considered independent of $Cmax_1$. In addition, al longitudinal PK-PD model for HR was developed. The analysis data set comprised 2,890 HR values from 157 healthy subjects in studies RPCS001 and RPC01-102 and 29,335 HR values from 1,900 patients with RMS in studies RPC01-201A, RPC01-201B and RPC01-301. A subset of 26 healthy subjects assigned to placebo treatment contributed 336 HR values to the analysis data set. Maximum change in HR was 3.88 bpm (75.3%CV). Further, IIVs were identified for baseline HR (8.37%CV) and the amplitude of the cosine function (112.2%CV). Relationships for sex and population on HR baseline and baseline observed HR on

E_{max} were identified. Simulations showed that the reduction in HR after 0.25 mg is less than that compared with the reduction after administration of higher doses. Median HR nadir (HR nadir) for 0.25, 0.5, 1 and 3 mg doses were 67, 62, 59, and 54 bpm, respectively. Simulated HR for the initial 7-day dose escalation (0.25 mg QD on Days 1 to 4, 0.5 mg QD on Days 5 to 7) followed by either 0.5 mg or 1 mg QD on Days 8 to 10. During and after the dose escalation period, similar chronotropic effects were observed.

Exposure-ALT/AST model: The response metric was a binary value defined according to the criterion of ≥ 3 or ≤ 5 times of upper limit of normal values (ULN). There was a total of 2,659 patients with RMS in the Phase 3 studies, RPC01-201B and RPC01-301. Of 1,774 patients who received ozanimod HCl, 0.96% (n=17) and 4.6% (n=82), respectively, had at least one value of ALT and AST ≥ 3 times of ULN, respectively. A Logistic regression model (logit(p) = a + bx where p is the probability of ALT/AST elevation, a is an intercept parameter, b is a slope parameter, and x represents ozanimod (AUC_{ss}), linking ozanimod AUC_{ss} and the probability of ALT/AST elevation ≥ 3 or ≤ 5 times of ULN was used.

2. Report Celgene-A2PG-0004: In this E-R analyses the exposure of ozanimod´s major active metabolite, CC112273, to the reduction in ALC (efficacy surrogate endpoint) and to the elevation of hepatic enzymes (safety endpoints) ALT and AST ≥ 3 of ULN were investigated. Overall, 17,285 ALC measurements following placebo and ozanimod treatment from 1,937 volunteers (healthy or RMS patients) were included in the dataset. Further, 9,069 quantifiable CC112273 concentrations (with 17-month LTS period) from 1,641 volunteers were included data were obtained from studies RPC01-1910, RPC01-1911, RPC01-1001, RPC01-201B, and RPC01-301. Reduction on ALC were described by a direct inhibitory E_{max} model with estimated reduction (E_{max}) of 0.72 (0.649, 0.809). EC_{50} was estimated to 3540pmol/L (2541, 4539) (pooled data from healthy volunteers and RMS patients). At request, the Applicant reported that for both PK-PD analyses, an inhibitory E_{max} model was used to characterize the effect of ozanimod or CC112273 concentrations on ALC. However, for CC112273 the reduction on ALC was described by a direct inhibitory E_{max} model with estimated reduction (E_{max}) of 0.72 (0.649, 0.809), while for ozanimod, an indirect response model with inhibitory effect of ozanimod on ALC production was used. The E-R analysis for ALT and AST was performed using the logistic regression methods with data from the two Phase 3 clinical trials. Results suggested that the probability of ALT elevation ≥ 3x ULN was not dependent on CC112273 concentration.

The two doses used in early clinical development and advanced clinical trials (0.5 mg and 1 mg) were based on the percentage of ALC reduction as the main driver for clinical efficacy and therefore, the rational for the choice of the 1 mg and 0.5 mg doses as high and low dose in the Phase 2 clinical trials, was made according to ALC count results from the Phase 1 study. Upon request, the Applicant clarified that study RPCS001 was the first-in-human study to evaluate the safety, tolerability, PK and PD of single oral doses of ozanimod 0.3 mg to 3 mg and multiple oral doses 0.3 mg to 2 mg QD for 7 days, 0.3 mg to 1.5 mg QD for 28 days, and 2 mg QD for 10 days (preceded by a 7-day dose escalation). The ozanimod starting dose (0.3 mg) in this study were selected based on the NOAEL in the toxicology studies. Doses during the study were escalated based on the monitoring of dose-limiting toxicity. Results from this study showed the median ALC reductions from baseline after 28-day dosing of ozanimod 0.3, 1, and 1.5 mg were approximately 34%, 65%, and 68%, respectively, indicating that the maximal PD effect was achieved at the 1 mg dose.

2.5.4. Discussion on clinical pharmacology

Different population PK models were developed for ozanimod and the three main active metabolites RP101988, RP101075, and CC112273. For ozanimod, body weight and age were identified as covariates on CL/F, and different CL/F were identified for the studies RPCS001 and RPC01-102. For CC112273 the following covariates were found on PK parameters: sex, current smoker, hepatic impairment, body

weight, baseline total bilirubin level and RMS patient on CL/F; sex, hepatic impairment and body weight on V2/F; and sex, hepatic impairment and body weight on K12. Overall, the usage of modelling and simulation techniques in order to gain information on the PK was supported. The modelling strategy was considered acceptable and the models seemed to describe the data sufficiently. The appropriate information is reflected in the section 5.2 of the SmPC. It should be noted that no PK data was available on administration of ozanimod to patients aged 55 years and over and paediatric or adolescent patients (<18 years of age) as also included in section 5.2 of SmPC.

Although all relevant studies and PD aspects were approached by the Applicant in the clinical pharmacology overview and summary, a few issues needed further discussion in order to clarify relevant pharmacodynamic questions. Regarding secondary pharmacology, ozanimod appeared to have more limited effects comparing to other S1P modulators, possibly related to a higher specificity to $S1P_1$ and $S1P_5$ receptors. Although no QT prolongation effect was detected in the PD package studies and the bradycardic effects were reduced with the dose-escalation protocol, further clarification was required in relation to the potential for synergistic effects with bradycardic medicines other than the ones used in the clinical pharmacology studies and the known exacerbation of QT prolongation in patients taking bradycardic medicines. The Applicant agreed to include this clarification in the section 4.5 of the SmPC with a dedicated sentence regarding possible interactions with unstudied bradycardic medicines. Upon request, the bradycardic effect of ozanimod was further elucidated with the addition of a characterization of the mechanism involved in bradycardia and explanation of a lesser bradycardic effect of ozanimod compared with other S1P modulators in the 5.1 Pharmacodynamic properties section. A deeper discussion was performed regarding the rational used in the different E-R analysis and the interpretation of some results. Also, an explanation of the rational used for the translation/selection of the 1 mg dose for Phase I studies was provided by the Applicant.

2.5.5. Conclusions on clinical pharmacology

In general, the clinical pharmacology was very thorough and supported by several Phase I trials along with additional data from Phase II and III studies. The modelling strategy was considered acceptable and the PK models seemed to describe the data sufficiently. Thus, the PK of ozanimod was considered adequately described. The pharmacological profile of ozanimod was adequately documented. The proposed clinical dose of ozanimod 1 mg preceded by 7 days of dose escalation was documented.

2.6. Clinical efficacy

Table 6: Listing of pivotal Clinical studies

Protocol Number (Regions)	No. of Centers [i)]	Study Dates (Start–Completion)[ii)]	No. of Subjects: Randomized / Completed / Discontinued	Population / Design / Control	Route and Regimen	Subject Demographics: Sex Mean Age Race	Primary Endpoint
RPC01-201B (Europe, North America, South Africa)	150	03 Dec 2013 – 13 Apr 2017	1320 randomized (1313 dosed) 1138 completed 175 discontinued	Male or female subjects aged 18 to 55 years, inclusive, with MS as diagnosed by the revised 2010 McDonald criteria[c]. Patients must be exhibiting a relapsing clinical course consistent with RMS and have a history of brain MRI lesions consistent with MS. Randomized, double-blind, double-dummy, active-controlled parallel-group study Active control: IFN β-1a	Once daily oral dosing with ozanimod 1 mg or ozanimod 0.5 mg, or IFN β-1a 30 µg IM weekly injection for 24 months. A 7-day dose escalation was used for ozanimod	**Sex**: Male: 431 (32.8%) Female: 882 (67.2%) **Age (years)**: Mean (SD): 35.5 (8.93) Min, Max: 18, 55 **Race**: White: 1291 (98.3%) Black: 18 (1.4%) Asian: 1 (0.1%) Other: 3 (0.2%)	ARR over 24 months
RPC01-301 (Europe, New Zealand, North America)	152	03 Dec 2014 – 22 Dec 2016	1346 randomized 1272 completed Month 12 Visit 1255 completed 91 discontinued	Male or female subjects aged 18 to 55 years, inclusive, with MS as diagnosed by the revised 2010 McDonald criteria[c]. Patients must be exhibiting a relapsing clinical course consistent with RMS and have a history of brain MRI lesions consistent with MS. Randomized, double-blind, double-dummy, active-controlled, parallel-group study Active control: IFN β-1a	Once daily oral dosing with ozanimod 1 mg or ozanimod 0.5 mg, or IFN β-1a 30 µg IM weekly injection for 12+ months[d]. A 7-day dose escalation was used for ozanimod	**Sex**: Male: 452 (33.6%) Female: 894 (66.4%) **Age (years)**: Mean (SD): 35.6 (9.27) Min, Max: 18, 55 **Race**: White: 1340 (99.6%) Black: 2 (0.1%) Asian: 2 (0.1%) Other: 2 (0.1%)	ARR during treatment period

Table 7: Description of supportive studies of ozanimod in RMS

Protocol Number (Regions)	No. of Centers[i)]	Study Dates (Start–Completion)[ii)]	No. of Subjects: Randomized / Completed / Discontinued	Population / Design / Control	Route and Regimen	Subject Demographics: Sex Mean Age Race	Primary Endpoint
RPC01-201A (Europe, North America)	55	Placebo-controlled period 18 Oct 2012 – 13 Apr 2014 **Blinded extension** 01 May 2013 – 11 May 2016	Placebo-controlled period 258 randomized 252 completed 6 discontinued Blinded extension 249 randomized 223 completed 26 discontinued	Male or female subjects aged 18 to 55 years, inclusive, with MS as diagnosed by the revised 2010 McDonald criteria[c]. Patients must be exhibiting a relapsing clinical course consistent with RMS and have a history of brain MRI lesions consistent with MS. Placebo-controlled period: randomized, double-blind, placebo-controlled, parallel-group study Optional blinded extension: randomized, double-blind, parallel-group study	Once daily oral dosing with ozanimod 1 mg, ozanimod 0.5 mg, or placebo for 24 weeks. A 7-day dose escalation was used for ozanimod. In the **extension period**, subjects assigned to either ozanimod treatment group in the placebo-controlled period continued at the same dose. Subjects assigned to placebo in the placebo-controlled period were randomized 1:1 to ozanimod 1 mg or ozanimod 0.5 mg.	**Sex**: Male: 77 (29.8%) Female: 181 (70.2%) **Age (yrs)**: Mean (SD): 38.5 (9.19) Min, Max: 19, 55 **Race**: White: 254 (98.4%) Black: 3 (1.2%) Asian: 1 (0.4%) Other: 0	Total number of GdE lesions from Week 12 to Week 24
RPC01-3001 (Europe, New Zealand, North America, South Africa)	227	16 Oct 2015 – Ongoing (data cut-off 30 Jun 2018)	2494 enrolled 2323 ongoing 171 discontinued	Male or female subjects with RMS who completed 1 of the following parent studies: RPC01-201A Extension, RPC01-201B, RPC01-301, or RPC01-1001 **Open-label extension study**	Once daily oral dosing with ozanimod 1 mg. Subjects started with a 7-day dose escalation, except those entering from RPC01-201A Extension or RPC01-1001 with a gap of ≤ 14 days.	**Sex**: Male: 826 (33.1%) Female: 1668 (66.9%) **Age (yrs)**: Mean (SD): 37.7 (9.22) Min, Max: 19, 57 **Race**: White: 2474 (99.2%) Black: 14 (0.6%) Asian: 3 (0.1%) Other: 3 (0.1%)	Long-term safety and tolerability

GdE = gadolinium-enhancing; IFN = interferon; IM = intramuscular; Max = maximum; Min = minimum; MRI = magnetic resonance imaging; MS = multiple sclerosis; PK = pharmacokinetics; RMS = relapsing multiple sclerosis; SD = standard deviation.
a Number of centers with subjects randomized (controlled studies) or enrolled (open-label studies).
b Start date = first subject's first visit date. Completion date = last subject's last visit date.
[c] Polman, 2011.

2.6.1. Dose response study

Study RPC01-201A

Methodology

Study setting

Study RPC01-201A was a Phase 2, Multi-center, Randomized, Double-blind, Placebo-controlled (Part A) and Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients. This study was conducted at 55 study centres in 13 countries. Patients who met eligibility criteria as assessed during the 30-day screening period were randomized (1:1:1) to receive 1 of 2 oral, daily doses of RPC1063 (0.5 mg or 1 mg) or matching placebo for 24 weeks. The randomization was stratified by country. Initial study treatment consisted of a 7-day dose titration regimen that consisted of RPC1063 0.25 mg on Days 1 to 4 and RPC1063 0.5 mg on Days 5 to 7. All patients were dosed with their assigned treatment level beginning on Day 8. Treatment lasted for 24 weeks including a 1-week dose titration period. The database lock date was 28 May 2014.

Eligibility criteria

Subjects had 1) a documented diagnosis of RMS meeting the revised 2010 McDonald criteria (Polman 2011) 2) a relapsing clinical course consistent with RMS and history of brain MRI lesions consistent with MS, 3) Ages 18-55 years 4) an EDSS score between 0 and 5.0 at baseline, and 5) at least one documented relapse within the last 12 months prior to screening, or at least one documented relapse within the last 24 months prior to screening with evidence of at least one GdE T1 brain MRI lesion within the last 12 months prior to randomization.

Outcomes and endpoints

Brain MRI scans to evaluate number of total GdE and new/enlarging T2 lesions were performed at Week 0 (baseline), and Weeks 8, 12, 16, 20, and 24. Other efficacy assessments included the EDSS and neurological examination (performed at the screening visit, Week 12, and Week 24), the Multiple Sclerosis Functional Composite (MSFC) and low-contrast letter acuity (LCLA) tests (screening, Week 0 [baseline], Week 12, and Week 24), and the MSQOL-54 (Week 0 [baseline] and Week 24). Safety assessments, including vital signs, electrocardiogram (ECG), 24-hour Holter monitoring, optical coherence tomography (OCT), pulmonary function tests (PFT) and clinical laboratory measurements, were performed at baseline and at scheduled times during the 24-week treatment period. Patients were evaluated for relapses and AEs throughout the study.

Objectives:

Primary:

- To demonstrate the superior efficacy of RPC1063 compared to placebo by showing a reduction in the cumulative number of total GdE lesions from Week 12 to Week 24 in patients with RMS.

Secondary:

- To assess the proportion of patients who were free of GdE lesions at Week 24
- To assess the effect of RPC1063 on the cumulative number of new/enlarging T2 lesions from Week 12 to Week 24
- To compare the clinical efficacy of RPC1063 to placebo in patients with RMS as assessed by reduction in the ARR and proportion of relapse-free patients at Week 24
- To assess the safety and tolerability of RPC1063 in patients with RMS
- To assess the PK and PD of RPC1063 in patients with RMS.

Additional clinical exploratory aims: to compare the clinical efficacy of RPC1063 to placebo at Week 24 as assessed by the EDSS, MSFC, LCLA and MSQOL-54

Statistical Methods:

The primary endpoint of mean cumulative total number of GdE lesions from Week 12 to Week 24 was compared between each RPC1063 treatment group and the placebo group using the stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline (absent or present). As a result of performing the interim analysis, each comparison was assessed using a 2-sided test at the alpha=0.04944 level of significance in a hierarchical fashion so that the study-wise type I error was maintained at alpha=0.05.

A method of last observation carried forward (LOCF) was used for patients with missing postbaseline lesions. If a patient was missing only 1 or 2 consecutive postbaseline scans, then the last valid non missing, postbaseline observation was carried forward to impute the missing value. However, if there were no postbaseline values to be carried forward or if the patient was missing more than 2 consecutive scans, then the mean number of lesions from patients in the same treatment group at the same visit was used as the imputed value (single imputation using mean of visit (MOV)).

The first sensitivity analysis used a negative binomial regression model to test the mean cumulative total number of GdE lesions, adjusting for the baseline number of GdE lesions and region. Since corticosteroids may have had a short-term effect on GdE lesions, the second sensitivity analysis excluded MRI scans obtained from patients within 24 days of steroid treatment.

Summary statistics on the number of GdE lesions at baseline and each visit were reported, along with the change from baseline and the percent change from baseline. In addition, the proportion of patients with 0, 1, 2, 3, 4, and ≥5 GdE lesions at baseline and each visit were reported.

The key secondary endpoint of number of GdE lesions at Week 24 and number of new or enlarging T2 hyperintense lesions from Week 12 to Week 24 were analysed using the stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline (absent or present). A sensitivity analysis used a negative binomial regression model, adjusted for the baseline number of GdE lesions.

The proportion of patients who were GdE lesion-free at Week 24 was analysed using Fisher's exact test.

The final key secondary endpoint of ARR at the end of Week 24 was analysed using a Poisson regression model. The model compared the treatment groups, adjusted for region, the number of relapses within 24 months prior to the study, and the presence of GdE lesions. A sensitivity analysis used a negative binomial regression model to compare the ARR with the same covariates as specified for the Poisson model.

Results:

Demographics and Baseline Characteristics

A total of 258 patients were randomized (placebo, n=88 patients; RPC1063 0.5 mg, n=87; RPC1063 1 mg, n=83). There were no notable differences among treatment groups. Overall, the majority of patients were female (70.2%) and white (98.4% of patients overall), with a mean (SD) age of 38.5 (9.19) years, with 54.7% of patients less than or equal to 40 years old. Approximately 90% of patients were enrolled in the Eastern European region with Poland accounting for 51.2% of patients. There were no notable differences among treatment groups for country stratification factors or enrolment by region. Overall, the mean (SD) age at MS symptom onset was similar among treatment groups (31.3 [9.27] years overall). Patients had a mean EDSS of 1.88 at entry and the mean number of relapses in the prior 24 months was approximately 2 (1.8-2).

Efficacy:

Primary efficacy endpoint:

- The mean cumulative total number of GdE lesions from Week 12 to Week 24 in the intent-to-treat population was statistically significantly reduced by 86% in the RPC1063 0.5 and 1 mg treatment groups, as compared to placebo (both p<0.0001). Imputation was used only in 7 patients (3 LOCF and 4 MOV). Sensitivity analyses confirmed the primary analyses.

Key secondary efficacy endpoints:

- The mean total number of GdE lesions at Week 24 was statistically significantly reduced by 91% and 94% in the RPC1063 0.5 and 1 mg groups, respectively, as compared to placebo (both p<0.0001). Sensitivity analyses confirmed the primary analyses.
- The number of new or enlarging T2 lesions from Week 12 to Week 24 was statistically significantly reduced by 84% and 91% in the RPC1063 0.5 and 1 mg treatment groups, respectively, as compared to placebo (p<0.0001). Sensitivity analyses confirmed the primary analyses.
- The adjusted ARR at Week 24 was reduced by 31% and 53% in the RPC1063 0.5 and 1 mg treatment groups, respectively, as compared to placebo (p=0.271 and p=0.053, respectively). Sensitivity analyses confirmed the primary analyses.

Clinical exploratory endpoints

- Overall, the changes in EDSS score, MSFC Z-score, LCLA score and MSQOL-54 score from baseline to Week 24 were not statistically significant between the placebo and RPC1063 1 mg treatment groups or between the placebo and RPC1063 0.5 mg treatment groups.

Conclusion:
From Study RPC01-201A the two dose levels for ozanimod QD (0.5 mg and 1 mg) were selected for the pivotal Phase 3 studies.

In the placebo-controlled period of Study RPC01-201A, both doses showed similar efficacy for the primary endpoint of the total number of GdE brain MRI lesions from Weeks 12 to 24. However, the ozanimod 1 mg dose was numerically better than the 0.5 mg dose for new or enlarging hyperintense T2-weighted brain MRI lesions from Week 12 to Week 24 and for the adjusted ARR at Week 24, with no meaningful differences in safety noted. Both doses of ozanimod (1 mg and 0.5 mg) were carried forward in the controlled Phase 3 studies to further establish efficacy on the primary endpoint, ARR, as well as safety profiles of the 2 doses.

Data from the Phase 1 study RPCS 001 provided evidence that the magnitude of the negative chronotropic and adverse conduction effects of S1P modulation was exposure-dependent and could be mitigated by gradually increasing exposure. Based on Phase 1 data, a 7-day dose escalation regimen was implemented in the Phase 2 study and supported the ability of a dose-escalation regimen to mitigate the chronotropic and dromotropic effects of ozanimod. Thus, in order to mitigate potential cardiac effects, an initial 7-day dose escalation regimen was used for all subjects in the pivotal studies. The a 7-day dose titration regimen consisted of ozanimod 0.25 mg on Days 1 to 4 and ozanimod 0.5 mg on Days 5 to 7. Patients allocated to ozanimod 1mg received the first 1mg on day 8.

2.6.2. Main studies

RPC01-201B and RPC01-301

To support efficacy of Ozanimod, the Applicant provided two main studies, with single and pooled data for efficacy assessment, most of the results analysis being performed on pooled data. The proposed main

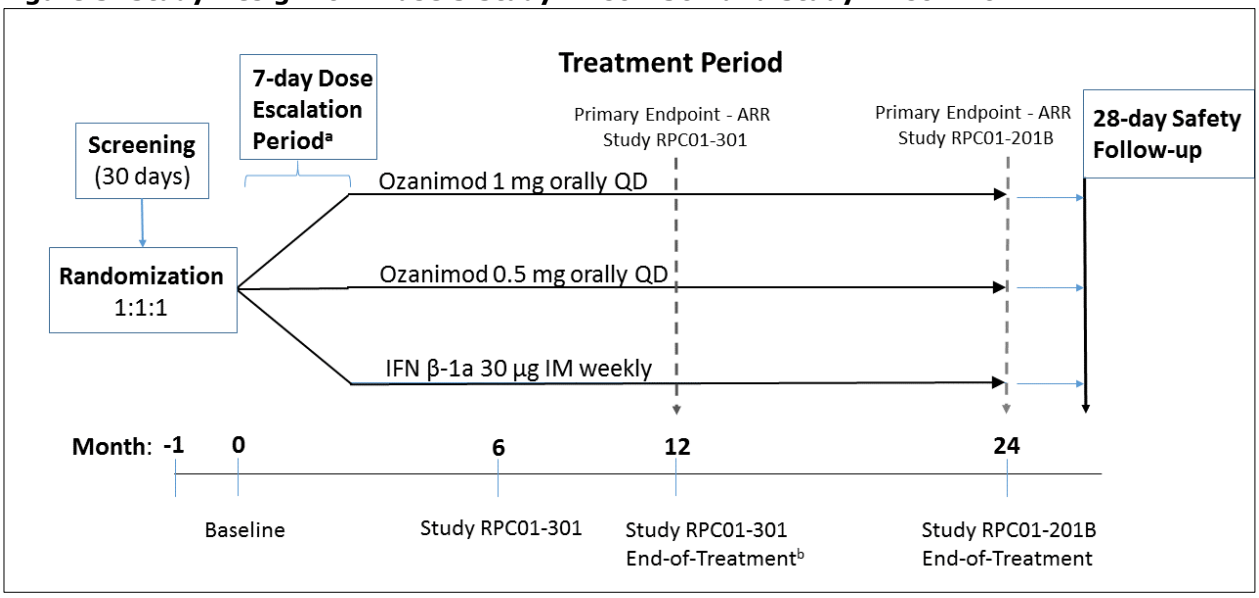
studies provided the response of MS patients to two different doses of ozanimod, covering the spectrum of RMS from low to high disease activity.

Study RPC01-201B: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled (Part A) and Double-Blind, Double-Dummy, Active Controlled (Part B), Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients. Part B.
Study RPC01-301: A Phase 3, Multi-Center, Randomized, Double-Blind, Double-Dummy, Active-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients.

Methods

The pivotal Phase 3 studies of ozanimod in RMS (Study RPC01-301 and Study RPC01-201B) utilized a similar study design. Both studies consisted of a 7-day dose-escalation period followed by a randomized, double-blind, double-dummy, active-controlled, parallel-group treatment period. The main difference between the 2 studies was the duration of the treatment period. In Study RPC01-301 (12+ month study), the treatment period lasted until the last enrolled subject was treated for 12 months, and in Study RPC01-201B (24-month study), the treatment period lasted for 24 months.

Figure 3: Study Design for Phase 3 Study RPC01-301 and Study RPC01-201B



ARR = Annualized Relapse Rate; CSR = clinical study report; EDSS = Expanded Disability Status Scale; IFN = interferon; IM = intramuscular; MRI = magnetic resonance imaging; QD = once daily.
[a] Participants randomized to ozanimod received 0.25 mg on Days 1 to 4, 0.5 mg on Days 5 to 7, and 0.5 or 1.0 mg on Day 8 and thereafter.
[b] The end of treatment occurred when the last active subject received 12 months of treatment with study drug.
Note: Brain MRIs were performed at Screening, Month 6, and Month 12 for Study RPC01-301, and at Screening, Month 12, and Month 24 for Study RPC01-201B. EDSS assessments were performed every 3 months in each study.

Study Participants

Eligibility criteria for both controlled Phase 3 studies were similar. Subjects had 1) a documented diagnosis of RMS meeting the revised 2010 McDonald criteria (Polman et al. 2011), 2) a relapsing clinical course consistent with RMS and history of brain MRI lesions consistent with MS, 3) ages 18-55 years 4) an EDSS score between 0 and 5.0 at baseline, and 5) at least one documented relapse within the last 12 months prior to screening, or at least one documented relapse within the last 24 months prior to screening with evidence of at least one GdE T1 brain MRI lesion within the last 12 months prior to

randomization. Subjects who were MS-treatment naïve or who had received previous MS therapies, except for lymphocyte-depleting (alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, and bone marrow transplant) and for lymphocyte-trafficking blockers (natalizumab, fingolimod or any other $S1P_1$) were eligible. Documentation of immunocompetence to Varicella zoster or vaccination 30-days prior to baseline was required.

Subjects were ineligible if they had 1) evidence of a relapse within 30 days prior to screening, 2) treatment with systemic corticosteroid or adrenocorticotrophic hormone within 30 days prior to screening, 3) disease duration of more than 15 years if EDSS ≤2.0, 4) uveitis, 5) ALC< 800/µL, 6) forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC)<70% of predicted values, 7) resting HR< 55 bpm at screening, 8) incompatibility with IFN use (e.g., intolerable side effects), and 9) presence of >20 GdE lesions on baseline brain MRI scan.

Concomitant treatment with medications with a known impact on the cardiac conduction system (e.g., beta-blockers, calcium channel blockers, or Class 1A or Class 3 antiarrhythmics) were not permitted during the study. Systemic corticosteroids were not permitted during the study except for subjects experiencing a protocol-defined relapse. As per protocol, methylprednisolone 1 g per day over 5 consecutive days maximum was permitted as rescue medication. Treatments were permitted for symptoms related to MS such as spasticity, incontinence, pain, and fatigue.

Treatments

Subjects were randomized 1:1:1 to receive one of the following 3 regimens for 24 (Study RPC01-201B) or 12 (Study RPC01-301) months:

- 30 µg IFN β-1a IM injection weekly
- 0.5 mg ozanimod HCl oral capsule daily
- 1 mg ozanimod HCl oral capsule daily

Subjects randomized to ozanimod HCl 1 mg or 0.5 mg also received weekly matching placebo IM injections, and subjects randomized to IFN β-1a 30 µg also received daily matching placebo oral capsules.

Objectives

Primary:

Study RPC01-201B: to assess whether the clinical efficacy of ozanimod was superior to IFN β-1a (Avonex®) in reducing the rate of clinical relapses at the end of Month 24 in patients with RMS.

Study RPC01-301: to assess whether the clinical efficacy of ozanimod was superior to IFN β-1a (Avonex®) in reducing the rate of clinical relapses in patients with RMS.

Secondary:

- To assess the effect of ozanimod on the proportion of patients with new/enlarging T2 lesions at Month 24 for Study RPC01-201B and at Month 12 for Study RPC01-301.
- To evaluate whether the efficacy of ozanimod was superior to IFN β-1a in delaying the accumulation of disability, as assessed by the EDSS.
- To evaluate whether the efficacy of ozanimod was superior to IFN β-1a in delaying the accumulation of disability, as assessed by the MSFC and visual function as measured by the LCLA.
- To assess the effect of ozanimod on brain atrophy over 24 months for Study RPC01-201B and over 12 months for Study RPC01-301.

- To evaluate the effect of ozanimod on patient-reported quality of life as assessed by the MSQOL-54.
- To assess the safety and tolerability of ozanimod in patients with RMS.

Exploratory:

- To evaluate the effects of ozanimod on number and volume of GdE T1 lesions.
- To evaluate the effects of ozanimod on volume of T2 lesions and number of new or enlarging T2 lesions.
- To evaluate the effects of ozanimod on volume of unenhancing T1 lesions and number of new unenhancing T1 lesions.
- To evaluate the effects of ozanimod on measures of brain volume change.

Outcomes/endpoints

The endpoints listed below were assessed at Month 12 for Study RPC01-301 and at Month 24 for Study RPC01-201B.

Primary Endpoint: ARR during the treatment period.

Key Secondary Endpoints in Ranked Order:

- The number of new or enlarging hyperintense T2-weighted brain MRI lesions.
- The number of GdE brain MRI lesions.
- Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 point or more CDP-3M and CDP-6M (pooled analysis).

Other Secondary Endpoints:

- Proportion of subjects who are GdE lesion-free.
- Proportion of subjects who are new or enlarging T2 lesion-free.
- Percent change in normalized brain volume on brain MRI scans from baseline.
- Change in MSFC score from baseline (including the LCLA as a component).
- Change in MSQOL-54 score from baseline.

Exploratory Endpoints: change in other MRI variables as described in the objectives.

Study assessments

The primary and secondary efficacy endpoints used in the ozanimod clinical studies including clinical outcomes (ARR and confirmed disability progression (CDP)) and MRI measures of disease activity (new or enlarging hyperintense T2-weighted and number of GdE brain lesions) are endpoints that have been used in recent RMS Phase 3 studies. These endpoints are accepted clinical and radiographic outcomes consistent with MS guidelines (CHMP, 2015).

Disease activity assessed by MRI was conducted every 6 months in Study RPC01-301 and every 12 months in Study RPC01-201B, and at the Early Termination Visit. Assessment of patient disability (EDSS) was performed every 3 months in both studies. Functional activity (MSFC and LCLA) and quality of life (MSQOL-54) assessments were conducted every 6 months.

For each study, the analyses of the efficacy endpoints were performed using standard statistical approaches according to a pre-specified hierarchical testing procedure.

ARR was based on confirmed, protocol-defined relapses. A relapse was defined as the occurrence of new or worsening neurological symptoms attributable to MS that persisted for >24 hours, was not attributable to confounding clinical factors (e.g., fever, infection, injury, and adverse reactions to concomitant medications), and was immediately preceded by a relatively stable or improving neurological state for

≥30 days. A clinical relapse was confirmed by the treating investigator when it was accompanied by objective neurologic worsening, as measured by a change in EDSS (of at least half a point on the EDSS, or 2 points on one of the appropriate Functional System [FS] scores, or 1 point on 2 or more of the appropriate FS scores), as assessed by the same independent EDSS evaluator blinded to treatment and previous EDSS assessments. Further details about relapse assessment can be found in the blinding section.

Time to first confirmed relapse was an endpoint used to assess treatment effects on relapse frequency, and complemented the effects observed in the ARR analysis.

Number of new or enlarging hyperintense T2-weighted brain MRI Lesions reflects the 'burden of disease' overall including processes as diverse as oedema, inflammation, demyelination, axonal loss and gliosis in MS. T2 lesions have been related to relapses and may accumulate over time. New or enlarging T2 MRI lesions are an objective measurement to complement and validate the primary endpoint of ARR.

Number of GdE Brain MRI Lesions represents the leakage of gadolinium into the perivascular space as a result of local breakdown of the blood brain barrier due to inflammation. GdE lesions in MS are associated with greater relapse frequency and disability progression. GdE is a sensitive tool for identifying acute inflammation because it is transient, persisting for approximately 6 to 8 weeks.

CDP using EDSS: EDSS is a standardized, widely accepted, numerical scale used to evaluate disability in people with MS (Kurtzke, 1983), according to signs and symptoms observed during a standard neurological examination. These clinical observations are classified in 7 FS, each of them grading signs and symptoms for different neurological functions: pyramidal, cerebellar, brainstem, sensory, bowel or bladder, visual, and cerebral. The score ranges from 0.0 (normal exam) to 10.0 (death due to MS). The MS disease progression was defined as a sustained worsening in EDSS of 1.0 point or more, confirmed after a 3-month and a 6-month period. To confirm that disease progression is sustained, this increase had to be present at a visit 3 months later (CDP-3M) and after 6 months (CDP-6M), with all intervening EDSS scores also meeting CDP criteria and excluding use of EDSS scores to confirm CDP if recorded during a relapse. The same blinded evaluator was to perform all EDSS assessments for an individual subject. Confirmation of MS disease progression must not have occurred at the time of a relapse. If the subject was scheduled to be evaluated to confirm disability at the time of a relapse, the disability event was assessed at a later visit, which may have been the next scheduled visit, or at an unscheduled visit conducted after the relapse resolved. The date of the initial visit at which the minimum increase in the EDSS was met was the date of onset of the progression (tentative progression). Disability progression could be confirmed at the early withdrawal visit, according to the rules above, as long as the early withdrawal visit was not also a relapse assessment visit. Death due to MS was to be counted as a confirmed progression. If the subject was in the midst of a tentative progression at the time of death, the progression date was to be the date of the start of the progression. Otherwise, the progression date was to be the date of death.

Brain Volume Loss: percent changes from baseline in normalized whole-brain, cortical grey matter, and thalamic volumes were analysed.

MSFC is a composite endpoint developed by the National MS Society Clinical Outcomes Task Force including 1) the timed 25-foot walk (T25FW) as ambulatory component (lower extremity function), 2) the 9 hole peg test (9HPT) as upper limb component, and 3) the paced auditory serial addition test (PASAT) as a measure of executive function cognition that assesses processing speed, flexibility, and calculation ability. The PASAT was used as a cognitive component in Study RPC01-201B but was replaced with the symbol digit modality test (SDMT) in Study RPC01-301. The SDMT has greater physician and patient acceptance compared to PASAT. Both, the PASAT and SDMT are considered valid measures of processing speed, however in contrast to the PASAT, the SDMT does not measure aspects other of cognitive function. Moreover, the SDMT performance can be influenced e.g. by visual acuity and ocular

motor functions. Finally, there are practice effects that may hamper the use of SDMT in clinical trials. Another measure felt to be underrepresented in the EDSS assessment is vision and thus the study included LCLA score, a measure of low-contrast visual acuity validated in MS patients to the MSFC. The MSFC results were reported using z-scores, as prespecified according to the study statistical analysis plan (SAP). The MSFC z-score is calculated by creating z-scores for each component of the MSFC. An increase in z-score represents improvement.

MSQOL-54 is a validated patient-reported outcome measure to assess health-related quality of life in patients with MS (Vickrey, 1995). The MSQOL-54 is a structured, self-report questionnaire that the patient can generally complete with little or no assistance. It may also be administered by an interviewer. Interviewers should be trained in basic interviewing skills and in the use of this instrument. This 54-item instrument generates 12 subscales along with 2 summary scores, and 2 additional single-item measures. The subscales are physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The 2 summary scores are the physical health composite summary and the mental health composite summary and are combined to provide scale scores ranging from 0 to 100; a higher scale score indicates improved quality of life. The single item measures are satisfaction with sexual function and change in health. There is no minimally clinically important difference information for MSQOL-54 specific to MS.

Sample size

Assuming extra-Poisson variation ($\sigma 2=1.3$) (Polman, 2011), a total sample size of 1,059 subjects (353 per arm) (Nicholas, 2011) provides 80% power to detect a 43% reduction in the ARR (ARR following treatment with IFN β-1a was assumed to be approximately 0.3 [Mikol, 2008]) with $\alpha = 0.025$. To account for an assumed dropout rate of approximately 12%, approximately 1200 subjects (400 per arm) were to be enrolled in each controlled Phase 3 clinical study, which was estimated to provide sufficient power to meet the primary ARR endpoint within each study.

Randomisation

On Day 1, eligible subjects were randomized via Interactive Response Technology (IRT). Randomization was stratified by baseline EDSS (≤ 3.5 vs. > 3.5) and country. Eligible subjects were randomized 1:1:1 to receive either ozanimod 1 mg QD, ozanimod 0.5 mg QD, or IFN β-1a 30 µg IM weekly (approved dose) in a double-dummy manner. A dose escalation regimen was used for ozanimod. IFN β-1a was selected as an active control for the ozanimod controlled Phase 3 clinical studies because it is an established, effective therapy for patients with MS and offers meaningful benefit in clinical and MRI measures of MS disease activity compared to placebo.

Subjects who completed these studies were eligible to enrol in the open-label extension (OLE) Study, RPC01-3001, in which all subjects received ozanimod.

Blinding (masking)

This was a randomized, double-blind, double-dummy, active-controlled study. Ozanimod and IFN β-1a and their respective matching placebo capsules/injections were identical in physical appearance. The treatment each subject received was not disclosed to the treating investigator, blinded evaluator, study center personnel, subject, or sponsor and their representatives. The treatment codes were held according to an IRT. Further instructions related to blinding were provided in a separate IRT manual.

A "dual assessor" approach was used to evaluate efficacy and safety to prevent potential unblinding as a result of observed efficacy, AEs, or laboratory changes. Each site had at least 2 investigators: a principal or treating investigator and a blinded evaluator (examining investigator or rater who performed EDSS, MSFC, and LCLA assessments). A separate, blinded MSFC assessor, trained in administering the MSFC and LCLA, may have been used for the assessment of these instruments. The treating investigator and the blinded evaluator (and MSFC assessor, if applicable) were not allowed to switch roles and communication between them was restricted. Back-ups for all personnel were to be selected at each site in case of absence. However, whenever possible, the blinded evaluator (and MSFC assessor, if applicable) were to remain constant for all EDSS, MSFC, and LCLA assessments performed for a given subject.

The treating investigator was a neurologist experienced in the care of patients with MS. The treating investigator was responsible for the management of the routine neurological care of the subject, assessment (including assignment of causality), assessment and treatment of AEs, including suspected neurological worsening and MS relapses, and review of central laboratory results every 3 months throughout the study (except for Total WBC and all differential WBC counts which were blinded information after the onset of study treatment for the treating investigator and all site personnel) and, if necessary, at unscheduled visits between scheduled visits. The treating investigator had access to both safety and efficacy data and was to make all treatment decisions based on the subject's clinical response and laboratory findings. The treating investigator did not perform any efficacy assessments.

The blinded evaluator and MSFC assessor (if applicable) were the efficacy assessor and were neurologists or other healthcare practitioners trained in administering the neurostatus version of the EDSS, MSFC and LCLA. The EDSS reviewers were Level C certified (the highest level) using the neurostatus standardized examination and assessment prior to study initiation and examiners were re-certified every 2 years throughout the conduct of the study. The blinded evaluator could also have performed the MSFC and LCLA, or these may have been performed by a separate, blinded MSFC assessor trained in administering the MSFC and LCLA. The blinded evaluator (and MSFC assessor, if applicable) was not involved with any other aspect of the subject's care and management and remained blinded to AEs, concomitant medications, laboratory data, MRI data, treatment assignment, and any other data that had the potential for revealing the treatment assignment during EDSS evaluations, which occurred every 3 months. The study required the same blinded evaluator(s) to perform all EDSS assessments for an individual subject when possible. The blinded evaluator was responsible for administration of the EDSS and did not have access to other data for the subject or to prior EDSS data when performing exams. Blinded evaluators and MSFC assessors were to communicate with subjects only as needed to complete the neurologic examinations and to assess the EDSS, MSFC, and LCLA scores. There was to be no communication about the subjects between the treating investigator and the blinded evaluator or any other information flow about the subjects that could potentially unblind the blinded evaluator. At request, the Applicant further clarified that EDSS, MFSC, and LCLA assessments were captured on paper source worksheets by the blinded assessor(s). The blinded EDSS evaluators and MSFC assessors were not granted access to the electronic data capture system. The paper source worksheets containing the data from the EDSS, MFSC, and LCLA assessments were entered into the electronic data capture system by study personnel who did not perform any of these blinded study assessments (e g, study coordinator, principal investigator, or alternate delegate). This approach to data handling helped ensure that the EDSS, MFSC, LCLA assessors remained blinded to any data that could have had the potential of revealing the treatment assignment. In addition to the electronic data capture system access restrictions, the Sponsor's Clinical Research Associates verified that the EDSS/MFSC/LCLA assessors remained blinded to all subject records during routine onsite monitoring visits.

At request of CHMP, the Applicant additionally clarified the procedure for confirming potential relapses in the studies. Subjects were instructed to telephone the treating investigator within 48 hours of symptom onset of a possible relapse. A template questionnaire was provided to treating investigators to

guide in determining whether the symptom onset was in the presence of fever or infection. If fever or infection were excluded, an unscheduled relapse assessment including neurological examination, EDSS, MSFC and LCLA assessments by the blinded EDSS evaluator was to be scheduled as soon as possible, preferably within 7 days of symptom onset. Individual results from telephone questionnaires and the determination as to whether a relapse assessment visit should or should not have been scheduled were not collected in the trials. It was the responsibility of the treating investigator to determine whether a relapse assessment should have been scheduled. As the blinded evaluator responsible for determining EDSS did not have access to other patient data or to subjects' prior EDSS data when performing neurological exams, knowledge of the previous EDSS scores should have had none to minimal influence on the determination of current EDSS scores. After completion of the relapse assessment, the treating investigator made the final determination as to whether an event represented a protocol-defined (ie, confirmed) relapse by evaluating the subject's neurological signs and symptoms in conjunction with the objective EDSS/FSS scores provided by the blinded EDSS evaluator.

Subjects were instructed not to disclose their treatment assignment or symptoms related to their treatment regimen, and injection sites were to be covered. As flu-like symptoms occur very commonly with IFN β-1a 30-µg im, in particular at the beginning of treatment, respective symptoms could have led to de-blinding of the study treatment. The Phase 3 studies recommended the prophylactic use of acetaminophen (paracetamol) or ibuprofen (or alternatively, naproxen or aspirin in case a patient could not take acetaminophen or ibuprofen) within 1 hour prior to each use of injectable study drug and then periodically thereafter for the 24 hours following each injection. This recommendation to use acetaminophen or ibuprofen prophylactically was aimed at reducing potential bias with respect to subjects or investigators being potentially unblinded to treatment assignment.

Central blinded reviewers who had no knowledge of a subject's treatment or outcome performed MRI evaluations. The MRI reading center was also blinded to country, site, and treatment assignment.

A subject's treatment assignment was not broken unless medical treatment of that subject depended upon knowing the active treatment group.

Statistical methods

Analysis Populations

The statistical analyses followed a modified Intent-to-Treat (mITT) approach including all randomized subjects who received at least 1 dose of study drug.

The mITT population, which was the primary population for all efficacy analyses, included all randomized subjects who received at least 1 dose of study drug grouped according to their randomized treatment, regardless of the actual treatment received.

The per protocol (PP) Population was subset of subjects in the mITT Population with high treatment compliance and without any exclusionary protocol deviations

The Safety Population included all randomized subjects who received at least 1 dose of study drug. Subjects were grouped according to the treatment they received. The Safety Population was the primary population for all safety analyses.

Primary endpoint

All relapses were to be identified as confirmed or unconfirmed prior to database lock. For each study, the primary analysis of ARR (confirmed relapses only) was performed using a Poisson regression model. The model compared treatment groups, adjusted for region, age at baseline, and the baseline number of GdE lesions with the natural logarithmic transformation of time on study as an offset term (as an

approach to handle missing data). The adjusted relapse rates and their associated 95% CIs, the rate ratios and their associated 95% CIs, and p-values were reported. Statistical testing included 2 treatment comparisons; ozanimod 1 mg group versus the IFN β-1a group and ozanimod 0.5 mg group versus the IFN β-1a group (2 treatment contrasts). To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha=0.025 level. The analysis was repeated in each of the pre-specified subgroups. Forest plots showing the rate ratios and 95% CIs for the overall result and the results in each subgroup were constructed.

Two pre-specified sensitivity analyses were to be performed. The first sensitivity analysis was to repeat the primary analysis counting both confirmed and unconfirmed relapses. The second sensitivity analysis was to use a negative binomial regression model, instead of the Poisson regression model, to compare relapse rates. This model was run twice: once repeating the primary analysis (confirmed relapses only) and once repeating the first sensitivity analysis (confirmed + unconfirmed relapses). The same covariates and offset term were used as specified in the primary analysis.

In addition to the specified sensitivity analyses, a Kaplan-Meier analysis on the difference in time to first confirmed relapse curves were also performed. The estimated median time to first confirmed relapse was reported, along with the associated 95% CI and log-rank p-values.

During the assessment of the procedure, the Applicant was requested to base discussion of results on negative binomial regression model that better accounts for overdispersion instead of the Poisson regression model. As two *post hoc* sensitivity analyses, the Applicant was also requested to provide additional analyses using a treatment policy strategy for the intercurrent event treatment discontinuation based on the assumption of the absence of a treatment effect after treatment discontinuation and to perform a multiple imputation analysis using a jump-to-reference (J2R) approach and a copy-reference (CR) approach as more appropriate approaches to handle missing data.

Key Secondary Efficacy Endpoints

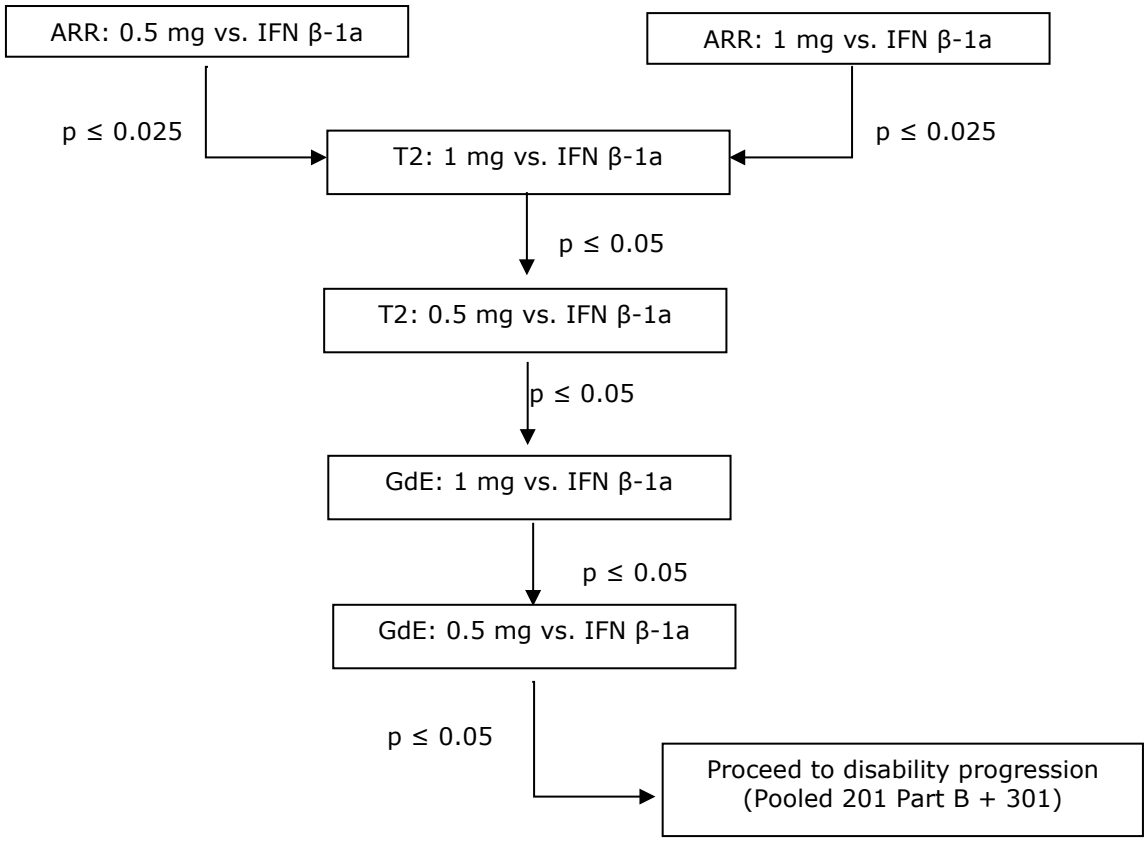
To control for type 1 error, the three key secondary endpoints were tested in order in a sequential, closed hierarchical testing procedure that ranked the 1 mg ozanimod dose above the 0.5 mg ozanimod dose and the key secondary endpoints in the following order:

1. The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months or over 24 months depending on the study.
2. The number of GdE brain MRI lesions at Month 12 or at Month 24 depending on the study.
3. Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months (both only on pooled data).

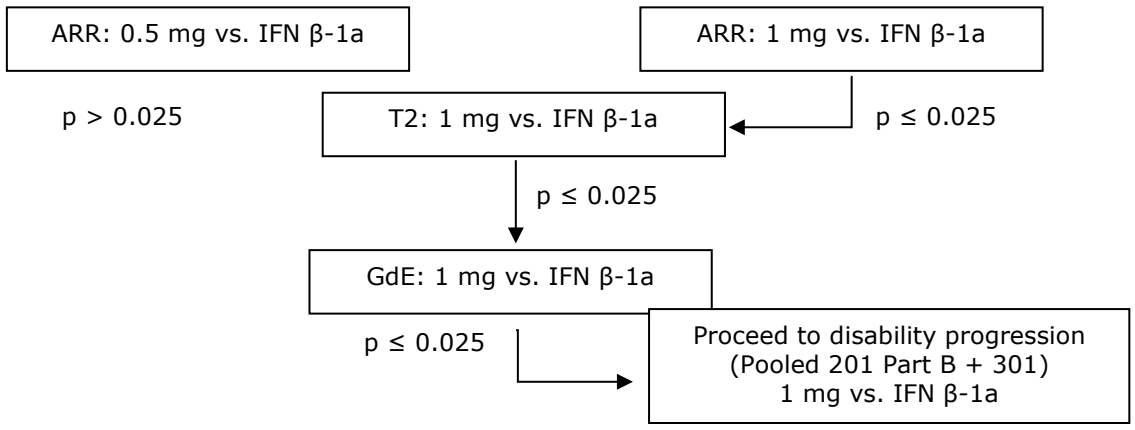
If both doses were significant on the primary endpoint, then the first comparison on the key secondary endpoint was between the 1 mg ozanimod group and the IFN β-1a group at the 5% level of significance. If that comparison was successful, then the same endpoint was tested for the 0.5 mg ozanimod group versus the IFN β-1a group comparison at the 5% level of significance. This procedure was to continue down the rank ordered key secondary endpoint list until a comparison failed to reach statistical significance, after which all subsequent comparisons were considered exploratory. If only 1 ozanimod dose was significant on the primary endpoint, then the hierarchical testing procedure was employed on the rank ordered key secondary endpoint list for the surviving dose only, at the 2.5% level of significance for each key secondary endpoint (Figure 4). For the third key secondary endpoint of time to onset of sustained disability progression, data from Study RPC01-201B and Study RPC01-301 were pooled for hypothesis testing.

Figure 4: Hierarchical Testing Procedure

A: Both ozanimod doses successful on the primary endpoint



B: One ozanimod dose successful on the primary endpoint (1 mg example)



ARR = annualized relapse rate; CDP = confirmed disability progression; GdE = gadolinium enhancing; EDSS = Expanded Disability Status Scale; IFN = interferon; MRI = magnetic resonance imaging

1. Number of new or enlarging hyperintense T2-weighted brain MRI Lesions

The primary analysis of the number of new or enlarging T2 hyperintense lesions over 12/24 months (depending on the study) was performed using a negative binomial regression model adjusted for region, age at baseline, and baseline number of GdE lesions, and included the natural log transformation of the

number of available MRI scans as an offset term (as an approach to handle missing data). The rate ratios and their associated 95% CIs, relative reductions, and p-values were reported. The analysis was repeated in each of the pre-specified subgroups. Forest plots showing the rate ratios and 95% CIs for the overall result and the results in each subgroup were constructed.

Three sensitivity analyses were initially performed to evaluate the leverage of missing data: the first analysis repeated the primary T2 analysis using the mean number of T2 lesions from subjects from the same treatment group to impute missing T2 values (single imputation). The second analysis repeated the primary T2 analysis using LOCF method for imputing missing T2 data values. Only data from postbaseline MRI scans were carried forward to the Month 6 and Month 12 timepoints for analysis of Study RPC01-301 and to the Month 12 and month 24 timepoints for analysis of the Study RPC01-201B. The third analysis repeated the primary T2 analysis using only subjects with complete T2 data at relevant MRI visits (observed cases analysis). All 3 sensitivity analyses included the natural log transformation of exposure time on study (instead of the number of available MRI scans) as the offset term. However, during the assessment, the Applicant was requested to perform a *post hoc* sensitivity analyses using multiple imputation analysis using both J2R and CR approaches as more appropriate approaches to handle missing data.

2. Number of GdE brain MRI lesions at Month 12

The analyses of the number of GdE lesions (at Month 12 in Study RPC01-301 and at Month 24 in Study RPC01 201B) were performed using a negative binomial regression model adjusted for region, age at baseline, and baseline number of GdE lesions, and included the natural logarithmic transformation of the number of available MRI scans as an offset term (as an approach to handle missing data). The rate ratios and their associated 95% CIs, relative reductions, and p-values were reported. The analysis was repeated in each of the pre-specified subgroups. Forest plots showing the rate ratios and 95% CIs for the overall result and the results in each subgroup were constructed.

Three sensitivity analyses were initially performed to evaluate the leverage of missing data: the first analysis repeated the primary GdE analysis using the mean number of GdE lesions from subjects from the same treatment group to impute missing GdE values (single imputation). The second analysis repeated the primary GdE analysis using last LOCF method for imputing missing GdE data values. Only data from postbaseline MRI scans were carried forward to the Month 12/24 timepoint for this analysis. The third analysis repeated the primary GdE analysis using only subjects with complete GdE data at Month 12/24 (observed cases analysis). All sensitivity analyses included the natural log transformation of exposure time on study (instead of the number of available MRI scans) as the offset term. Same as above, multiple imputation analyses using both J2R and CR approaches were requested during the assessment.

3. Time to onset of 3-months and 6-months confirmed disability progression

Based on based on rates of disability progression seen in other RMS studies with an S1P receptor modulator (Cohen, 2010; Kappos, 2010), a pre-specified pooling plan finalized prior to unblinding was proposed by the Applicant and agreed upon by the EMA/CHMP and FDA.

The primary analysis of time to disability progression was analysed using a Cox proportional hazards model with factors for treatment group, adjusted for region, age at baseline, and baseline EDSS score. Handling of ties was according to Efron. The hazard ratio and associated 95% CIs, and p-values were reported. A Kaplan-Meier analysis on the difference in time to CDP curves was also performed. The estimated median time to disability progression was reported along with the associated 95% CIs and log-rank p-values. Each of these analyses was performed on 3-months and 6-months CDP.

A subject was censored if follow-up ended before a sustained progression (event) occurred because the subject prematurely discontinued from the study, the subject completed the study (administrative

censoring) or the subject did not have an event before the cut-off day of data collection for the analysis (administrative censoring). The censor date was the date of the last EDSS assessment or date of last dose of study drug, whichever was later for those who prematurely discontinued from the study, the date they completed the study or the cut-off day for the other subjects. Subjects in the mITT population who withdrew from the study after the baseline visit but prior to the first clinical evaluation scheduled visit were to be censored at entry (left censoring).

Two different types of sensitivity analyses were performed in the study.

1. Analysis to address the robustness of CDP definition for EDSS=0: counting subjects with a baseline EDSS=0 as a progression only if the EDSS score increased by at least 1.5 points.
2. Analyses to address the random censoring assumption:
   a) Unconfirmed progressions as confirmed progression event in each analysis (prespecified).
   b) Premature study discontinuations as confirmed progression events in each analysis (prespecified).
   c) Both unconfirmed progressions and premature discontinuations as progression events in each analysis (prespecified).
   d) Tentative progressions at last EDSS assessment as confirmed progression event in each analyses (prespecified).
   e) Using the OLE Study RPC01-3001 for confirmation of tentative progression in either of the parent studies as confirmation of a progression event (post-hoc). This strategy has been used as primary CDP analysis in another pivotal study (EPAR Ocrevus EMA/790835/2017) (Hauser, 2017).

Similarly, sensitivity analyses using multiple imputation analyses using both J2R and CR approaches were requested during the assessment.

Other Secondary Efficacy Endpoints

Brain Volume Loss: percent changes from baseline in normalized brain volume, cortical grey matter, and thalamic volume were analysed using the prespecified parametric analysis of covariance (ANCOVA) and a post hoc nonparametric ANCOVA. Both of these models were adjusted for region and baseline EDSS category. Missing data was handled using LOCF. The non-parametric ANCOVA was conducted due to concerns that the distribution of these brain volumes may not follow a normal distribution. Additionally, the Applicant was requested to provide a sensitivity analysis based on log-transformed data.

MSFC: the change from baseline in the MSFC scores and the actual values at each visit were summarized in each treatment group using LOCF to address missing data. The changes in MSFC scores at Months 12 and 24 were analysed and compared between treatment groups using an ANCOVA model adjusting for region, EDSS category at baseline, and the baseline MSFC score.

MSQOL-54 comparisons of the change from baseline to Month 12 (Study RPC01-301) and Month 24 (Study RPC01-201B) for the 2 summary scores only between treatment groups were analysed by an ANCOVA model adjusted for region, EDSS category at baseline, and baseline summary score of interest. Missing data were to be imputed using a mixed-effects regression model (random slope and intercept). For the pooled analysis, only descriptive statistics were provided.

Handling of Missing Data in the pooled analyses

The handling of missing data was the same for the primary analysis of the primary and the first and second key secondary endpoints as in the individual studies. However, the sensitivity analyses for missing data in the first and second key secondary endpoints were conducted slightly differently and included 1) increasing the visit windows for Months 12 and 24 from the windows specified in the individual

SAPs, 2) imputing the treatment group means for missing values as done in the individual studies, and 3) using the natural logarithm of time on study over 12 and 24 months for Study RPC01-301 and Study RPC01-201B, respectively. The approach for handling missing data for the pooled analyses for the third key secondary endpoint is explained above.

Subgroup analyses

Pre-defined subgroup analyses were performed for the primary and secondary efficacy endpoints of single as well as the pooled phase 3 studies for the following subgroups:

- Baseline EDSS score (EDSS ≤3.5 vs. EDSS >3.5).
- Baseline presence of Gd-enhancing lesions (present vs. absent).
- Prior treatment status (treatment naïve vs. previously treated).
- Age at Baseline (age ≤40 vs. age >40).
- Sex (female vs. male).
- Race (White vs. non-White).
- Weight (< median vs. ≥ median).
- Number of relapses in the past 12 months (<2 vs. ≥2) for ARR endpoint only.
- Regions (North America, Western Europe, South Africa, Eastern Europe). Due to the small number of subjects, North America, Western Europe, and South Africa were combined as Rest of World".

Post-hoc subgroup analyses:

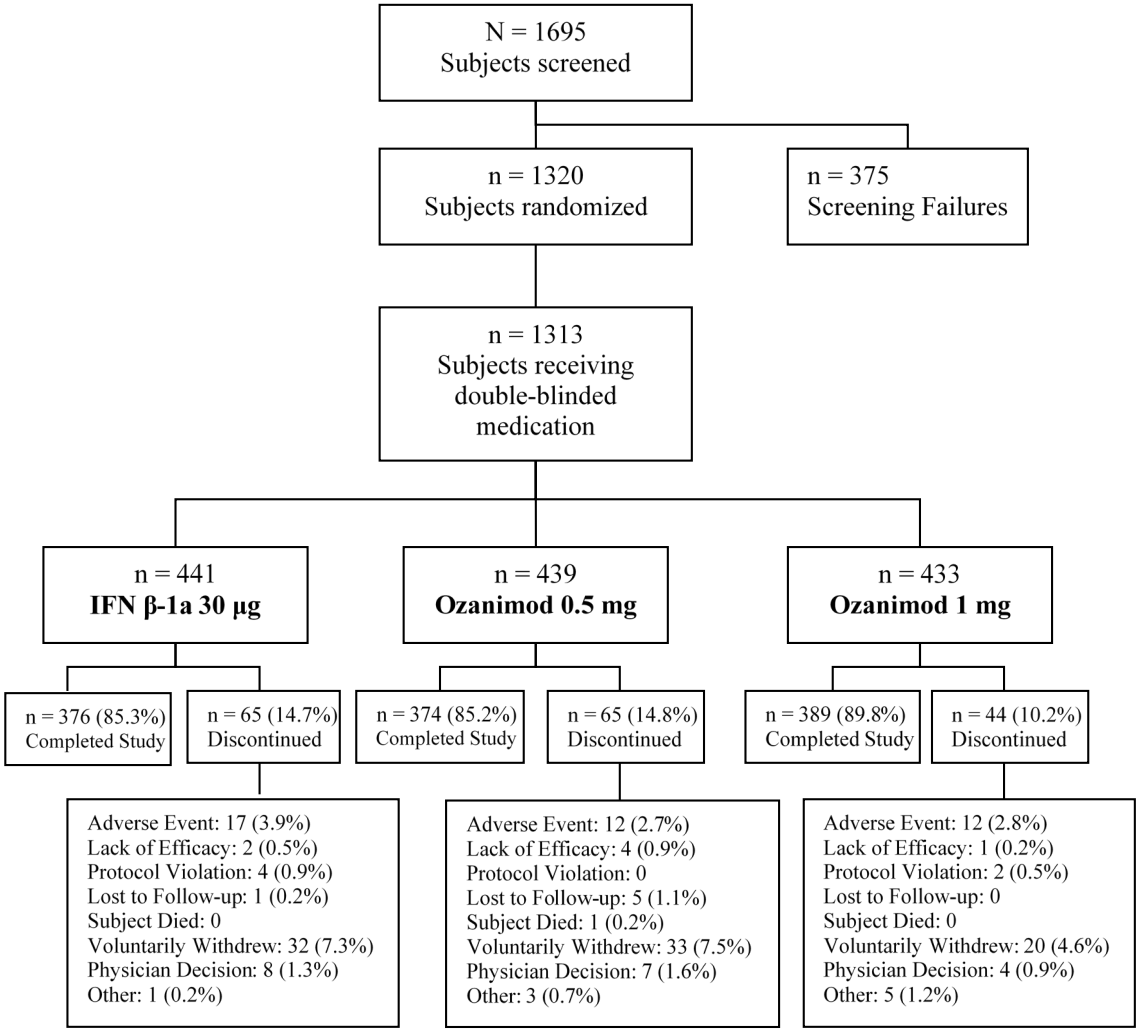
- In line with the recommendation of performing subgroup analysis by region provided in SA (EMEA/H/SA/2779/1/2014/SME/III), the Applicant was requested to further explore B/R balance for non-EU and EU population to explore generalizability of results towards an EU population.
- The Applicant also provided subgroup analyses according to other features including number of relapses in the past 24 months (0-2 vs. >2), number of T2 lesions (using median as cut-off), baseline EDSS score (using median 2.5 as cut-off), prior use of DMT, change in lymphocytes (using median as cut-off) and, high disease activity at entry as defined by (1) ≥ 2 relapses in the prior 12 months and ≥ 1 baseline GdE lesion, and/or (2) having received ≥ 1 year of DMT in the prior 2 years, having the most recent relapse in the previous 12 months while on that DMT, and having ≥ 9 baseline hyperintense T2-weighted brain MRI lesions or ≥ 1 baseline GdE lesion. A 3rd criterion for definition of high disease activity of "Patients with an unchanged or increased relapse rate in the year prior to the study (Year -1) as compared to the previous year (Year -2)" pre-specified in the SAP for individual studies was not used for subgroup analysis of the pooled phase III study data, because this criterion was found to characterize 95% of study population in the mITT population, and was therefore not considered to yield new information beyond the primary analysis.
- The Applicant was requested to provide subgroup analyses for subjects with and without prior IFN β-1a.
- Finally, the was requested to provide all subgroup analyses based on a negative binomial model (primary endpoints) and with and without using J2R approach (primary and key secondary endpoints) in line with same requests posed by CHMP for main results.

As pre-specified in the SAP, any subgroup that did not have at least 5% of the overall sample size (approximately 60 subjects) was not included in subgroup analyses.

Results

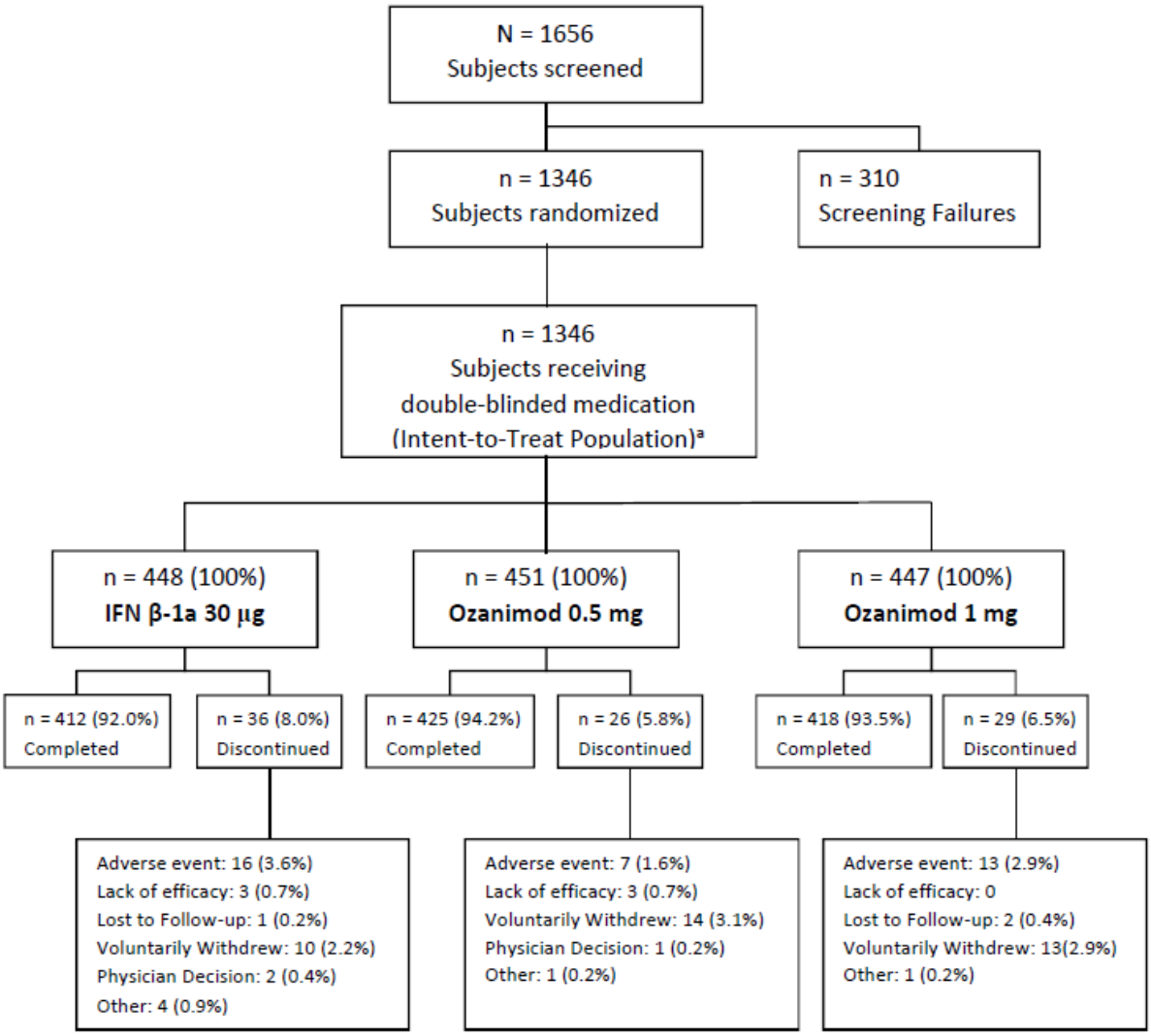
Participant flow

Figure 5: Intent to treat population for Study RPC01-201B



Abbreviation: IFN: Interferon
[a] Intent-to-Treat Population was to include all randomized subjects who received at least 1 dose of study drug (mITT). This population was to be used as the primary population for the analysis of all efficacy endpoints. All subjects in the mITT Population were to be analysed according to the treatment they were randomized to receive and not according to what they actually received, if different.

Figure 6: Intent to treat population for Study RPC01-301



Abbreviation: IFN: Interferon
[a] Intent-to-Treat Population was to include all randomized subjects who received at least 1 dose of study drug (mITT). This population was to be used as the primary population for the analysis of all efficacy endpoints. All subjects in the mITT Population were to be analysed according to the treatment they were randomized to receive and not according to what they actually received, if different.

Recruitment

Regarding the periods of recruitment and follow-up, the Applicant reported the following dates:

- Study RPC01-201B: Date first subject, first visit: 03 December 2013, Date last subject, last visit: 13 April 2017. Database lock date: 12 May 2017.
- Study RPC01-301: Date first subject, first visit: 03 December 2014, Date last subject, last visit: 22 December 2016, Database lock date: 08 February 2017.

At request of CHMP, the Applicant provided data on participating/recruiting study centres per country as well as on subjects per study that showed no indication that the overall results of the pivotal studies were substantially influenced by single study centres.

Conduct of the study

Blinding measures

Blinding and particularly the dual assessor approach and the procedure for certification of relapses was further clarified at request during the procedure.

Given that unblinding was understood to influence observers' impartiality, the procedures for reporting, assessing, and confirming relapses were reviewed for any evidence of reporting bias. The proportion of relapses that were confirmed by the treating investigator was similar (>90%) across the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups in both Phase 3 studies.

An additional source of potential unblinding is the different AE-profile of ozanimod compared to the active comparator, IFN β-1a in particular regarding flu-like symptoms. At request, the Applicant provided subgroup analyses of subjects with or without flu-like symptoms. Additionally, since flu-like symptoms were post-baseline measurements influenced by treatment, at request, the Applicant also provided a principal strata analysis for the stratum of subjects that would obtain flu-like symptoms under IFN β-1a and those who would not obtain flu-like symptoms under IFN β-1a, as well as the corresponding analyses regarding the flu-like symptoms obtained under ozanimod. Two different models for the principal stratum analysis (1:1 matching and propensity score weighting) were used along with two different analysis models (Poisson as pre-specified as the primary analysis and negative binomial modelling). The results were rather consistent across the four different analyses showing different effect sizes for subjects with flu-like symptoms as compared to those without. Considering subjects that would obtain flu-like symptoms under IFN β-1a as subjects for which treatment allocation (to IFN β-1a) could have been guessed by the investigator, the difference in the treatment effect size (ARR) between subjects that were potentially unblinded and those who were not was approximately 10 %, suggesting an increase from a 37% reduction to a reported 47% reduction in the effect due to potential unblinding.

Protocol amendments

There were protocol amendments to the pivotal Study RPC01-201B to harmonise data so that pooling could be performed and to incorporate feedback from the US Food and Drug Administration (FDA) under their Special Protocol Assessment of both pivotal Phase 3 studies, RPC01-201 and RPC01-301. The changes involved the reordering of secondary endpoints and revisions to the hierarchical testing procedure.

Protocol compliance and reasons for protocol violations

86.7% and 93.2% of subjects completed Study RPC01-201B, and Study RPC01-301, respectively

Across two pivotal phase 3 trials, eleven patients' cases of erroneously dispensed study drug kits occurred at single visits and that no more than one case occurred in any study centre. Corrective actions included retraining of study sites (described in most cases), review of proper IP dispensing procedures, documentation of discrepancies and preparation of corrective action plans. Additionally, three subjects were identified as having used the wrong needle size (subcutaneous instead of intramuscular) for the administration of IFN β-1a.

GCP inspections

A total of 14 investigator site inspections have been conducted by 5 health authorities, namely Moldovan Medicine and Medical Devices Agency, State Expert Center of Ministry of Health of Ukraine, Federal Agency for Medicines and Health Products—Belgium, EMA, and US FDA on dates ranging from 02 Dec 2015 to 26 Sep 2019. Of the 12 reports available, one major protocol deviation was identified. This apparently did not have an impact on patient's health or study results. A routine GCP inspection of study RPC01-301 has been performed by EMA, which identified no critical and 7 and 4 major findings, respectively across the two investigated sites. Despite these findings, the data reported by these sites were still considered to be of sufficient quality to be used for the evaluation of the clinical trial. One US FDA inspection is pending results.

Baseline data

The demographic characteristics of subjects were generally well-balanced across treatment groups within each Phase 3 study as well as across the studies, with 98.2% of the sample representing subjects with RRMS. The majority of subjects were female (66.8% of subjects) and white (98.9% of subjects), with a mean age of 35.5 (range 18 to 55 years) and mean BMI of 24.19 kg/m2. The majority of subjects were enrolled in the Eastern European region (89.7% of subjects) (Table 8).

Approximately 70% of the population was DMT-naïve in spite of a mean disease duration> 6 years and presence of significant level of inflammatory activity as per inclusion criteria. Active disease was further evidenced by the presence of GdE lesions at baseline in 45.0% of subjects with at least 1 GdE lesion, including 28.1% of subjects with ≥ 2 GdE lesions. A total of 22.8% of subjects met the definition of a highly active MS at baseline as defined as (1) ≥ 2 relapses in the prior 12 months and ≥ 1 baseline GdE lesion, and/or (2) having received ≥ 1 year of DMT in the prior 2 years, having the most recent relapse in the previous 12 months while on that DMT, and having ≥ 9 baseline hyperintense T2-weighted brain MRI lesions or ≥ 1 baseline GdE brain MRI lesion (Table 8).

Table 8: Disease History and Baseline MRI Characteristics (mITT Population)

	RPC01-301 (12+ Months)				**RPC01-201B (24 Months)**			
Variable/ Statistic	**IFN β-1a 30 µg (N=448)**	**Ozanimod 0.5 mg (N=451)**	**Ozanimod 1 mg (N=447)**	**Total (N=1346)**	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 0.5 mg (N = 439)**	**Ozanimod 1 mg (N = 433)**	**Total (N = 1313)**
Years since MS Symptom Onset								
Mean (SD)	6.88 (5.877)	7.16 (6.255)	6.85 (6.449)	6.96 (6.195)	6.36 (6.065)	6.23 (5.547)	6.92 (6.201)	6.50 (5.947)
Years since MS Diagnosis								
Mean (SD)	3.71 (4.361)	3.70 (4.518)	3.60 (4.193)	3.67 (4.357)	3.63 (4.613)	3.50 (4.207)	3.97 (5.171)	3.70 (4.679)
Type of MS								
RRMS, n (%)	441 (98.4)	443 (98.2)	438 (98.0)	1322 (98.2)	432 (98.0)	432 (98.4)	425 (98.2)	1289 (98.2)
EDSS Score								
Mean (SD)	2.62 (1.138)	2.65 (1.135)	2.61 (1.160)	2.62 (1.144)	2.49 (1.158)	2.48 (1.166)	2.55 (1.145)	2.51 (1.156)
≤ 3.5, n (%)	370 (82.6)	360 (79.8)	360 (80.5)	1090 (81.0)	377 (85.5)	368 (83.8)	366 (84.5)	1111 (84.6)
Number of relapses in the last 12 months, n (%)								
0	7 (1.6)	7 (1.6)	10 (2.2)	24 (1.8)	7 (1.6)	10 (2.3)	8 (1.8)	25 (1.9)
1	330 (73.7)	330 (73.2)	323 (72.3)	983 (73.0)	306 (69.4)	281 (64.0)	317 (73.2)	904 (68.8)
≥ 2	111 (24.8)	114 (25.3)	114 (25.5)	339 (25.2)	128 (29.0)	148 (33.7)	108 (24.9)	384 (29.2)
Presence of GdE lesions								
n (%)	216 (48.2)	202 (44.8)	214 (47.9)	632 (47.0)	196 (44.4)	190 (43.3)	178 (41.1)	564 (43.0)
MRI measures, mean (SD)								
GdE lesion count	1.7 (3.22)	1.6 (2.95)	1.8 (3.41)	1.7 (3.20)	1.8 (3.54)	1.8 (3.62)	1.6 (3.78)	1.7 (3.65)
T2 lesion count	53.7 (37.80)	53.6 (35.56)	54.5 (39.48)	53.9 (37.61)	48.7 (32.62)	48.7 (36.27)	47.9 (32.37)	48.4 (33.78)
DMT history, n (%)								
Prior DMT use	151 (33.7)	132 (29.3)	128 (28.6)	411 (30.5)	126 (28.6)	131 (29.8)	123 (28.4)	380 (28.9)
DMT-naïve	297 (66.3)	319 (70.7)	319 (71.4)	935 (69.5)[a]	315 (71.4)	308 (70.2)	310 (71.6)	933 (71.1)[a]

Variable/ Statistic	RPC01-301 (12+ Months)				RPC01-201B (24 Months)			
	IFN β-1a 30 µg (N=448)	Ozanimod 0.5 mg (N=451)	Ozanimod 1 mg (N=447)	Total (N=1346)	IFN β-1a 30 µg (N = 441)	Ozanimod 0.5 mg (N = 439)	Ozanimod 1 mg (N = 433)	Total (N = 1313)
High Disease Activity[a,b]								
n (%)	103 (23.0)	101 (22.4)	102 (22.8)	306 (22.7)	104 (23.6)	107 (24.4)	90 (20.8)	301 (22.9)
Normalized Whole Brain Volume, cm^3								
Mean (SD)	1443.355 (78.731)	1447.437 (79.458)	1455.980 (77.941)	1448.929 (78.831)	1449.581 (77.156)	1452.852 (71.978)	1441.949 (79.228)	1448.153 (76.250)

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; IFN = interferon; ITT = intent-to-treat; MS = multiple sclerosis; MRI = magnetic resonance imaging; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation.
[a] Data on file.
[b] Defined as (1) ≥ 2 relapses in the prior 12 months and ≥ 1 baseline GdE lesion, and/or (2) having received ≥ 1 year of DMT in the prior 2 years, having the most recent relapse in the previous 12 months while on that DMT, and having ≥ 9 baseline hyperintense T2-weighted brain MRI lesions or ≥ 1 baseline GdE lesion.

Numbers analysed

The randomized population included all randomized subjects (Table 9).

The Safety population included all randomized subjects who received at least 1 dose of study drug grouped according to the treatment they received (Table 9).

The mITT population included all randomized subjects who received at least 1 dose of study drug grouped according to their randomized treatment, regardless of the actual treatment received (Table 9).

The PP Population was subset of subjects in the mITT Population with high treatment compliance and without any exclusionary protocol deviations (Table 9).

Table 9: Population included in the different analyses sets

Study	RPC01-301 (12+ Months)			RPC01-201B (24 Months)		
Arm	**IFN β-1a 30 µg**	**Ozanimod 0.5 mg**	**Ozanimod 1 mg**	**IFN β-1a 30 µg**	**Ozanimod 0.5 mg**	**Ozanimod 1 mg**
Randomized population[a]	448 (100)	451 (100)	447 (100)	443 (100)	443 (100)	434 (100)
Safety Population[a]	445 (99.3)	453 (100.4)[b]	448 (100.2)[b]	440 (99.3)	439 (99.1)	434 (100)
mITT Population[a]	448 (100)	451 (100)	447 (100)	441 (99.5)	439 (99.1)	433 (99.8)
PP Population[a]	447 (99.8)	450 (99.8)	445 (99.6)	436 (98.4)	436 (98.4)	432 (9.5)

IFN = interferon; mITT =modified intent-to-treat (only those receiving at least 1 dose of study drug); PP = Per protocol
[a] Denominators for percentages are the number of subjects randomized (randomized population).
[b] 3 subjects were randomized to the IFN β -1a group but received and were dosed from ozanimod kits in error at some visits (2 subjects received ozanimod 0.5 mg and 1 subject received ozanimod 1 mg).

Outcomes and estimation

Efficacy results from the 2 controlled Phase 3 studies provide the basis for the efficacy claim for ozanimod. This assessment focused on the most clinically important endpoints: ARR, time to first relapse, MRI endpoints (GdE and T2 brain lesions, brain volume change), disability progression, MSFC, and MSQOL-54.

The Applicant has used the term "statistically significant" referring to p-values ≤ 0.050 for treatment comparisons that were subject to multiplicity adjustment in the hierarchical testing scheme described in the pre-defined SAP. The term "nominally significant" refers to p-values ≤ 0.050 for treatment comparisons that were not subject to multiplicity adjustment, either because the treatment comparison was not included in the hierarchy or was a post hoc analysis.

Annualized Relapse Rate and Time to First Relapse

In both studies, treatment with ozanimod 1 mg and 0.5 mg resulted in statistically significant, clinically meaningful reductions in ARR compared with IFN β-1a (Table 10).

In Study RPC01-201B, the percent reduction in ARR compared to IFN β-1a at Month 24 was approximately 38% with ozanimod 1 mg and approximately 21% with ozanimod 0.5 mg. In Study RPC01-301, the percent reduction in ARR compared to IFN β-1a at the end of the treatment period was approximately 48% and 31%, respectively. A dose-dependent effect was observed favouring the 1 mg dose over the 0.5 mg dose in both studies (**Table 10**). In a prespecified analysis of pooled data, treatment with ozanimod 1 mg resulted in a 22.2% reduction in ARR relative to ozanimod 0.5 mg.

Table 10: Summary of ARR and Relapse-free Rate Over the Treatment Period – Studies RPC01 301 and RPC01 201B (mITT Population)

	RPC01-301 (12+ Months)			**RPC01-201B (24 Months)**		
Endpoint Parameter	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 0.5 mg (N = 451)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 0.5 mg (N = 439)**	**Ozanimod 1 mg (N = 433)**
ARR[a]						
Total Number of Relapses	184	125	97	236	186	143
Adjusted ARR (95% CI)[b]	0.350 (0.279,0.440)	0.241 (0.188,0.308)	0.181 (0.140,0.236)	0.276 (0.234,0.324)	0.218 (0.183,0.259)	0.172 (0.142,0.208)
Percent Reduction (Oza/IFN β-1a 30µg)	--	31.242	48.211	--	20.948	37.662
p-value[c]	--	**0.0013**	**< 0.0001**	--	**0.0167**	**< 0.0001**
Relapse-free Rate						
KM Estimate	0.663	0.772	0.781	0.642	0.715	0.756
p-value[d]	--	*0.0022*	*0.0002*	--	*0.0702*	*0.0012*

ARR = Annualized Relapse Rate CI = confidence interval; IFN = interferon; mITT =modified intent-to-treat (only those receiving at least 1 dose of study drug)

[a] The endpoint was assessed during the treatment period for Study RPC01-301 and through the end of Month 24 for Study RPC01-201B. The primary analysis included confirmed relapses only.

[b] Based on the Poisson regression model, adjusted for region (Eastern Europe vs Rest of the World), age at baseline, and the baseline number of GdE lesions, and included the natural log transformation of time on study as an offset term.

[c] The comparison of each ozanimod group vs IFN β-1a group was performed at the 2-sided, 0.025 significance level according to the hierarchical statistical testing procedure.

[d] P-value for the comparison between the ozanimod and IFN β-1a treatment groups was based on the log rank test.

Notes: P-values in bold are considered statistically significant. P-values in italics are considered nominally significant.

These results were supported by prespecified sensitivity analyses, including confirmed and unconfirmed relapses and analyses using a negative binomial distribution. It should be noted that considering the negative binomial model as the appropriate analysis to account for overdispersion, the 0.5 mg Ozanimod dose did not show a significant effect for the primary endpoint in Study RPC01-201B (p=0.0593) (Table

11). The sensitivity analyses based on J2R and CR approach provided consistent treatment results comparing ozanimod to IFN β-1a. Analyses for PP population were also presented (Table 11).

Table 11: Sensitivity and PP analyses of the primary endpoint – Study RPC01-201B and Study RPC01-301

		Study RPC01-201B (24 Months)	Study RPC01-301 (12+ Months)
Population	**Sensitivity Analysis**	**% Reduction [95% CI]; p-value**	**% Reduction [95% CI]; p-value**
ITT	Poisson – with unconfirmed relapses	0.5 mg vs. IFN β-1a: 18.006 [1.343, 31.854]; *0.0354* 1 mg vs IFN: 38.039 [24.121, 49.404]; *<0.0001*	0.5 mg vs. IFN β-1a: 31.986 [14.843, 45.678]; *0.0008* 1 mg vs IFN: 45.278 [30.527, 56.898]; *<0.0001*
ITT	Negative binomial – confirmed relapses only	0.5 mg vs. IFN β-1a: 21.434 [-0.951, 38.855]; 0.0593 1 mg vs IFN: 38.037 [19.443, 52.339]; *0.0004*	0.5 mg vs. IFN β-1a: 30.260 [9.504, 46.256]; *0.0067* 1 mg vs IFN: 48.050 [31.419, 60.648]; *<0.0001*
ITT	Negative binomial – with unconfirmed relapses	0.5 mg vs. IFN β-1a: 18.258 [-4.260, 35.912]; 0.1044 1 mg vs IFN: 38.331 [20.308, 52.278]; *0.0002*	0.5 mg vs. IFN β-1a: 31.097 [10.577, 46.909]; *0.0051* 1 mg vs IFN: 45.110 [27.880, 58.224]; *<0.0001*
PP	Poisson – confirmed relapses only	0.5 mg vs. IFN β-1a: 20.693 [3.794, 34.624]; *0.0187* 1 mg vs IFN β-1a: 37.176 [22.597, 49.009]; *<0.0001*	0.5 mg vs. IFN β-1a: 31.912 [14.373, 45.859]; *0.0010* 1 mg vs IFN β-1a: 47.811 [33.176, 59.241]; *<0.0001*

Based on the KM estimate, subjects in the ozanimod 1 mg and 0.5 mg treatment groups remained relapse-free at a higher rate compared with the IFN β-1a treatment group in both Study RPC01-201B at 24 months (approximately 76% and 72% versus 64%, respectively) and Study RPC01-301 at 18 months (approximately 78% and 77% versus 66%, respectively). The *nominal* p-values from the log rank test for comparing the ozanimod 1 mg and 0.5 mg treatment groups versus IFN β 1a were 0.0012 and 0.0702, respectively, for Study RPC01-201B and 0.0002 and 0.0022, respectively, for Study RPC01-301 (Table 10).

MRI Measures of Disease Activity

New or Enlarging Hyperintense T2-Weighted Brain MRI Lesions (1st key secondary endpoint)

Using the results for primary endpoint derived from the pre-specified Poisson regression model as reference, in both studies, treatment with ozanimod 1 mg and 0.5 mg resulted in statistically significant, clinically meaningful reductions in new or enlarging hyperintense T2-weighted brain MRI lesions compared with IFN β-1a (**Table 12**).

In Study RPC01-201B, a statistically significant reduction in the total adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan was demonstrated with ozanimod 1 mg ($p< 0.0001$) and ozanimod 0.5 mg ($p=0.0001$) compared to IFN β-1a (1.835, 2.092, and 3.183 lesions, respectively), corresponding to a 42.4% and 34.3% reduction over 24 months, respectively. In Study RPC01-301, a statistically significant reduction in the total adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan was demonstrated with ozanimod 1 mg ($p<0.0001$) and ozanimod 0.5 mg ($p=0.0032$), compared to IFN β-1a (1.465, 2.139, and 2.836 lesions, respectively), corresponding to a 48.3% and 24.6% reduction over 12 months, respectively. A numerical dose-dependent effect was observed favouring the 1 mg dose over the 0.5 mg dose in both studies (**Table**

12). The sensitivity analyses based on J2R and CR approach provided consistent treatment results comparing ozanimod to IFN β-1a.

In a prespecified analysis of pooled data at Month 12 and Study RPC01-201B data at Month 24, treatment with ozanimod 1 mg relative to ozanimod 0.5 mg resulted in a 23.5% and 12.3% reduction, respectively, in new or enlarging hyperintense T2-weighted brain MRI lesions.

As noted above, the 0.5 mg Ozanimod dose did not show a significant effect for the primary endpoint in Study RPC01-201B when considering the preferred the negative binomial model strategy. Consequently, results for 0.5 mg Ozanimod should not be considered as statistically significant in Study RPC01-201B.

Number of Gadolinium-enhancing Brain MRI Lesions (2nd key secondary endpoint)

In both studies, treatment with ozanimod 1 mg and 0.5 mg resulted in statistically significant, clinically meaningful reductions in GdE lesions compared with IFN β-1a (**Table 12**).

In Study RPC01-201B, a statistically significant reduction in the adjusted mean number of GdE brain MRI lesions was demonstrated with ozanimod 1 mg (p=0.0006) and ozanimod 0.5 mg (p=0.0030) compared to IFN β-1a (0.176, 0.197, and 0.373 lesions, respectively), corresponding to a 52.9% and 47.2% reduction at Month 24, respectively. In Study RPC01-301, a statistically significant reduction in the adjusted mean number of GdE brain MRI lesions was demonstrated with ozanimod 1 mg (p<0.0001) and ozanimod 0.5 mg (p=0.0182), compared to IFN β-1a (0.160, 0.287, and 0.433 lesions, respectively), corresponding to a 63.0% and 33.8% reduction at Month 12, respectively. A numerical dose-dependent effect was observed favouring the 1 mg dose over the 0.5 mg dose in both studies (**Table 12**). The sensitivity analyses based on J2R and CR approach provided consistent treatment results comparing ozanimod to IFN β-1a.

In a prespecified analysis of pooled data at Month 12 and Study RPC01-201B data at Month 24, treatment with ozanimod 1 mg relative to ozanimod 0.5 mg resulted in a 34.5% and 10.8% reduction, respectively, in GdE brain MRI lesions.

As noted above, the 0.5 mg Ozanimod dose did not show a significant effect for the primary endpoint in Study RPC01-201B when considering the preferred the negative binomial model strategy. Consequently, results for 0.5 mg Ozanimod should not be considered as statistically significant in Study RPC01-201B

Percentage of Whole-Brain Volume Change (secondary endpoint)

Treatment with ozanimod 1 mg and ozanimod 0.5 mg resulted in *nominally* significant reductions in mean percentage whole brain change compared to IFN β-1a (**Table 12**). Similar results were obtained for cortical grey matter, and thalamic volume changes. The reduction in brain volume change was observed by Month 6 in both ozanimod 1 mg and 0.5 mg treatment groups (nominal p=0.0145 and 0.0027, respectively). The requested sensitivity analyses based on log-transformed data were in line with primary analyses. The difference in relative change in normalized whole-brain volume corresponded to a relative treatment difference of approximately 28% after 12 months of treatment.

Table 12: Summary of MRI Measures of Disease Activity: New or Enlarging Hyperintense T2-weighted Brain MRI Lesions, Number of GdE Brain MRI Lesions, and Brain Volume Loss – Studies RPC01-301 and RPC01-201B (mITT Population)

Endpoint Parameter	RPC01-301 (12+ Months)			RPC01-201B (24 Months)		
	IFN β-1a 30 µg (N = 448)	**Ozanimod 0.5 mg (N = 451)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 0.5 mg (N = 439)**	**Ozanimod 1 mg (N = 433)**
Key Secondary MRI Endpoints						
Number of New or Enlarging Hyperintense T2-weighted Brain MRI Lesions[a]						
n	382	397	388	336	329	327
Adjusted mean (95% CI) per scan[b]	2.836 (2.331, 3.451)	2.139 (1.777, 2.575)	1.465 (1.203, 1.784)	3.183 (2.640, 3.838)	2.092 (1.741, 2.514)	1.835 (1.523, 2.211)
Percent reduction vs. IFN β-1a (95% CI)[b]	--	24.578 (9.019, 37.476)	48.330 (37.469, 57.304)	--	34.282 (18.675, 46.895)	42.351 (28.580, 53.467)
p-value[b]	--	**0.0032**	**< 0.0001**	--	*0.0001*	**< 0.0001**
Number of GdE Brain MRI Lesions[c]						
n	382	397	388	336	329	327
Adjusted mean (95% CI)[b]	0.433 (0.295, 0.635)	0.287 (0.197, 0.418)	0.160 (0.106, 0.242)	0.373 (0.256, 0.543)	0.197 (0.131, 0.296)	0.176 (0.116, 0.266)
Percent reduction vs. IFN β-1a (95% CI)[b]	--	33.757 (6.777, 52.929)	62.973 (46.406, 74.419)	--	47.244 (19.516, 65.420)	52.944 (27.530, 69.445)
p-value[b]	--	**0.0182**	**< 0.0001**	--	*0.0030*	**0.0006**
Other Secondary MRI Endpoints						
Percent Change from Baseline in Normalized Whole Brain Volume[d]						
n	406	420	397	397	398	390
Mean (SD)	-0.61 (0.686)	-0.49 (0.610)	-0.41 (0.640)	-0.94 (0.944)	-0.71 (0.746)	-0.71 (0.878)
Difference in means vs. IFN β-1a (95% CI)[e]	--	0.12 (0.03, 0.20)	0.19 (0.10, 0.28)	--	0.22 (0.11, 0.34)	0.24 (0.12, 0.36)
p-value[e]	--	*0.0092*	*< 0.0001*	--	*0.0002*	*< 0.0001*
p-value[f]	--	*0.0231*	*< 0.0001*	--	*0.0010*	*< 0.0001*

ANCOVA = analysis of covariance; CI = confidence interval; EDSS = expanded disability status scale; GdE = gadolinium-enhancing; IFN = interferon; ITT = intent-to-treat; IVRS = interactive voice randomization system; MRI = magnetic resonance imaging; SD = standard deviation.

[a] Number of new or enlarging hyperintense T2-weight brain MRI lesions were assessed over 12 months in Study RPC01-301 and over 24 months in Study RPC01-201B.

[b] Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs Rest of the World), age at baseline, and baseline number of GdE lesions. The natural log transformation of the number of available MRI scans over 12 or 24 months is used as an offset term.

[c] Number of GdE brain MRI lesions were assessed at Month 12 in Study RPC01-301 and at Month 24 in Study RPC01-201B.

[d] Brain volume changes based on last observation carried forward (LOCF) analysis.

[e] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study is based on the ANCOVA model adjusted for region and EDSS category per IVRS.

[f] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study and studies pooled based on the ranked based ANCOVA model (Quade, 1967) adjusted for region and EDSS category per IVRS.

Notes: P-values in bold are considered statistically significant. P-values in italics are considered nominally significant.

Time to Confirmed Disability Progression (3rd key secondary endpoint)

A low and similar percentage of subjects experienced disability progression in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups, with CDP-3M percentages progressed of 7.6%, 6.5%, and 7.8%, respectively, and CDP-6M percentages progressed of 5.8%, 4.8%, and 4.0%, respectively. The hazard ratios (HR) of 0.950 for ozanimod 1 mg and 0.822 for ozanimod 0.5 mg correspond to a

numerical 5% and 17.8% relative risk reduction, respectively, for CDP-3M compared to IFN β-1a (Table 13). Regarding CDP-6M the HRs of 1.413 for 1 mg ozanimod and of 1.189 for ozanimod 0.5 mg correspond to a numerical relative risk increase for CDP-6M of 41.3% and 18.9% compared to IFN β-1a (Table 13).

Pre-specified sensitivity analyses for CDP-3M were in line with main analyses. Regarding CDP-6M, some sensitivity analyses numerically favoured ozanimod over IFN β-1a and vice versa, however, none of the comparisons that numerically favoured IFN β-1a were (nominally) statistically significant (Table 13).

Results from a *post-hoc* sensitivity analyses including visits of the OLE Study RPC01-3001 (during which all subjects received ozanimod 1 mg) were generally more favourable for ozanimod but none of them was significant (Table 13). Upon request, the Applicant presented absolute differences between the ozanimod 1 mg and IFN β-1a KM estimates for CDP-6M. According to this analysis, no statistically significant difference for CDP-6M outcomes was found between both treatment groups, while an approx. 4% higher CDP-6 rate after 2 years could not be excluded as derived from the lower limit of the 95% CI of survival rates (Figure 7).

Table 13: Confirmed Disability Progression at 3 and 6 Months – Pooled Phase 3 Studies (mITT Population)

Endpoint **Parameter**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 0.5 mg (N = 890)**	**Ozanimod 1 mg (N = 880)**
Primary Analysis (CDP During Controlled Phase 3 Studies Only)			
CDP-3M			
Number (%) of subjects with CDP-3M	69 (7.8)	58 (6.5)	67 (7.6)
Hazard Ratio versus IFN β-1a (95% CI)[a]	--	0.822 (0.579, 1.165)	0.950 (0.679, 1.330)
p-value[a]	--	0.2698	0.7651
CDP-6M			
Number (%) of subjects with CDP-6M	36 (4.0)	43 (4.8)	51 (5.8)
Hazard Ratio versus IFN β-1a (95% CI)[a]	--	1.189 (0.763, 1.851)	1.413 (0.922, 2.165)
p-value[a]	--	0.4447	0.1126
Prespecified Sensitivity Analysis: CDP-3M considering tentative progression at last EDSS assessment in parent study as CDP			
CDP-3M			
Number (%) of subjects with CDP-3M including tentative progression	99 (11.1)	86 (9.7)	80 (9.1)
Hazard Ratio versus IFN β-1a (95% CI)[a]	--	0.835 (0.625, 1.115)	0.766 (0.570, 1.029)
p-value[a]	--	0.2219	0.0768
CDP-6M			
Number (%) of subjects with CDP-6M including tentative progression	86 (9.7)	78 (8.8)	76 (8.6)
Hazard Ratio versus IFN β-1a (95% CI)[a]	--	0.874 (0.643, 1.187)	0.837 (0.614, 1.140)
p-value[a]	--	0.3878	0.2585
Post Hoc Sensitivity Analysis (CDP With Onset in Parent Study, Confirmed in Parent Study or OLE)			
CDP-3M			
Number (%) of subjects with CDP-3M confirmed in parent study or OLE	79 (8.9)	70 (7.9)[b]	70 (8.0)
Hazard Ratio versus IFN β-1a (95% CI)[a]	--	0.854 (0.619, 1.178)	0.848 (0.615, 1.170)
p-value[a]	--	0.3357	0.3153
CDP-6M			

Endpoint Parameter	IFN β-1a 30 µg (N = 889)	Ozanimod 0.5 mg (N = 890)	Ozanimod 1 mg (N = 880)
Number (%) of subjects with CDP-6M confirmed in parent study or OLE	59 (6.6)	57 (6.4)[b]	64 (7.3)
Hazard Ratio versus IFN β-1a (95% CI)[a]	--	0.935 (0.649, 1.345)	1.040 (0.730, 1.482)
p-value[a]	--	0.7160	0.8275

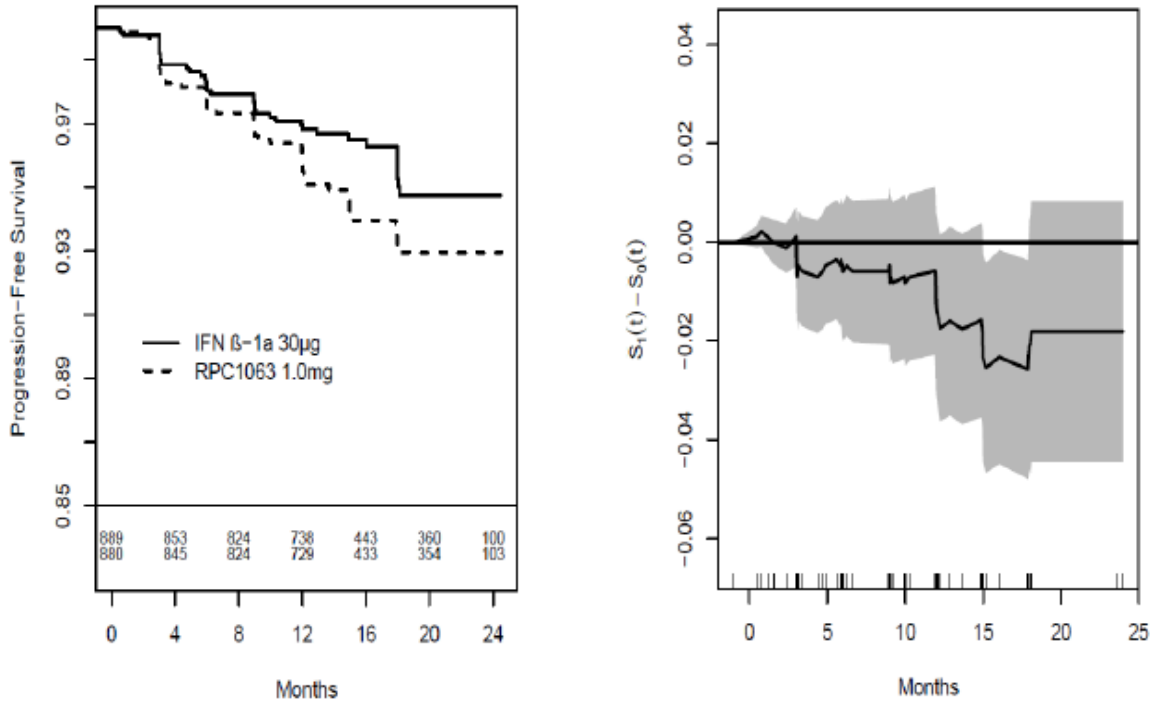
CDP-3M = confirmed disability progression at 3 months; CDP-6M = confirmed disability progression at 6 months; CI = confidence interval; EDSS = Expanded Disability Status Scale; ITT = intent-to-treat; OLE = open-label extension.

[a] Based on the Cox proportional hazard model with factors for treatment group and adjusted for region (Eastern Europe vs Rest of World), age at baseline, and baseline EDSS score.

[b] Subjects received ozanimod 1 mg during the OLE.

Note: Pooled analysis includes Studies RPC01-301 and RPC01-201B.

Figure 7: Kaplan-Meier Estimates of CDP-6M for Ozanimod 1 mg and IFN β-1a (left) and additionally presented absolute differences between Kaplan-Meier Estimates for CDP-6M (Ozanimod 1 mg - IFN β-1a) (right)



Other clinical endpoints

Change in Multiple Sclerosis Functional Composite Score

As supportive results, the Applicant provided MSFC analyses. Unlike the mild (estimates ranging from -0.022 to -0.067) consistent worsening in the MSFC z-score MSFC (LCLA) z-score with IFN β-1a in the individual studies and in the pooled analysis, subjects treated with ozanimod had either minimal worsening or improvement (estimates ranging from -0.010 to +0.036) from baseline compared with IFN β-1a (Table 14). In the Study RPC01-201B, results were overall more favourable for ozanimod 0.5 mg than for ozanimod 1mg compared to the IFN β-1a group while the opposite trend was shown in Study RPC01-301. Nominally significant improvements in MSFC and MSFC (LCLA) z-scores at Month 24 were observed in the ozanimod 0.5 mg, compared to the IFN β-1a group (nominal p-value of 0.0246 and 0.0123, respectively) in Study RPC01-201B (Table 14). Numerically favourable treatment effects were seen with ozanimod 1 mg, but nominal significance was not achieved. In Study RPC01-301 more

favourable treatment effects were observed for ozanimod 1mg group, but nominal significance was not achieved (Table 14).

These differences between the treatment groups with respect to the z-score composite endpoints were primarily driven by the SDMT/PASAT z-score component endpoint. PASAT-3 was used in Study RPC01-201B and SDMT was used in Study RPC01-301. In Study RPC01-201B, where PASAT-3 was used, no significant findings were observed at Month 24 and overall participants of the three groups showed a mild improvement on the PASAT-3 performance from baseline (Table 14). In Study RPC01-301 where SDMT was used, the mean change from baseline in the SDMT total correct responses at Month 12 were 1.1, 0.8, and 0.4 for ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a, respectively; with nominal p-values of 0.0016 (ozanimod 1 mg versus IFN β-1a) and 0.0222 (ozanimod 0.5 mg vs. IFN β-1a). In the pooled analysis, a statistically significant treatment difference between both dose groups of ozanimod and IFN β-1a were observed (Table 14). Comparisons for Total Correct Responses were in the same direction (Table 14).

In a *post hoc* analysis in which a change from baseline in SDMT of ≥ 4 was considered clinically meaningful, a numerically greater proportion of subjects in the ozanimod 1 mg and 0.5 mg treatment groups in Study RPC01-301 achieved clinically meaningful improvements in SDMT relative to IFN β-1a at Month 6 (30.0%, 27.5%, and 22.2%, respectively) and Month 12 (35.6%, 32.1%, and 27.9%, respectively). Additionally, at Month 12, a numerically lower proportion of subjects in the ozanimod 1 mg and 0.5 mg treatment groups experienced a clinically meaningful impairment in SDMT (negative change from baseline) compared with IFN β-1a (22.0%, 23.5%, and 28.2%, respectively).

Table 14: MSFC, MSFC (LCLA), and SDMT/PASAT-3 at Months 12 and 24 – ITT Population (LOCF)

	Pooled Phase 3 Studies (12 Months)			**RPC01-301 (12+ Months)**			**RPC01-201B (24 Months)**		
Parameter	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 0.5 mg (N = 890)**	**Ozanimod 1 mg (N = 880)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 0.5 mg (N = 451)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 0.5 mg (N = 439)**	**Ozanimod 1 mg (N = 433)**
MSFC z-score: Change from Baseline									
n[a]	889	889	879	448	450	447	441	439	432
Mean (SD)	-0.030 (0.388)	0.006 (0.409)	-0.009 (0.393)	-0.024 (0.366)	-0.004 (0.408)	0.006 (0.382)	-0.067 (0.745)	0.032 (0.475)	-0.006 (0.779)
Difference in Means (95% CI), ozanimod vs. IFN β-1a[b]	-	0.037 (0.001, 0.073)	0.026 (-0.009, 0.062)	-	0.019 (-0.030, 0.069)	0.040 (-0.009, 0.090)	-	0.101 (0.013, 0.190)	0.060 (-0.029, 0.148)
p-value[b]	-	*0.0428*	0.1477	-	0.4394	0.1091	-	*0.0246*	0.1874
MSFC (LCLA) z-score: Change from Baseline									
n[a]	884	885	875	447	450	447	437	435	428
Mean (SD)	-0.028 (0.342)	0.008 (0.365)	-0.009 (0.351)	-0.022 (0.334)	-0.007 (0.351)	0.003 (0.328)	-0.052 (0.601)	0.036 (0.440)	-0.010 (0.622)

Parameter	Pooled Phase 3 Studies (12 Months)			RPC01-301 (12+ Months)			RPC01-201B (24 Months)		
	IFN β-1a 30 µg (N = 889)	**Ozanimod 0.5 mg (N = 890)**	**Ozanimod 1 mg (N = 880)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 0.5 mg (N = 451)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 0.5 mg (N = 439)**	**Ozanimod 1 mg (N = 433)**
Difference in Means (95% CI), ozanimod vs. IFN β-1a[b]	-	0.037 (0.005, 0.069)	0.025 (-0.007, 0.057)	-	0.015 (-0.028, 0.059)	0.034 (-0.010, 0.077)	-	0.093 (0.020, 0.165)	0.043 (-0.030, 0.116)
p-value[b]	-	*0.0216*	0.1233	-	0.4942	0.1290	-	*0.0123*	0.2480
SDMT/PASAT-3 Total Correct Responses[d]: Observed Values									
n[a]	835	842	837	426	431	427	381	376	386
Mean (SD) Value at Baseline[c]	47.1 (12.55)	47.1 (12.32)	47.5 (12.79)	47.1 (13.48)	46.5 (13.31)	47.7 (13.70)	47.0 (11.53)	47.7 (11.20)	47.3 (11.77)
Mean (SD) Value at Time Point	47.4 (12.38)	48.1 (12.05)	48.3 (13.02)	46.9 (13.70)	47.4 (12.96)	48.8 (14.00)	48.8 (10.79)	49.7 (10.61)	48.8 (11.97)
Mean (SD) Change from BL	0.1 (6.71)	1.0 (7.15)	0.8 (7.74)	-0.4 (6.86)	0.8 (7.36)	1.1 (8.58)	1.2 (6.70)	2.1 (6.99)	1.5 (6.90)
Difference in Means (95% CI), ozanimod vs. IFN β-1a[b]	-	0.8 (0.2, 1.5)	0.7 (0.1, 1.4)	-	1.1 (0.2, 2.1)	1.6 (0.6, 2.5)	-	0.9 (-0.0, 1.8)	0.2 (-0.7, 1.1)
p-value[b]	-	*0.0117*	*0.0329*	-	*0.0222*	*0.0016*	-	0.0530	0.7263
SDMT/PASAT-3 z-scored: Change from Baseline									
n[a]	879	884	872	448	450	447	441	439	432
Mean (SD)	0.008 (0.548)	0.075 (0.581)	0.059 (0.617)	-0.029 (0.508)	0.061 (0.552)	0.073 (0.653)	0.111 (0.616)	0.169 (0.619)	0.102 (0.586)
Difference in Means (95% CI), ozanimod vs. IFN β-1a[b]	-	0.068 (0.016, 0.120)	0.055 (0.004, 0.107)	-	0.082 (0.010, 0.153)	0.111 (0.039, 0.182)	-	0.070 (-0.005, 0.145)	-0.005 (-0.081, 0.070)
p-value[b]	-	*0.0102*	*0.0362*	-	*0.0246*	*0.0024*	-	0.0657	0.8875

ANCOVA = analysis of covariance; CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ITT = intent-to-treat; LCLA = Low-Contrast Letter Acuity; LOCF = last observation carried forward; MSFC = Multiple Sclerosis Functional Component; PASAT = Paced Auditory Serial Addition Test; SD = standard deviation; SDMT = Symbol Digit Modalities Test.

[a] Number of subjects at time of assessment (Pooled Phase 3 Studies at Month 12, Study RPC01-301 at Month 12, and Study RPC01-201B at Month 24).

[b] Difference in means and p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups are based on the ANCOVA model, adjusted for region, EDSS category at baseline, and the baseline value of the parameter of interest.

[c] Baseline mean for the total population.

[d] PASAT-3 was used in Study RPC01-201B and SDMT was used in Study RPC01-301; SDMT/PASAT-3 were combined in the pooled analysis.
Notes: P-values in italics are considered nominally significant.

Change in Multiple Sclerosis Quality of Life-54 Summary Scores

The physical health composite summary score was improved in both ozanimod dose groups compared with the IFN β-1a group in the active-controlled Phase 3 studies (Table 15) and in the pooled Month 12 analysis. In Study RPC01-201B, the difference reached *nominal* significance for the ozanimod 0.5 mg group at 24 months (p=0.0228) but showed only numerical improvement for the ozanimod 1 mg group compared with IFN β-1a. In Study RPC01-301, the difference reached nominal significance for the ozanimod 1 mg group at 12 months (p=0.0364) but the difference for the ozanimod 0.5 mg group showed directionally favourable change that did not reach statistical significance.

For the mental health composite summary score, no apparent differences were observed between the ozanimod and IFN β-1a dose groups in the active-controlled Phase 3 studies (Table 15) and in the pooled Month 12 analysis.

Table 15: MSQoL-54 Summary Scores Change from Baseline at Month 12 and Month 24 – mITT Population

	Study RPC01-301 (12+ Months)			**Study RPC01-201B (24 Months)**		
Parameter	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 0.5 mg (N = 451)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 0.5 mg (N = 439)**	**Ozanimod 1 mg (N = 433)**
Physical Health Composite Summary Score						
n	445	448	443	441	439	433
Mean (SD)	0.046 (12.578)	1.414 (12.343)	1.925 (11.870)	-1.526 (12.319)	0.609 (12.315)	0.209 (12.321)
Difference in means[a] (95% CI)	-	1.024 (-0.510, 2.559)	1.642 (0.104, 3.180)	-	1.849 (0.258, 3.440)	1.345 (-0.252, 2.943)
p-value[a]	-	0.1905	*0.0364*	-	*0.0228*	0.0988
Mental Health Composite Summary Score						
n	448	451	446	441	439	433
Mean (SD)	-0.123 (15.240)	0.283 (15.686)	0.260 (15.800)	-1.831 (16.422)	-1.182 (14.379)	-1.517 (15.544)
Difference in means[a] (95% CI)	-	-0.170 (-2.045, 1.705)	0.356 (-1.523, 2.234)	-	0.587 (-1.339, 2.513)	0.380 (-1.553, 2.313)
p-value[a]	-	0.8587	0.7104	-	0.5501	0.6997

CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ITT = intent-to-treat; IVRS = interactive voice response system; SD = standard deviation.
[a] Difference in means and p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups are based on the analysis of covariance model, adjusted for region (Eastern Europe vs Rest of World), EDSS category per IVRS, and the Baseline summary score of interest.
Note: Missing data were imputed using a mixed-effects regression model (random slope and intercept).
Note: P-values in italics are considered nominally significant.

Ancillary analyses

Analyses of ARR and MRI Endpoints

The efficacy of ozanimod was assessed across multiple sub-populations in prespecified single and pooled analyses of the 2 controlled Phase 3 studies using the primary efficacy endpoint and the three key secondary efficacy endpoints.

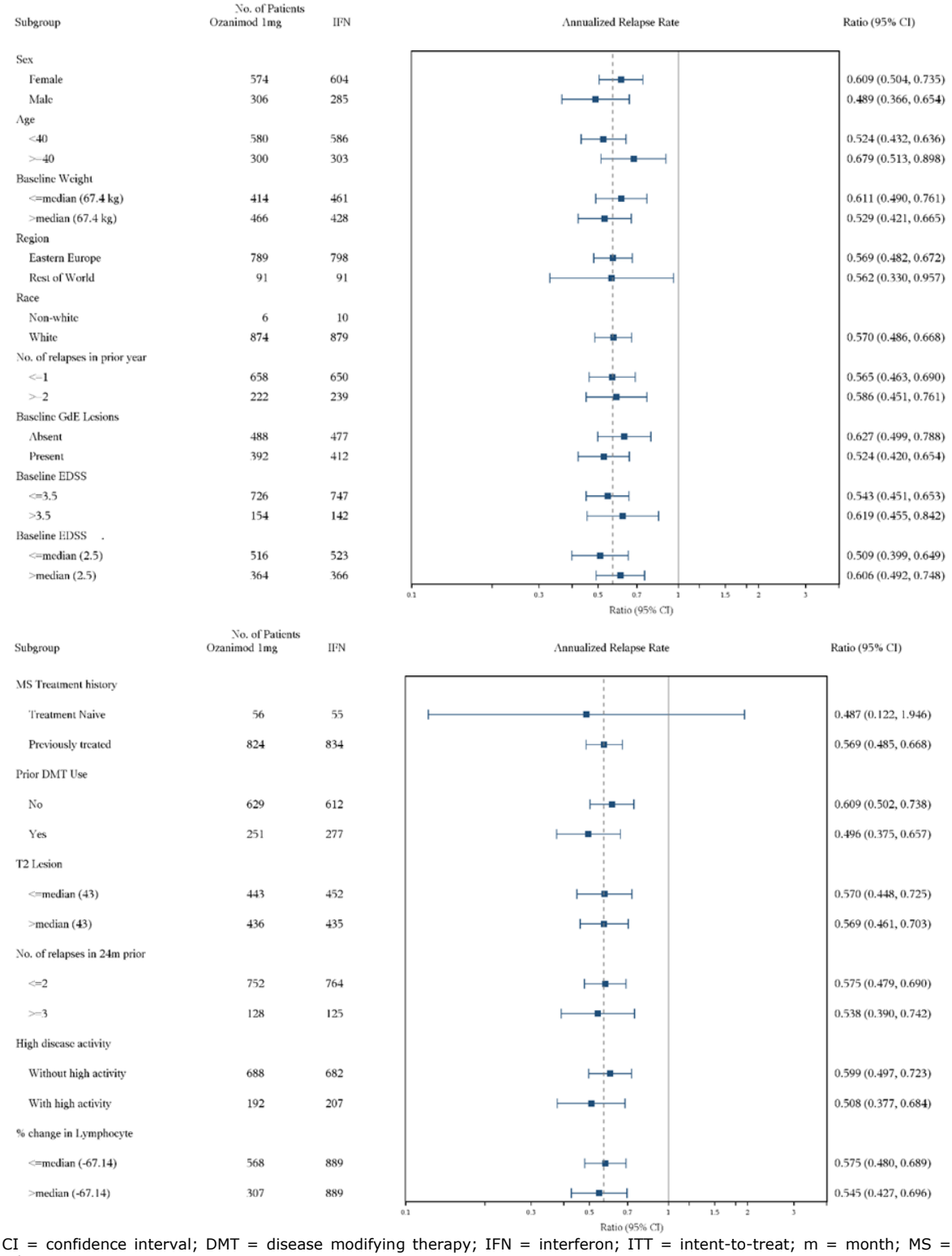
A treatment effect in favour of ozanimod 1 mg versus IFN β-1a was observed for ARR across all subgroups analysed (Figure 8) regardless of baseline clinical or MRI disease activity (including those meeting and not meeting the criteria of highly active MS, see footnote for definition). A treatment effect was also observed regardless of prior DMT use. The treatment effect favouring ozanimod 1 mg was nominally significant in all subgroups where there were sufficient numbers of subjects across treatment groups for a meaningful comparison. With ozanimod 0.5 mg, a treatment effect in favour of ozanimod versus IFN β-1a was observed across multiple subgroups.

A treatment effect in favour of ozanimod 1 mg versus IFN β-1a was observed for the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months and over 24 months, and for GdE brain MRI lesions at 12 months and at Month 24 across all subgroups analysed, regardless of baseline clinical or MRI disease activity. A treatment effect was also observed regardless of prior DMT use. The treatment effect favouring ozanimod 1 mg was generally nominally significant in all subgroups where there were sufficient numbers of subjects across treatment group for a meaningful comparison of T2 and GdE MRI brain lesions. In line with results for ARR, the results for the ozanimod 1mg dose were consistently of greater benefit than the 0.5 mg dose.

Results for the subgroup analysis for time to onset of CDP showed similar effects with ozanimod and IFN β-1a and with the overall population.

Additional sensitivity subgroup analyses based on a negative binomial model with and without using a J2R approach for treatment discontinuation produced rather consistent results. The only subgroup analyses in which the ARR Ratio was not numerically in favour of 1 mg ozanimod compared to IFN β-1a concerned the very small subgroup of subjects without any prior MS treatment (i.e. also without any acute relapse treatment, < 10% of study population) in Study RPC01-201B. However, the respective ARR Ratios were near 1 (1,013 in the worst case). In contrast, the point estimates in this subgroup were clearly numerically in favour of ozanimod (0.463 to 0.470) in the respective pooled analyses.

Figure 8: Forest Plot ARR Ratio During the Treatment Period by Subgroups (Ozanimod 1 mg vs IFN β-1a) – Pooled Phase 3 Studies (mITT Population)



CI = confidence interval; DMT = disease modifying therapy; IFN = interferon; ITT = intent-to-treat; m = month; MS = multiple sclerosis.
Dashed vertical line denotes the ARR ratio for ozanimod 1 mg versus IFN-β1a. Solid vertical line represents the threshold for ARR favouring ozanimod versus IFN β-1a.
"MS Treatment History" includes symptomatic treatment (primarily corticosteroids) as well as DMTs.
Based on the Poisson regression model, adjusted for study, treatment group, subgroup factor, and treatment by subgroup factor interaction, and included the natural log transformation of time on study as on offset term.
High disease activity defined as (1) ≥ 2 relapses in the prior 12 months and ≥ 1 baseline GdE lesion, and/or (2) having received ≥ 1 year of DMT in the prior 2 years, having the most recent relapse in the previous 12 months while on that DMT, and having ≥ 9 baseline hyperintense T2-weighted brain MRI lesions or ≥ 1 baseline GdE lesion.

Post hoc subgroup analysis evaluating efficacy and safety non-EU and EU populations

Baseline characteristics between groups were similar being the most remarkable differences between subgroups the ones in EDSS (2.43 in EU vs. 2.65 in non-EU), duration on study (19 in EU vs. 17 months in non-EU) and MS treatment history with DMD (1.5% more in EU than in Non-EU). The magnitude of treatment effects were similar in both groups for measures of focal inflammatory activity (ARR, hyperintense T2-weighted and GdE brain MRI lesions). The frequency of Treatment emergent adverse event (TEAE) occurring in >5% of the patients was higher in EU population (79.7% in EU vs. 65.1% in Non-EU).

Post hoc subgroup analysis for subjects with and without prior use of INF β-1a

Subjects with prior interferon treatment (including the active comparator Avonex®) were allowed for inclusion in the pivotal studies, and approximately 10% of subjects in the pivotal studies had prior IFN β-1a. Using Poisson regression model as well as the negative binomial model, a statistically significant treatment effect was found on ARR in both subgroups. Both analysis methods revealed a difference between both subgroups in favour of subjects with prior IFN β-1a treatment (heterogeneity p-value: 0.0261 using the negative binomial model and 0.0112 using the Poisson model) (Table 16).

Table 16: Summary of Annualized Relapse Rate During the Treatment Period by Prior IFN β-1a Treatment Users versus Non-users (Pool A1, ITT Population)

Endpoint	IFN β-1a 30µg		Ozanimod 1 mg	
	Prior Use	No Prior Use	Prior Use	No Prior Use
Prior IFN β-1a Users (Poisson Regression)				
N	100	789	84	796
Adjusted Relapse Rate (95% CI)	0.380 (0.293, 0.492)	0.314 (0.283, 0.348)	0.103 (0.060, 0.177)	0.191 (0.167, 0.217)
Rate ratio vs. IFN β-1a (95% CI)	N/A		0.271 (0.148, 0.495)	0.608 (0.515, 0.718)
p-value			<.0001	<.0001
Heterogeneity p-value			0.0112	
Endpoint	**IFN β-1a 30µg**		**Ozanimod 1 mg**	
	Prior Use	**No Prior Use**	**Prior Use**	**No Prior Use**
Prior IFN β-1a Users (Negative Binomial)				
N	100	789	84	796
Adjusted Relapse Rate (95% CI)	0.389 (0.276, 0.549)	0.320 (0.280, 0.364)	0.103 (0.057, 0.188)	0.192 (0.164, 0.223)
Rate ratio vs. IFN β-1a (95% CI)	N/A		0.265 (0.133, 0.529)	0.599 (0.490, 0.733)
p-value			0.0002	<.0001
Heterogeneity p-value			0.0261	

CI = confidence interval; GdE = gadolinium-enhancing; IFN = interferon; ITT = intent-to-treat; N/A = not applicable

Persistence and Tolerance Effects

Study RPC01-3001 is an ongoing, multi-site, open-label extension (OLE) study to evaluate the long-term safety and efficacy of ozanimod in subjects with RMS who completed 1 of the following (parent) studies: RPC01-201A Extension, RPC01-201B, RPC01-301, or RPC01-1001 (a clinical pharmacology study in subjects with MS). All subjects were assigned to ozanimod 1 mg daily.

As of the data cut-off date of 30 June 2018, 2,495 subjects (84.6% of all subjects randomized in the parent studies) had consented to the OLE study, 2323 (93.1%) subjects were ongoing, and 172 (6.9%) subjects discontinued the study early. Duration of treatment with ozanimod 1 mg was up to 30 months

in OLE Study RPC01-3001. There were 398 subjects (52%) with at least 3 years, and 44 subjects (6%) with at least 4 years of ozanimod 1 mg treatment throughout the parent and OLE studies combined.

Open-label treatment with ozanimod 1 mg resulted in a sustained low unadjusted ARR in subjects who were already treated with ozanimod 1 mg during the parent studies (0.174 in parent studies and 0.164 in OLE) and led to decreased relapse rates in subjects who switched from ozanimod 0.5 mg to 1 mg (from 0.213 in parent studies to 0.161 in OLE) or from INF β-1a treatment to ozanimod 1 mg (0.285 to 0.160). A similar pattern was observed for the adjusted ARR, which was 0.153 in the parent studies and 0.133 in OLE in the 1mg/1mg ozanimod group, changed from 0.184 to 0.131 in the ozanimod 0.5 mg/1 mg group and changed from 0.246 to 0.126 in the IFN β-1a/ozanimod 1 mg group.

An additional analysis of ARR on a yearly basis was performed to evaluate the durability of effect This analysis included relapse data until the 5th year of treatment (i.e. year 4-5 in Table 17) collected from the Phase 3 parent studies (Study RPC01-301 and Study RPC01-201B) and the OLE (Phase 3 Parent + OLE). For the INF β-1a / ozanimod 1 mg and ozanimod 1 mg/ ozanimod 1 mg cohorts, ARR at each time interval was analysed while all subjects were uniformly exposed to the ozanimod 1 mg dose. However, for the ozanimod 0.5 mg/ ozanimod 1 mg cohort, the ARR analysis is based on subjects being exposed to the 0.5 mg dose for the 0 to 1 year time interval, and a mix of ozanimod 0.5 mg and 1 mg for the 1 to 2 year interval as some subjects from Study RPC01-301 enrolled into the OLE and began receiving the ozanimod 1 mg dose. After 2 years, the ARR analysis for this cohort included all subjects being exposed to the ozanimod 1 mg dose as subjects from Study RPC01-201B enrolled into the OLE.

Table 17: Summary of annualized relapse rate over time during the parent phase III studies and open-label extension study – mITT population

	Year 0 to 1[a]	Year 1 to 2[a]	Year 2 to 3[a]	Year 3 to 4[a]	Year 4 to 5[a]
IFN β-1a 30 µg / ozanimod 1 mg[b]					
N	740	704	34	1	0
Total Number of Relapses	126	56	0	0	0
Subject Years on Treatment	723.66	404.08	8.04	0.22	0
Unadjusted ARR[c]	0.174	0.139	0.000	0.000	NA
Adjusted ARR (95% CI)[d]	0.146 (0.113, 0.188)	0.114 (0.080, 0.161)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Ozanimod 0.5 mg / ozanimod 1 mg[e]					
N	756	756	743	380	39
Total Number of Relapses	179	124	111	23	0
Subject Years on Treatment	755.48	750.21	647.81	186.69	5.14
Unadjusted ARRc	0.237	0.165	0.171	0.123	0.000
Adjusted ARR (95% CI)[d]	0.202 (0.160, 0.255)	0.139 (0.104, 0.185)	0.131 (0.093, 0.184)	NE (NE, NE)	NE (NE, NE)
Ozanimod 1 mg / ozanimod 1 mg[e]					
N	760	760	751	398	44
Total Number of Relapses	149	114	107	30	1
Subject Years on Treatment	759.48	755.65	656.99	202.67	6.47
Unadjusted ARR[c]	0.196	0.151	0.163	0.148	0.155
Adjusted ARR (96% CI)[d]	0.169 (0.133, 0.214)	0.129 (0.097, 0.171)	0.124 (0.088, 0.174)	NE (NE, NE)	NE (NE, NE)

IFN = interferon; ARR = Annualized Relapse Rate; CI = confidence interval; NA = not applicable; NE = Not estimated.

The reduction in the number of new/enlarging hyperintense T2-weighted brain MRI lesions and GdE T1 brain MRI lesions followed a similar pattern to that of the reduction seen in ARR over time.

The proportion of subjects with CDP-3M or CDP-6M continued to be low during OLE Study RPC01-3001. The overall proportion of subjects with CDP-3M and CDP-6M during the OLE mITT population were 7.0% and 5.1%, respectively. Neither the median time to CDP-3M or CDP-6M, nor the time to the 25% percentile could be estimated, due to the low event rate.

Summary of main studies

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 18: Summary of efficacy for Study RPC01-201B

Title: A Phase 2/3, Multi-Center, Randomized, Double-Blind, Double-Dummy, Active Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients			
Study identifier	RPC01-201B		
Design	Multi-center, randomized, double-blind, double-dummy, active-controlled, parallel-group, fixed-dose		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 months not applicable ongoing (data cut-off: 30 Jun 2018)
Hypothesis	Superiority		
Treatments groups	Ozanimod 1 mg		Ozanimod HCL 1 mg, capsule, oral, once daily, 24 months after 1-week titration. n=434 randomised
	Ozanimod 0.5 mg		Ozanimod HCL 0.5 mg, capsule, oral, once daily, 24 months after titration (4 days of lower dose. n=443 randomised
	IFN β-1a		IFN β-1a 30-µg, prefilled syringes IM weekly, 24 months. n= 443 randomised
Endpoints and definitions	Primary endpoint	ARR	ARR at the end of 24 months during the study (based on confirmed protocol defined relapses)
	1st key secondary endpoint	# T2 MRI lesions	Number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months
	2nd key secondary endpoint	# GdE MRI lesions	Number of GdE brain MRI lesions at Month 24
	3rd key secondary endpoint	CDP-3 CDP-6	Time to onset of disability progression as defined by sustained worsening in EDSS of ≥ 1 point confirmed after 3 and 6 months
	Secondary endpoint	MSFC (LCLA)	Change in MSFC z-score from baseline to month 24 (T25FW, 9HPT, PASAT, LCLA)
	Secondary endpoint	MSQOL-54	Change in MSQOL-54 score from baseline to month 24; physical and mental health summary scores.
	Secondary endpoint	BVL	% change in normalized brain volume (brain volume loss) on MRI from baseline to month 24
Database lock	12 May 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	ITT (randomised, received at least one dose of study drug) at month 24			
Descriptive statistics and estimate variability	Treatment group		IFN β-1a	Ozanimod 0.5	Ozanimod 1 mg
	Number of subjects		441	439	433
	Primary endpoint Adjusted-ARR (95% CI)		0.276 (0.234, 0.324)	0.218 (0.183, 0.259)	0.172 (0.142, 0.208)
	1st key secondary endpoint # T2 lesions (Adj. mean over 24 months) (95% CI)		6.357 (5.273, 7.665)	4.178 (3.477, 5.020)	3.665 (3.041, 4.416)
	2nd key secondary endpoint # GdE lesions (Adj. mean at 24 months) (95% CI)		0.373 (0.256, 0.543)	0.197 (0.131, 0.296)	0.176 (0.116, 0.266)
	3rd key secondary endpoint CDP-3M CDP-6M (number (%))		50 (11.3) 29 (6.6)	41 (9.3) 32 (7.3)	54 (12.5) 42 (9.7)
	3rd key secondary endpoint CDP-3M CDP-6M Pooled data (201B, 301) (number (%))		69 (7.8) 36 (4.0)	58 (6.5) 43 (4.8)	67 (7.6) 51 (5.8)
	Secondary endpoint MSFC (LCLA) mean (SD)		-0.052 (0.601)	0.036 (0.021)	-0.010 (0.622)
	Secondary endpoint MSQOL-54 -physical -mental mean (SD)		-1.526 (12.319) -1.831 (16.422)	0.609 (12.315) -1.182 (14.379)	0.209 (12.321) -1.517 (15.544)
	Secondary endpoint BVL mean (SD)		-0.937 (0.944)	-0.707 (0.746)	-0.707 (0.878)
Effect estimate per comparison	Primary endpoint Adj -ARR[1]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Rate Ratio (Oza/IFN)	0.791	0.623
		(95% CI)	(0.652, 0.958)	(0.506, 0.768)
		P-value	0.0167	<0.0001
	1st key secondary endpoint # T2 MRI lesions[2]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Rate Ratio (Oza/IFN)	0.657	0.576
		(95% CI)	(0.531, 0.813)	(0.465, 0.714)
		P-value	0.0001*	<0.0001*
	2nd key secondary endpoint # GdE MRI lesions[2]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Rate Ratio (Oza/IFN)	0.528	0.471
		(95% CI)	(0.346, 0.805)	(0.306, 0.725)
		P-value	0.0030*	0.0006*
	3rd key secondary endpoint CDP-3M[3]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Hazard Ratio(Oza/IFN)	0.798	1.045
		(95% CI)	(0.528, 1.206)	(0.711, 1.537)
		P-value	0.2849	0.8224
	3rd key secondary endpoint CDP-6M[3]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Hazard Ratio(Oza/IFN)	1.098	1.435
		(95% CI)	(0.664, 1.815)	(0.893, 2.305)
		P-value	0.7154	0.1353
	3rd key	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a

	secondary endpoint CDP-3M[3] Pooled data	Hazard Ratio(Oza/IFN)	0.822	0.950
		(95% CI)	(0.579, 1.165)	(0.679, 1.330)
		P-value	0.2698	0.7651
	3rd key secondary endpoint CDP-6M[3] Pooled data	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Hazard Ratio(Oza/IFN)	1.189	1.413
		(95% CI)	(0.763, 1.851)	(0.922, 2.165)
		P-value	0.4447	0.1126
	Secondary endpoint MSFC (LCLA)[4]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Difference in means	0.093	0.043
		(95% CI)	(0.020, 0.165)	(-0.030, 0.116)
		P-value	0.0123	0.2480
	Secondary endpoint MSQOL-54 -physical[4] -mental[4]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Difference in means	1.849 0.587	1.345 0.380
		(95% CI)	(0.258, 3.440) (-1.339, 2.513)	(-0.252, 2.943) (-1.553, 2.313)
		P-value	0.0228 0.5501	0.0988 0.6997
	Secondary endpoint BVL[4, 5]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Difference in means	0.224	0.244
		(95% CI)	(0.106, 0.342)	(0.125, 0.363)
		P-value	0.0002	<0.0001
Notes	All analyses based on ITT population [1]**Primary efficacy parameter**: ARR was analysed using a Poisson regression model adjusted for region (Eastern Europe vs. Rest of World), baseline age, and baseline number of GdE lesions, with natural log transformation of time on study as an offset term. Comparison of ARRs in each ozanimod groups to IFN at the alpha=0.025 level. [2]#T2/GdE lesions: Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs. Rest of the World), age at baseline, and baseline number of GdE lesions. The natural log transformation of the number of available MRI scans over 12 months is used as an offset term. [3]CDP-3M/6M: Based on the Cox proportional hazard model with factors for treatment group, adjusted for region (Eastern Europe vs. Rest of the World), age at Baseline, and Baseline EDSS score [4]Based on ANCOVA, adjusted for region (Eastern Europe vs. Rest of the World), EDSS category per IVRS, and the baseline score of interest (e.g. MSFC (LCLA) z-score). [5]Post-hoc analysis of BVL (due to non-normal distribution of data) using rank-ANCOVA (and observed values) was generally similar to pre-specified analysis (using ANCOVA, shown above) *Statistically significant according to the hierarchical statistical testing procedure.			

Table 19: Summary of efficacy for Study RPC01-301

Title: A Phase 3, Multi-Center, Randomized, Double-Blind, Double-Dummy, Active-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients		
Study identifier	RPC01-301	
Design	Multi-center, randomized, double-blind, double-dummy, active-controlled, parallel-group, fixed-dose	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12+ months not applicable ongoing (data cut-off: 30 Jun2018)
Hypothesis	Superiority	
Treatments groups	Ozanimod 1 mg	Ozanimod HCL 1 mg, capsule, oral, once daily, 12+ months after 1-week titration; n=447 randomised

	Ozanimod 0.5 mg		Ozanimod HCL 0.5 mg, capsule, oral, once daily, 12+ months after titration (4 days of lower dose); n=451 randomised
	IFN β-1a		IFN β-1a 30-µg, prefilled syringes IM weekly, 12+ months; n= 448 randomised
Endpoints and definitions	Primary endpoint	ARR	ARR at the end of 12 months during the study (based on confirmed protocol defined relapses)
	1st key secondary endpoint	# T2 MRI lesions	Number of new or enlarging hyperintense T2-weighted MRI lesions over 12 months
	2nd key secondary endpoint	# GdE MRI lesions	Number of GdE brain MRI lesions at Month 12
	3rd key secondary endpoint	CDP-3M CDP-6M	Time to onset of disability progression as defined by sustained worsening in EDSS of ≥ 1 point confirmed after 3 and 6 months
	Secondary endpoint	MSFC (LCLA)	Change in MSFC z-score from baseline to month 12 (T25FW, 9HPT, SDMT, LCLA)
	Secondary endpoint	MSQOL-54	Change in MSQOL-54 score from baseline to month 12: physical and mental health summary scores.
	Secondary endpoint	BVL	% change in normalized brain volume (brain volume loss) on MRI from baseline to month 12
Database lock	08 February 2017		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time	ITT (randomised, received at least one dose of study drug) at month 12			
Descriptive statistics and estimate variability	Treatment group		IFN β-1a	Ozanimod 0.5	Ozanimod 1 mg
	Number of subjects		448	451	447
	Primary endpoint Adjusted-ARR (95% CI)		0.350 (0.279, 0.440)	0.241 (0.188, 0.308)	0.181 (0.140, 0.236)
	1st key secondary endpoint # T2 MRI lesions (Adjusted mean over 12 months)		5.679 (4.667, 6.910)	4.267 (3.544, 5.137)	2.927 (2.403, 3.564)
	2nd key secondary endpoint # GdE lesions (Adj. mean at 24 months) (95% CI)		0.433 (0.295, 0.635)	0.287 (0.197, 0.418)	0.160 (0.106, 0.242)
	3rd key secondary endpoint CDP-3M CDP-6M (number (%))		19 (4.2) 7 (1.6)	17 (3.8) 11 (2.4)	13 (2.9) 9 (2.0)
	Secondary endpoint MSFC (LCLA) mean (SD)		-0.022 (0.334)	-0.007 (0.351)	0.003 (0.328)
	Secondary endpoint MSQOL-54 mean (SD) -physical -mental		0.046 (12.578) -0.123 (15.240)	1.414 (12.343) 0.283 (15.686)	1.925 (11.870) 0.260 (15.800)
	Secondary endpoint BVL Mean (SD)		-0.61 (0.686)	-0.49 (0.610)	-0.41 (0.640)
Effect estimate per comparison	Primary endpoint adj-ARR[1]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Rate Ratio (Oza/IFN)	0.688	0.518
		(95% CI)	(0.547, 0.864)	(0.405, 0.663)
		P-value*	0.0013	<0.0001
	1st key	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a

	secondary endpoint # T2 MRI lesions[2]	Rate Ratio (Oza/IFN)	0.754	0.517
		(95% CI)	(0.625, 0.910)	(0.427, 0.625)
		P-value	0.0032*	<0.0001*
	2nd key secondary endpoint # GdE MRI lesions[2]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Rate Ratio (Oz/IFN)	0.662	0.370
		(95% CI)	(0.471, 0.932)	(0.256, 0.536)
		P-value	0.0182*	<0.0001*
	3rd key secondary endpoint CDP-3M	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Hazard Ratio(Oza/IFN)	0.886	0.690
		(95% CI)	(0.460, 1.705)	(0.340, 1.402)
		P-value	0.7163	0.3055
	3rd key secondary endpoint CDP-6M	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Hazard Ratio(Oza/IFN)	1.535	1.238
		(95% CI)	(0.595, 3.963)	(0.460, 3.337)
		P-value	0.3755	0.6725
	Secondary endpoint MSFC (LCLA)[4]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Difference in means	0.015	0.034
		(95% CI)	(-0.028, 0.059)	(-0.010, 0.077)
		P-value	0.4942	0.1290
	Secondary endpoint MSQOL-54 -physical[4] -mental[4]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Difference in means	1.024 -0.170	1.642 0.356
		(95% CI)	(-0.510, 2.559) (-2.045, 1.705)	(0.104, 3.180) (-1.523, 2.234)
		P-value	0.1905 0.8587	0.0364 0.7104
	Secondary endpoint Whole brain volume change[5]	Comparison groups	Ozanimod 0.5 mg vs. IFN β-1a	Ozanimod 1 mg vs. IFN β-1a
		Difference in means	0.12	0.19
		(95% CI)	(0.03, 0.20)	(0.10, 0.28)
		P-value	0.0092	<0.0001
Notes	All analyses based on ITT population [1]**Primary efficacy parameter**: ARR was analysed using a Poisson regression model adjusted for region (Eastern Europe vs Rest of World), baseline age, and baseline number of GdE lesions, with natural log transformation of time on study as an offset term. Comparison of ARRs in each ozanimod groups to IFN β-1a at the alpha=0.025 level. [2]#T2/GdE lesions: Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs. Rest of the World), age at baseline, and baseline number of GdE lesions. The natural log transformation of the number of available MRI scans over 12 months is used as an offset term. [3]CDP-3M/6M: Based on the Cox proportional hazard model with factors for treatment group, adjusted for region (Eastern Europe vs Rest of the World), age at Baseline, and Baseline EDSS score [4]Based on ANCOVA, adjusted for region (Eastern Europe vs. Rest of the World), EDSS category per IVRS, and the Baseline MSFC score. [5]Post-hoc analysis of BVL (due to non-normal distribution of data) using rank-ANCOVA (and observed values) was generally similar to pre-specified analysis (using ANCOVA, shown above), however, difference of Ozanimod 5 mg vs. IFN β-1a did not reach nominal statistical significance. *Statistically significant according to the hierarchical statistical testing procedure.			

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

Please see main studies. Major analysis has been performed across trials (pooled analysis).

Clinical studies in special populations

Not available. Patients above 55 years have not been included in efficacy trials.

Supportive study

RPC01-1001: A Phase 1, Multicentre, Randomized, 12-Week, Open-label Study to Evaluate the Multiple-dose Pharmacokinetics and Pharmacodynamics of RPC1063 in Patients with RMS.

Study objectives

The primary objective was to characterize the PK of ozanimod following multiple-dose administration in subjects with RMS.
The secondary objectives were: (1) to characterize the PD of ozanimod following multiple-dose administration in subjects with RMS; (2) to describe the relationship between PK and PD for ozanimod in subjects with RMS; and (3) to characterize the safety of ozanimod in subjects with RMS.
The exploratory objective was to explore additional biomarkers of ozanimod in subjects with RMS.

Study population, disposition and baseline features

Twenty-two subjects completed the study. Two subjects in Group 1 (0.5mg) discontinued from the study early; 1 withdrew and 1 rolled over into the OLE Study RPC01-3001.

Overall, demographics and baseline characteristics were similar between the 2 groups [group 1 (0.5mg) and group 2 (1mg)] (mean age of approximately 39, mean body weight of approximately 87 kg; 71% female; and 75% white).

Summary of main results:

Pharmacokinetic Results:
Median T_{max} of ozanimod, RP101988, and RP101075 was approximately 6 to 8 hours. Individual RP112273 T_{max} values were highly variable, ranging from approximately 0 to 24 hours and median RP112273 T_{max} values also varied between doses and dosing days, ranging from approximately 6 to 10 hours although a high proportion of the Tmax values occurred at the 24-hour assessment time. The PK sampling schedule in this study may not have been optimal to characterize RP112273 T_{max} (e.g., no PK samples were collected between 10 and 24 hours postdose).
The intersubject variabilities (CV%) for $C_{max,ss}$ and $AUC_{tau,ss}$ on Day 85 ranged from approximately 29% to 45% for ozanimod, RP101988, and RP101075. The CV% for RP112273 $C_{max,ss}$ and $AUC_{tau,ss}$ on Day 85 ranged from approximately 40% to 63%.
On Day 85, the M/P $AUC_{tau,ss}$ ratios for RP112273, RP101988, and RP101075 were approximately 23- to 39-fold, 1.2- to 1.4-fold, and 0.14- to 0.18-fold, respectively.
On Day 85, ozanimod, RP112273, RP101988, and RP101075 accounted for approximately 3% to 6%, 85% to 93%, 4% to 8%, and 0.5% to 0.8%, respectively, of the total agonist exposure. RP112273 is therefore the predominant active metabolite of ozanimod.
The mean $t_{1/2}$ values for ozanimod, RP101988, and RP101075 were approximately 17 to 25 hours. The mean $T_{1/2}$ for RP112273 was approximately 236 to 308 hours (ie, approximately 10 to 13 days). The PK sampling schedule in this study may not have been optimal to characterize RP112273 $T_{1/2}$ (i.e., not collected long enough after the last dose to adequately characterize the terminal phase).
Steady-state concentrations for ozanimod, RP101988, and RP101075 were reached by Day 28 of dosing, which was consistent with the observed $t_{1/2}$ values. RP112273 concentrations appeared to reach steady state between Days 28 and 85. The PK sampling schedule (i.e., Trough samples) in this study may not have been adequate to discern steady state for RP112273 (ie, no samples between Days 28, 56, and 85).

Plasma concentrations of the minor metabolite, RP101442, were not measurable in most subjects.

Pharmacodynamic results:
During dose escalation, the mean (SD) percent change from baseline in ALC on Days 5 and 8 were similar between dose groups. Following dose escalation, dose-dependent reductions in ALC were observed. ALC continued to decrease up to Day 56. The mean reductions in ALC from baseline were similar between Days 56 and 85, indicating a nadir or plateau effect was reached by Day 56 for both groups. The mean reductions in ALC from baseline at nadir were approximately 50% and 70% for the 0.5 and 1 mg dose groups, respectively. Additionally, a mean ALC reduction expected to demonstrate a therapeutic effect was reached earlier (as early as Day 28) with the 1 mg dose than with the 0.5 mg dose. Following the last dose, subject ALC data were highly variable; therefore, the recovery phase of ALC postdose could not be adequately characterized.

Clinical results

There were no changes from baseline in EDSS score results.

Safety results:

No deaths, SAEs, discontinuations due to AEs were reported.
Six subjects (46.2%) in Group 1 and 10 subjects (90.9%) in Group 2 experienced at least 1 TEAE. The TEAEs that occurred in 2 or more subjects overall included headache, pain in extremity, anxiety, diarrhoea, seasonal allergy, urinary tract infection, and vitamin D decreased. All but 1 of the TEAEs were mild or moderate in severity. One subject in Group 2 had 1 severe TEAE of pain (verbatim term: body aches) considered by the investigator to be unlikely related to ozanimod. All but 1 of the TEAEs were considered by the investigator to be not related or unlikely related to ozanimod. One subject in Group 2 (1 mg) had 1 mild TEAE of ECG T wave amplitude decreased (verbatim term: flattened T waves) considered by the investigator to be possibly related to ozanimod.
No clinically meaningful trends or changes from baseline in laboratory tests, vital signs, ECGs (specifically no QTcF prolongation or second-degree AV block), or Columbia Suicide Severity Rating Scale were observed. No clinically meaningful differences in HR (observed and change from predose) observed during dose escalation days.

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical effects of ozanimod in subjects with RMS were studied in 2 Phase 3, randomized, double blind, double-dummy, active-controlled, multi-center studies (Study RPC01-201B and Study RPC01-301) with similar design and efficacy endpoints, but different timepoint for efficacy assessment: 24 months on Study RPC01-201B and at least 12 months on Study RPC01-301.

There were protocol amendments to the pivotal Study RPC01-201B involving the reordering of secondary endpoints and revisions to the hierarchical testing procedure. The Applicant's position that amendments did not have repercussion neither on data acquisition nor on study results and discussion was agreed by CHMP. Available reports of investigator site inspections including one EMA GCP inspection did not identify critical findings and the major protocol deviations identified did not apparently have an impact on patient's health or study results.

The comparator (IFN β-1a 30-µg IM) is probably the less efficacious and is also difficult to tolerate. Notwithstanding, most DMT trials used it as an active comparator, as therefore, it was considered acceptable.

The duration of the pivotal studies was considered rather short, in order to be able to demonstrate a beneficial effect regarding CDP in RRMS against an active comparator. This had already been commented in the centralised SA, however, only duration of Study RPC01-301 had been (slightly) increased to at least 12 months via global study amendment 1 (dated 26 Aug 2014). The relatively short study duration of the studies could have had a significant impact on endpoints strongly related to time such as CDP-3M and more importantly, CDP-6M. In Study RPC01-301, only patients who experienced a severe relapse without complete recovery (tentative disability progression) within the first 6 months would show CDP-6M by the end of the trial at 12 months. Considering the latency of therapeutic response and duration of studies, a very low rate of progressors was expected in the pivotal studies. This may have been reflected on the variability of CDP-3M among the 3 treatment arms and lack of a dose-effect on this measure.

The patient population is representative of an adult population with RRMS as the majority of subjects were female (66.8% of subjects) and white (98.9% of subjects), with a mean age of 35.5 (range 18 to 55 years) and diagnosed with RRMS (98%). It should be noted neither paediatric nor elderly (>55 years) population were represented in these studies according to the eligibility criteria. Both pivotal studies were conducted in approximately 150 recruiting study centres and the provided unadjusted ARR per study centres and study group, respectively did not indicate, that the overall results of the pivotal studies have been substantially influenced by single study centres. The selection of the study centres, favouring Eastern Europe, yielded a very high proportion of treatment naïve patients (over 70%), for a population with a mean 6 years of disease duration and active disease (99% had at least one relapse in the 12 months prior the study and approximately half of the population had GdE baseline lesions). This could have negatively impacted extrapolability of B/R towards an EU population. In fact, subgroup analysis by region was recommended in the centralised SA (EMEA/H/SA/2779/1/2014/SME/III) in order to assess the extrapolation of the overall results to the EU population. Upon request, the Applicant further explored B/R in subgroups of EU and non-EU population. Interestingly, more than expected EU patients were treatment naïve, which may be explained by the EU countries who participated in the study and their treatment policies. More importantly, differences between EU and non-EU population did not modify the B/R balance from the response as compared between IFN β-1a and ozanimod. The differences may rather reflect the enrolment strategy, easiness of enrolment in some countries (both EU and non-EU) and communication of adverse events to the study team rather than significant differences in disease epidemiology.

Regarding baseline disease activity, it should be noted that the included patient population had a rather low disease activity with regard to number of relapses prior to inclusion in the study (mean number of 1.3 in the past year in both studies, mean number of 1.7 (Study RPC01-301) and 1.8 (in Study RPC01-201B), respectively in the past two years). It is however noted that the proportion of subjects with high disease activity as measured by combined relapse and MRI criteria (as specified for subgroup analyses of the pooled phase 3 study data) appeared not to be lower in the ozanimod trials compared to trials with other S1P receptor modulators (approx. 23% and 18%, respectively). This latter comparison should be interpreted with caution, as there are no uniform definitions of high disease activity, and definitions varied across trials of different drugs. Disability progression in patients with RRMS is mainly due to lack of complete recovery from severe relapses. In this extend, the level of baseline inflammatory activity plays a key role on the probability of CDP as an event.

The study was analysed using a mITT approach (all randomized who received at least one dose of treatment). Compliance of the study was appropriate as the number of subjects excluded from the PP population due to major protocol violations was very low (<1%) in both studies. Across two pivotal phase 3 trials, 11 patients' cases of erroneously dispensed study drug kits occurred at single visits and that no more than one case occurred in any study centre. These cases were not expected to influence the overall efficacy results of both studies to a relevant extent as cases were well distributed across study groups

and because of the relatively short duration (<1 month) of incorrect IMP intake in all except for two cases compared to overall study duration. Additionally, three subjects administered IFN β-1a active drug potentially subcutaneously at the beginning of Study RPC01-201B due to wrong needle size, The Applicant provided sensitivity analyses excluding these three subjects who received potentially ineffective IFN β-1a treatment and the results were consistent to the mITT and PP analyses including these subjects, when either the primary analysis or the negative binomial model was used.

The Applicant pre-specified Poisson Regression as main analyses for ARR while Negative Binomial Model was preferred by CHMP to deal with overdispersion. These analyses were provided as sensitivity analysis and the results were used to decide which key secondary endpoints should be tested for claiming statistical significance in the hierarchical algorithm. Similarly, the CHMP requested the Applicant to provide sensitivity analyses using methods other than LOCF to better deal with missing data including J2R and CR imputation approaches

For evaluation of the primary endpoint, confirmation of relapses was based on EDSS (the standard assessment scale to evaluate disability in MS), EDSS was further used for confirmation of disease progression. For evaluation of further secondary endpoints, standard as well as exploratory brain MRI parameters, MSQOL-54 as disease specific Quality of life instrument as well as the MSFC as additional measurement of disability were used. While the MSFC originally consists of three components (T25FW, 9HPT and PASAT), the original cognitive component PASAT was replaced by SDMT in Study RPC01-301. Further, LCLA has been added as 4th component to the MSFC in both studies in order to include an evaluation for visual disfunction. The use of these scales as single variable or in combination as secondary endpoints were accepted. However, while the SDMT is a valid measure of processing speed, the correlation between Cognitive Functioning and SDMT score was weak to modest based on the Voice of Patient Study included in for Qualification Advice of Multiple sclerosis clinical outcome assessment (MSCOA) (EMA/CHMP/SAWP/336445/2019).

The definition of a confirmed relapse (including the extent of EDSS worsening required) as well as the definition of confirmed disability progression (sustained EDSS worsening ≥ 1 point, confirmed after 3 months (CDP-3M) and after 6 months (CDP-6M) was largely in line with that applied in other trials in RMS. The primary efficacy endpoint (ARR) as well as the secondary endpoints were generally endorsed. However, the ARR as a relapse-based primary endpoint cannot be taken as a surrogate for disability progression. As the primary endpoint was based on relapse assessment, in line with the Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2), progression of disability was evaluated as key secondary endpoint, though only as 3rd among the rank ordered key secondary endpoints which were tested in a hierarchical procedure. In the centralized SA (EMEA/H/SA/2779/1/2014/SME/III), it was commented that ordering of the secondary endpoints may be questioned as disability should be the most important secondary endpoint. However, the finally positive results of the 1st and 2nd key secondary endpoints did not influence the statistical evaluation of the progression of disability.

As flu-like symptoms occur very commonly with IFN β-1a, in particular at the beginning of treatment, respective symptoms could have led to de-blinding of the study treatment. Prophylactic treatment with anti-inflammatory substances or the analgesic/antipyretic acetaminophen before and up to 24 hours after every (IFN β-1a or matching placebo) injection, was therefore generally been recommended. Anti-inflammatory substances and analgesics were used in a higher proportion of IFN β-1a vs. ozanimod subjects in both studies. It remained unclear, however, how many subjects used these substances as prophylactic or as treatment of flu-like symptoms and over which period of time. In safety pool A1 (comprising the active controlled phase 3 RMS studies), influenza like illness further occurred in 49.9% of IFN β-1a but only in approx. 5% of subjects across both ozanimod dose groups. In order to prevent potential de-blinding as a result of the different adverse event profiles or laboratory changes of the study treatments, a dual assessor approach was used in both studies which was presented and further clarified

by the Applicant during the procedure. According to the Applicant, the prespecified procedures for maintaining the blind and the consistency of the relapse confirmation rate (>90%) by the treating investigator across treatment groups provided evidence for there being minimal bias in subjects' reporting of relapses and in treating investigators' confirmation of relapses, and therefore in the determination of ARR. Although, the CHMP considered unfortunate that the treating physician made the final decision as to whether an event represented a protocol-defined (confirmed) relapse, the CHMP acknowledged the position of the Applicant. Additionally, it was considered that a potential bias by de-blinding of the treating physician was still limited based on the following arguments: treating physicians were guided by a template questionnaire in determining whether an unscheduled relapse assessment (including blinded EDSS evaluation) was to be scheduled when they were informed by the patients of onset of a possible relapse and confirmation of a relapse required a pre-specified worsening in EDSS score as evaluated by the independent (blinded) efficacy investigator. Additionally, the provided a principal strata analysis for the stratum of subjects that would obtain flu-like symptoms under IFN β-1a and those who would not obtain flu-like symptoms under IFN β-1a, as well as the corresponding analyses regarding the flu-like symptoms obtained under Ozanimod. Although in both, the Flu IFN β-1a stratum as well as the no flu IFN β-1a stratum a reasonable treatment effect was seen, the difference in the treatment effect (ARR) size between subjects that were potentially unblinded and those who were not was approximately 10 %, suggesting an increase from a 37% reduction to a reported 47% reduction in the effect due to potential unblinding. Nevertheless, the CHMP agreed the difference between both strata may be due to unblinding but may also be due the different populations. Additionally, the effect of 37% could still be considered clinically relevant and statistically robust. Finally, some further reassurance was considered to be provided by the results of the MRI-derived key secondary endpoints, which were largely in line with the ARR results, as MRIs were read centrally blinded, i.e. by further independent blinded readers which were also locally separated from other treating/efficacy investigators. Overall, it was agreed that although the influence of unblinding and that of a different population could not be disentangled, the real effect might have been smaller without the effect of potential unblinding.

Efficacy data and additional analyses

A total of 2,659 subjects were included in the mITT population: 1,313 subjects in Study RPC01-201B and 1,346 subjects in Study RPC01-301. In these studies, 86.7% and 93.2% of subjects completed Study RPC01-201B and Study RPC01-301, respectively. These retention rates were considered acceptable.

Superior efficacy for ozanimod 1 mg and 0.5 mg in clinical and MRI measures of MS disease activity was demonstrated in each controlled Phase 3 clinical study relative to the active comparator, IFN β-1a 30-µg IM. A more evident treatment effect was observed with ozanimod 1 mg compared to ozanimod 0.5 mg. The key results from the controlled Phase 3 ozanimod clinical studies which were used to qualify results in section 5.1 of SmPC were:

- The primary endpoint (ARR) was met for both ozanimod doses versus IFN β-1a in each study based on a prespecified analysis. This corresponded to a 48.2% and 37.7% reduction with ozanimod 1 mg and a 31.2% and 20.9% reduction with ozanimod 0.5 mg, relative to IFN β-1a in the 12+ Month Study RPC01-301 and 24 Month Study RPC01-201B, respectively. Consistent treatment effects were observed across most sensitivity analyses including J2R and CR approaches for dealing with missing data. Considering negative binomial regression as preferred model for ARR analysis, Ozanimod 0.5mg did not meet primary endpoint in Study RPC01-201B.
- The first key secondary endpoint, mean number of new/enlarging T2 brain lesions over 12 and 24 months, was met for 1mg ozanimod dose versus IFN β-1a in both pivotal studies. The relative reductions in the number of new or enlarging hyperintense T2-weighted brain MRI lesions in the

ozanimod 1 mg and ozanimod 0.5 mg treatment groups were 48.3% and 24.6%, respectively, over 12+ Month Study RPC01-301 and 42.4% and 34.3%, respectively, over 24 Month Study RPC01-201B. Consistent treatment effects were observed across several sensitivity analyses including J2R and CR approaches for missing data. Considering negative binomial model, ozanimod 0.5mg did not meet primary endpoint therefore, p-values could only be considered as nominally significant for this key secondary endpoint in Study RPC01-201B.

- The second key secondary endpoint, mean number of GdE T1 brain lesions at months 12 and 24, was met for both 1mg ozanimod dose versus IFN β-1a in both pivotal studies. The relative reduction in number of GdE T1 brain MRI lesions in the ozanimod 1 mg and ozanimod 0.5 mg treatment groups compared to IFN β-1a were 63.0% and 33.8%, respectively, at 12+ Month Study RPC01-301 and 52.9% and 47.2%, respectively, at 24 Month Study RPC01-201B. Consistent treatment effects were observed across most sensitivity analyses including J2R and CR approaches for missing data. Considering negative binomial model, ozanimod 0.5mg did not meet primary endpoint therefore, p-values could only be considered as nominally significant for this key secondary endpoint in Study RPC01-201B.
- In subgroup analyses of ARR, the number of new or enlarging hyperintense T2-weighted brain MRI lesions, and the total number of GdE T1 brain MRI lesions, a treatment effect in favour of ozanimod 1 mg versus IFN β-1a was observed across all subgroups analysed. Of particular relevance was the finding of treatment effect in favour of ozanimod 1mg versus INF IFN β-1a observed for patients with and without highly active RMS.
- A low and similar percentage of subjects experienced disability progression in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups, with CDP-3M percentages progressed of 7.6%, 6.5%, and 7.8%, respectively, and CDP-6M percentages progressed of 5.8%, 4.8%, and 4.0%, respectively. In the prespecified pooled analysis, the risk of CDP-3M with both ozanimod 1 mg and 0.5 mg were similar to IFN β-1a (HR of 0.950 and 0.822, respectively). Regarding CDP-6M, the HRs versus IFN β-1a were 1.413 for 1 mg ozanimod and of 1.189 for ozanimod 0.5 mg

The magnitude of effect for the primary endpoint (ARR) and MRI key secondary endpoints was clinically relevant. During the treatment period for Study RPC01-301, compared with IFN β-1a, both doses of ozanimod led to a statistically significant reduction in ARR of 48.2% for the 1 mg dose ($p<0.0001$) and 31.2% for the 0.5 mg ($p=0.0013$). A greater relative reduction was observed with the ozanimod 1 mg dose and results from PP and pre-specified sensitivity analyses were highly consistent with primary analyses. Through the end of Month 24 for Study RPC01-201B, a dose response was also seen. However, considering the negative binomial model as the appropriate analysis to account for overdispersion, the 0.5 mg dose did not show a significant effect for the primary endpoint in Study RPC01-201B ($p=0.0593$) as nominally statistically significant differences to IFN β-1a for the 0.5mg dose were only reached in the analyses using the Poisson regression model (including PP analyses). Nevertheless, results of the PP analyses as well as results of several pre-specified sensitivity analyses of the primary endpoint (using the negative binomial regression model instead of the Poisson regression model of the primary analysis and evaluating only confirmed relapses, or confirmed and unconfirmed relapses for both models) were highly consistent with those of the primary analysis in the respective pivotal studies for the proposed 1mg ozanimod daily dose. The Applicant provided additional analyses using a treatment policy strategy for the intercurrent event treatment discontinuation based on the assumption of the absence of a treatment effect after treatment discontinuation. Moreover, the Applicant provided *post hoc* sensitivity analyses using J2R and CR approaches for multiple imputation analyses for dealing with missing data. The results were consistent and supported the primary pre-planned analysis.

Regarding the number of new/enlarging T2 brain lesions, there was a 42.4% (34.3%) reduction after 24 months (Study RPC01-201B) and to a 48.3% (24.6%) reduction after 12 months of treatment (Study

RPC01-301) for the 1 mg (0.5 mg) ozanimod dose compared to INF β-1a. The corresponding reductions for GdE brain lesions were 63.0% (33.8%) reduction after 24 months (Study RPC01-201B) and to a 52.9% (47.2%) reduction after 12 months of treatment (Study RPC01-301). Sensitivity analyses for these endpoints also consistently showed nominally significant differences, respectively. However, according to the pre-specified hierarchical multiplicity procedure and considering appropriate negative binomial model for the primary endpoint, key secondary endpoints could only be considered statistically significant for the 1mg dose in Study RPC01-201B. Results from multiple imputation analyses using J2R and CR were largely in line with pre-planned analyses.

With regard to the 3rd key secondary endpoint, disability progression confirmed after 3 and after 6 months (CDP-3M, CDP-6M), no statistically significant differences between ozanimod and IFN β-1a could be shown. HR vs. IFN β-1a derived from the primary analysis of CDP-3M of 0.950 for 1 mg ozanimod and of 0.822 for ozanimod 0.5 mg corresponded to a numerical 5.0% and 17.8% relative risk reduction, however differences to IFN β-1a were not statistically significant (1 mg ozanimod: p=0.7651, 0.5 mg ozanimod: p=0.2698). Several pre-specified sensitivity analyses consistently favoured ozanimod over IFN β-1a regarding CDP-3M (at least numerically).

Regarding CDP-6M the HRs of 1.413 for 1 mg ozanimod and of 1.189 for ozanimod 0.5 mg corresponded to a numerical relative risk increase for CDP-6M of 41.3% and 18.9% compared to IFN β-1a. These latter findings might raise concerns of an increased risk of CDP with ozanimod vs. IFN β-1a. However, the respective comparisons of CDP-6M were not statistically significant (1 mg ozanimod: p=0.1126, 0.5 mg ozanimod: p=0.4447). Similarly, some sensitivity analyses favoured ozanimod over IFN β-1a (at least numerically) some analyses favoured IFN β-1a, however, none of the comparisons that favoured IFN β-1a were nominally significant. These results were indeed based on very low event rates (with proportions of subjects with CDP-3M and CDP-6M across all study groups equal to 7.3% and 4.9%, respectively compared to the 12-24% for CDP-3M that had been assumed based on historical data). The short duration was also considered a limitation as discussed above. In this regard, results from a post-hoc sensitivity analyses including visits of the OLE Study RPC01-3001 to confirm the event as performed in ocrelizumab pivotal studies (EPAR Ocrevus EMA/790835/2017) showing very similar risks for CDP-6M in the 1 mg ozanimod group compared to IFN β-1a was considered reassuring. Additionally, the Applicant presented absolute differences between the ozanimod 1 mg and IFN β-1a KM estimates for CDP-6M. The Applicant's position that absolute differences between estimated probabilities may better reflect clinically meaningful differences than estimated hazard ratios in settings with low event rates was acknowledged by CHMP. According to this analysis, no statistically significant difference for CDP-6M outcomes was found between both treatment groups, while an approx. 4% higher CDP-6M rate after 2 years could not be excluded as derived from the lower limit of the 95% CI of survival rates. However, the Applicant has additionally provided a Bayesian analysis, which estimated the probability of a 4% (or greater) difference in CDP-6M to be low (5.4%), further formal testing to evaluate a true difference of at least 4% yielded a p-value of 0.948. Moreover, the Applicant argued that the point estimate of the analysis would commonly be used to evaluate the clinical relevance of a finding, and the respective (not statistically significant) difference of 1.8 % between ozanimod 1 mg and IFN β-1a was within the sampling variability based on the 95% CIs. Taking the totality of provided analyses of CDP-3M and CDP-6M data and arguments into consideration, no clear differences between ozanimod 1 mg and IFN β-1a could be shown with regard to disease progression.

Finally, considering the knowledge about the mechanism of action (S1P modulator) of the molecule in MS and that ozanimod 1 mg consistently showed higher effectiveness regarding focal inflammatory activity (relapses and T2 and GdE lesions) in comparison to IFN β-1a, an increased risk of CDP of ozanimod compared to IFN β-1a could be reasonably excluded.

In both pivotal studies, brain volume change from baseline to month 24 (Study RPC01-201B) and to month 12 (Study RPC01-301), respectively was lower in both ozanimod groups compared to IFN β-1a.

For the 1mg dose group in both studies, the pre-specified ANCOVA (with LOCF) as well as the rank-ANCOVA (with observed cases) model, which was performed post-hoc due to non-normal data distribution, were nominally statistically significant; the respective differences in mean % change resulting from the pre-specified analysis roughly correspond to a relative treatment difference of brain volume change of 25% after 2 years (Study RPC01-201B), and to a relative reduction of 33% after 1 year with 1 mg ozanimod compared to IFN β-1a. As analysis of brain volume change refers to a relative change with potentially skewed data due to a standard deviation of the original data that may be proportional to the mean, a sensitivity analysis based on log-transformed and back transformed normalised brain volume data was requested to the Applicant. Considering the bulk of data that supports the importance of brain volume change in MS, these results were considered to be relevant. However, it is currently not established, how effects on brain volume change translate into clinical effects (e.g. whether the same magnitude of brain volume change reductions translates into similar clinical effects over the MS course). Therefore, brain volume change cannot serve as a surrogate marker for disability and cannot justify a claim on disability progression without a clear and convincing effect on a clinical scale evaluating disease progression.

In both individual pivotal studies, results of the pre-specified subgroup analyses of the primary endpoint were generally consistent with the overall results for the 1 mg subgroup vs. INF β-1a (all resulting ARR ratios favoured 1 mg ozanimod over IFNβ-1a, and for most subgroups, the upper limit of the 95% CI was below 1). Similarly, in the subgroup analyses of the pooled pivotal studies, in which additional subgroups, e.g. based on disease activity were investigated, a consistent treatment effect was found with regard to 1 mg ozanimod vs. IFN β-1a. All pooled subgroup analyses were indicative of nominally statistical significance, except for the small number of treatment naïve subjects (i.e. subjects without any previous MS treatment including corticosteroids). It is of particular interest, that a treatment effect was found regardless of absence/presence of highly active disease, number of relapses in the prior one and two years, respectively, absent/present GdE lesions, number of T2 lesions, EDSS score at baseline, or prior DMT use status at baseline. Additional sensitivity subgroup analyses (of the individual as well as the pooled phase 3 studies) based on a negative binomial model with and without using a J2R approach for treatment discontinuation produced rather consistent results. Larger differences were obtained in the subgroup of patients without prior MS treatment in Study RPC01-201B. However, this subgroup was relatively small, appears less relevant and the pooled analysis provided a reasonable effect even in this group.

Subjects with prior S1P modulator treatment have been excluded from the pivotal trials, which was endorsed, as both substances in principle share the same mechanism of action. However, subjects with prior IFN treatment (including the active comparator IFN β-1a Avonex®) were allowed for inclusion in the pivotal studies, and approx. 10% of subjects in the pivotal studies had prior IFN β-1a. Additionally provided subgroup analysis for subjects with/without prior IFN β-1a treatment revealed a statistically significant difference between both subgroups in favour of subjects with prior IFN β-1a treatment (heterogeneity p-value: 0.0261 using the negative binomial model and 0.0112 using the Poisson model).

The consideration that blinding may not have been satisfactorily maintained in subjects with prior IFN β-1a treatment, as these subjects were familiar with the typical adverse events of Avonex, in particular flu-like symptoms, and/or that subjects with prior IFN β-1a, who were eligible for the pivotal studies, benefitted insufficiently from IFN β-1a treatment may provide a possible explanation for this difference. To address the CHMP's concern that blinding may not have been satisfactorily maintained in subjects with prior IFN β-1a treatment, the Applicant conducted principal strata analyses within the subset of subjects with prior IFN β-1a use that resulted in a large reduction in ARR in the 1 mg ozanimod compared to IFN β-1a group in the No-flu-stratum (strata of subjects who would not obtain flu-like symptoms while treated with IFN β-1a). Considering the following arguments: i) subjects with prior IFN β-1a treatment will be included in the target population, ii) the subgroup of patients with prior IFN β-1a treatment was

small (approx. 10 % of the overall mITT population) and iii) the small differences in the treatment effect between the overall mITT analysis and the analysis of the subgroup without prior IFN β-1a (approx. -42% and -39% reduction in ARR ratio in the 1 mg ozanimod vs. IFN β-1a groups), the CHMP agreed that the treatment effect of ozanimod could be appropriately estimated from the overall mITT population. Consequently, there was no need for specifying treatment effects for the subgroups with and without prior IFN β-1a treatment separately in section 5.1 of the SmPC.

The weight of the evidence from the efficacy endpoints suggested a more favourable benefit profile with ozanimod 1 mg, compared with the ozanimod 0.5 mg, as the overall magnitude of effect and consistency of response was greater with the 1 mg dose as compared to the 0.5 mg dose at Month 12 and Month 24 for relapses and MRI markers of focal inflammatory activity.

The maintenance of therapeutic response was assessed in the OLE Study RPC01-3001 (for which both pivotal studies, Study RPC01-201A Extension as well as phase I Study RPC 01-1001 served as parent studies; as of cut-off date of 30 June 2018). Although the informational value of OLE studies with regard to efficacy was naturally limited, results of ongoing OLE Study RPC01-3001 could be considered indicative of maintenance of effect of ozanimod 1mg with regard to relapses as ARR (adjusted and unadjusted) in the subgroup of subjects, who were already treated with ozanimod 1 mg in the parental studies, appeared stable and even tended to slightly improve (unadjusted ARR of 0.164 during OLE compared to 0.174 in parent study, and adjusted ARR of 0.133 during OLE compared to 0.153 during main part) and analyses of ARR on a yearly basis appeared to support these findings. Results in the T2 and GdE brain lesions were also maintained in subjects who remained on ozanimod 1 mg. Overall drop-out rate (6.9%) as well as drop-out due to lack of efficacy (1.0%) were low during OLE. However, whereas 760 subjects were constantly treated with 1 mg ozanimod though parent and OLE study, of which 398 were at least treated for 3 years, the number of subjects treated for at least 4 years was low as of data cut-off for MAA (30 Jun 2018) (n=44). Thus, efficacy results for longer than 3-year ozanimod exposure should be interpreted with particular caution.

While the proportion of subjects with CDP-3M or CDP-6M continued to be low during OLE Study RPC01-3001, results on CDP in these studies were difficult to interpret and these estimates would benefit from a longer follow-up. As stated in the CHMP MS guideline (EMA/CHMP/771815/2011, Rev. 2, Section 5.1 - Treatments intended to modify the natural course of the disease), it is "*highly desirable to evaluate whether the effect on progression is maintained on a long-term basis for DMT. As, in general, the course of multiple sclerosis with respect to disability is slow, this may need years of follow-up, e.g. 5 years or even longer. However, these data might be generated post-approval*." In this regard, The Applicant communicated that the final study results after all subjects will have been exposed to 1 mg ozanimod for a minimum of 5 years are scheduled to be available in 2022.

2.6.4. Conclusions on the clinical efficacy

The efficacy of ozanimod in subjects with relapsing remitting MS has been demonstrated with the presented primary and MRI secondary endpoints. Notwithstanding, efficacy regarding disability progression has not been shown. Therefore, the indication should not include MS forms evolving to SPMS with relapses.

2.7. Clinical safety

Patient exposure

The overall safety evaluation plan assesses the data obtained from a total of 23 clinical studies of ozanimod across all indications, including 7 Phase 2 and 3 studies and 16 clinical pharmacology studies. Ongoing blinded studies are not included in the safety analyses.

Clinical Pharmacology Studies

A total of 16 clinical pharmacology studies have been completed. Of these, 14 studies were completed before the data cut-off date of 30 Jun 2018:

- 1 was a single ascending dose and multiple ascending dose study in healthy subjects that evaluated the safety, tolerability, PK and PD.
- 5 were single-dose studies in healthy subjects that evaluated the food effect, mass balance, and DDIs with itraconazole/rifampin, cyclosporine, propranolol/diltiazem.
- 2 were single-dose studies that evaluated the effect of hepatic impairment or end stage renal failure on PK.
- 4 were multiple-dose studies in healthy subjects that evaluated the effect on the QT interval corrected for HR (ie, thorough QTc), DDI with oral contraceptives, and the effect of race (Japanese vs. Caucasian) on PK/PD (2 studies).
- 1 was a multiple-dose study in healthy subjects that evaluated the cardiac effects of ozanimod re-initiation after different drug washout intervals.
- 1 was a multiple-dose study in RMS patients that evaluated PK and PD.

Two additional studies conducted in healthy volunteers were initiated after the data cut-off date:

- 1 was a single-dose study to evaluate PK and drug interaction with modulators of the cytochrome P450 (CYP) 2C8 and/or 3A.
- 1 was a multiple-dose study to evaluate the effect of ozanimod on systolic blood pressure (SBP) following a single dose of pseudoephedrine.

The safety data from these 2 studies were not included in the pooled analyses.

Phase 2 and 3 Studies

Seven Phase 2 and 3 studies were included in the safety analysis plan: 4 in RMS, 2 in UC, and 1 in CD (**Table 20**).

Table 20: Description of Phase 2 and Phase 3 Studies of Ozanimod in RMS and IBD Indications

Protocol Number (Short Name)	No. of Centers[a]	Study Dates (Start–Completion)[b]	No. of Subjects: Randomized / Completed / Discontinued	Population / Design / Control	Route and Regimen	Subject Demographics: Sex Mean Age Race	Primary Endpoint
RMS Phase 2 Study							
RPC01-201A	55	Placebo-controlled period 18 Oct 2012 – 13 Apr 2014 Blinded extension 01 May 2013 – 11 May 2016	Placebo-controlled period 258 randomized 252 completed 6 discontinued Blinded extension 249 randomized 223 completed 26 discontinued	Male or female subjects aged 18 to 55 years, inclusive, with MS as diagnosed by the revised 2010 McDonald criteria[c]. Patients must be exhibiting a relapsing clinical course consistent with RMS and have a history of brain MRI lesions consistent with MS. Placebo-controlled period: randomized, double-blind, placebo-controlled, parallel-group study Optional blinded extension: randomized, double-blind, parallel-group study	Once daily oral dosing with ozanimod 1 mg, ozanimod 0.5 mg, or placebo for 24 weeks. A 7-day dose escalation was used for ozanimod. In the extension period, subjects assigned to either ozanimod treatment group in the placebo-controlled period continued at the same dose. Subjects assigned to placebo in the placebo-controlled period were randomized 1:1 to ozanimod 1 mg or ozanimod 0.5 mg.	Sex: Male: 77 (29.8%) Female: 181 (70.2%) Age (yrs): Mean (SD): 38.5 (9.19) Min, Max: 19, 55 Race: White: 254 (98.4%) Black: 3 (1.2%) Asian: 1 (0.4%) Other: 0	Total number of GdE lesions from Week 12 to Week 24
Phase 3 RMS Studies							
RPC01-201B	150	03 Dec 2013 – 13 Apr 2017	1320 randomized (1313 dosed) 1138 completed 175 discontinued	Male or female subjects aged 18 to 55 years, inclusive, with MS as diagnosed by the revised 2010 McDonald criteria[c]. Patients must be exhibiting a relapsing clinical course consistent with RMS and have a history of brain MRI lesions consistent with MS. Randomized, double-blind, double-dummy, active-controlled parallel-group study Active control: IFN β-1a	Once daily oral dosing with ozanimod 1 mg or ozanimod 0.5 mg, or IFN β-1a 30 µg IM weekly injection for 24 months. A 7-day dose escalation was used for ozanimod.	Sex: Male: 431 (32.8%) Female: 882 (67.2%) Age (yrs): Mean (SD): 35.5 (8.93) Min, Max: 18, 55 Race: White: 1291 (98.3%) Black: 18 (1.4%) Asian: 1 (0.1%) Other: 3 (0.2%)	ARR over 24 months

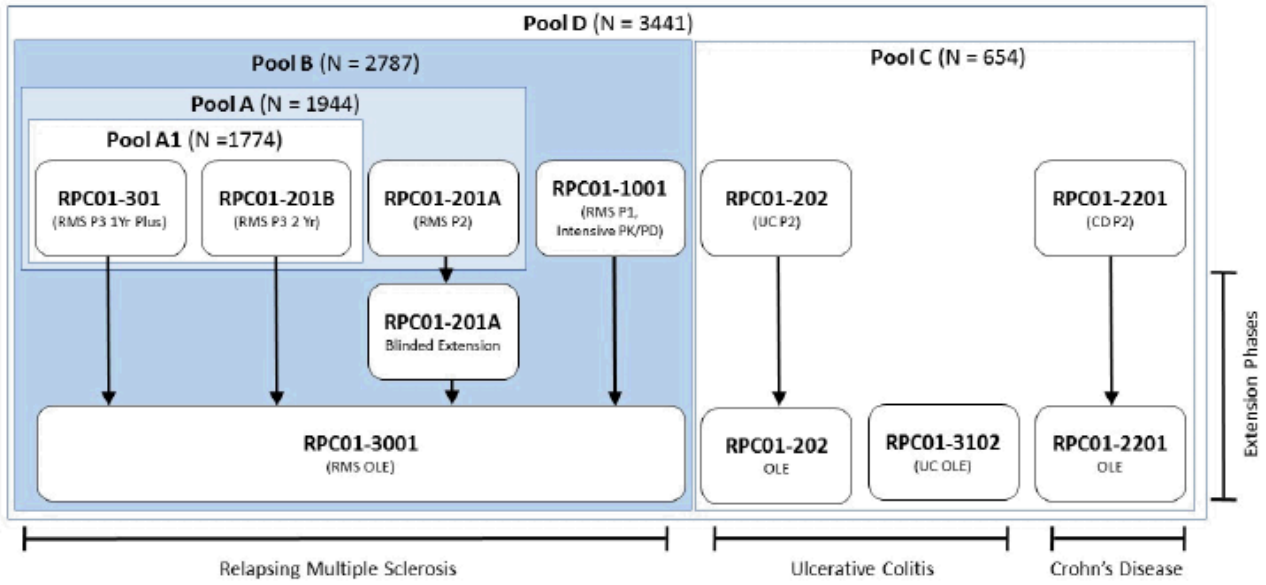
RPC01-301	158	03 Dec 2014 – 22 Dec 2016	1346 randomized 1272 completed Month 12 Visit 1255 completed 91 discontinued	Male or female subjects aged 18 to 55 years, inclusive, with MS as diagnosed by the revised 2010 McDonald criteria[c]. Patients must be exhibiting a relapsing clinical course consistent with RMS and have a history of brain MRI lesions consistent with MS. Randomized, double-blind, double-dummy, active-controlled, parallel-group study Active control: IFN β-1a	Once daily oral dosing with ozanimod 1 mg or ozanimod 0.5 mg, or IFN β-1a 30 µg IM weekly injection for at least 12 months. A 7-day dose escalation was used for ozanimod.	**Sex**: Male: 452 (33.6%) Female: 894 (66.4%) **Age (yrs)**: Mean (SD): 35.6 (9.27) Min, Max: 18, 55 **Race**: White: 1340 (99.6%) Black: 2 (0.1%) Asian: 2 (0.1%) Other: 2 (0.1%)	ARR during treatment period
RPC01-3001 (OLE)	226	16 Oct 2015 – Ongoing (data cut-off 30 Jun 2018)	2485 enrolled 2444 ongoing 41 discontinued	Male or female subjects with RMS who completed 1 of the following parent studies: RPC01-201A Extension, RPC01-201B, RPC01-301, or RPC01-1001 Open-label extension study	Once daily oral dosing with ozanimod 1 mg. Subjects started with a 7-day dose escalation, except those entering from RPC01-201A Extension or RPC01-1001 with a gap of ≤ 14 days.	**Sex**: Male: 820 (33.2%) Female: 1653 (66.8%) **Age (yrs)**: Mean (SD): 37.7 (9.22) Min, Max: 19, 57 **Race**: White: 2458 (99.4%) Black: 10 (0.4%) Asian: 2 (< 0.1%) Other: 3 (0.1%)	Long-term safety and tolerability
IBD Phase 2 and 3 Studies							
RPC01-202	57	26 Dec 2012 – Ongoing (data cut-off 30 Jun 2018)	199 enrolled 186 completed induction period 91 completed maintenance period 170 entered open-label period 78 ongoing in open-label period 92 discontinued open-label period	Male or female patients aged 18 to 75 years, inclusive, with active UC (Mayo score ≥ 6 with endoscopic subscore ≥ 2) confirmed by endoscopic and histologic evidence. Induction Period Randomized, double-blind, placebo-controlled, parallel-group study Maintenance Period Double-blind, placebo-controlled, parallel-group study Optional Open-label Period Open-label, single-dose study	Induction Period: Once daily oral dosing with ozanimod 1 mg, ozanimod 0.5 mg, or placebo for 9 weeks. A 7-day dose escalation was used for ozanimod. Maintenance Period: subjects with a response during induction continued on blinded treatment for an additional 23 weeks. Open-label Period: subjects who did not respond during induction, relapsed during maintenance, or complete maintenance received ozanimod 1 mg for up to 6 years.	**Sex**: Male: 115 (58.4%) Female: 82 (41.6%) **Age (yrs)**: Mean (SD): 40.8 (11.82) Min, Max: 18, 73 **Race**: White: 182 (92.4%) Asian: 8 (4.1%) Black: 4 (2.0%) Other: 2 (1.0%)	Clinical remission at Week 8 (Mayo score ≤ 2 with no subscore > 1)
RPC01-3102 (OLE)	166	02 Dec 2015 – Ongoing (data cut-off 30 Jun 2018)	399 enrolled (398 treated) 130 discontinued 268 ongoing	Male or female subjects with UC who completed 1 of the following parent studies: RPC01-3101 or at least 1 year in RPC01-202 open-label period[d]. Open-label extension study.	Once daily oral dosing with ozanimod 1 mg until end of year 2020. A 7-day dose escalation was used for subjects entering from Study RPC01-3101.	**Sex**: Male: 251 (63.1%) Female: 147 (36.9%) **Age (yrs)**: Mean (SD): 40.6 (13.16) Min, Max: 18, 71 **Race**: White: 335 (84.2%) Asian: 41 (10.3%) Black: 13 (3.3%) Other: 9 (2.3%)	Long-term safety and efficacy
RPC01-2201	28	17 Nov 2015 – Ongoing (data cut-off 30 Jun 2018)	69 enrolled 50 discontinued 19 ongoing	Male or female subjects aged 18 to 75 years, inclusive, with CD of at least 2 months' duration at screening; screening CDAI score of 220 to 450 with a SES-CD score ≥ 6; average daily stool score ≥ 4 and/or average daily abdominal pain score ≥ 2. Open-label study.	Induction Period: Once daily oral dosing with ozanimod 1 mg for 12 weeks. A 7-day dose escalation was used for ozanimod. Extension Period: based on the investigator's clinical judgment, subjects who completed induction continued treatment for an additional 148 weeks.	**Sex:** Male: 33 (47.8%) Female: 36 (52.2%) **Age (yrs):** Mean (SD): 37.7 (11.97) Min, Max: 18, 69 **Race:** White: 60 (87.0%) Black: 7 (10.1%) Asian: 1 (1.4%) Other: 1 (1.4%)	Change from BL in SES-CD at Week 12

ARR = annualized relapse rate; BL = baseline; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; IFN = interferon; IM = intramuscular; Max = maximum;
Min = minimum; MRI = magnetic resonance imaging; MS = multiple sclerosis; OLE = open-label extension; OLP = open-label period; RMS = relapsing multiple sclerosis;
SD = standard deviation; SES-CD = Simple Endoscopic Score for Crohn's Disease; UC = ulcerative colitis.
a Number of centers with subjects randomized (controlled studies) or enrolled (open-label studies).
b Start date = first subject's first visit date. Completion date = last subject's last visit date. Ongoing studies include data as of the cutoff date (30 Jun 2018).
c Polman, 2011.
d As of the safety data cutoff date, no subjects had rolled over from RPC01-202 to RPC01-3102.

Ongoing blinded studies (Ulcerative Colitis (UC) and Crohn's disease (CD) studies RPC01-3101 Cohort 1 and Maintenance Period, RPC01-3201, RPC01-3202, and RPC01-3203) were not included in the pooled analyses, but safety narratives were provided for deaths, suspected unexpected adverse reactions, and pregnancies. The unblinded Cohort 2 from UC study RPC01-3101 was also not included in the pooled analyses, but narratives were provided for deaths, SAEs, discontinuations due to AEs, and pregnancies.

Five data pools form the basis of the clinical safety analysis in the ozanimod Phase 2 and Phase 3 studies, with a sixth data pool comprising the Phase 1 studies in healthy volunteers or subjects with hepatic or renal impairment (Figure 9).

Figure 9: Safety Analysis Pooling Strategy (Numbers of Ozanimod-treated Subjects)



CD = Crohn's disease, OLE = open label extension, PK/PD = pharmacokinetic/pharmacodynamic, RMS = relapsing multiple sclerosis, UC = ulcerative colitis.
Note: N is given for the number of ozanimod-treated subjects in each pool. Pool B includes subjects who were treated with placebo or IFN β-1a and were rerandomized
to receive ozanimod in an extension phase. Pool E (Clinical Pharmacology Studies) not shown.
Study RPC01-3101 (parent study to RPC01-3102) is an ongoing blinded study not included in Pool C.
Study RPC01-2201 is an open-label study.

The primary focus of this safety overview was the 2 controlled Phase 3 RMS studies (Pool A1). Subjects in Pool A1 had similar exposure across 2 ozanimod treatment groups vs. an active control group within each study and remained on the same dose for the duration of each study. Pool A includes all controlled RMS studies, including the dose-ranging, placebo-controlled Phase 2 study. Pool B provides a comprehensive view of the safety of ozanimod in RMS subjects, as it comprises the Phase 1 RMS study and all Phase 2 and 3 RMS studies, including long-term data from the respective extension studies (comparisons to control were not provided in Pool B owing to the disparate exposures across the treatment groups). To further explore the safety of ozanimod, Pool C presented open-label data from the Phase 2 and 3 IBD studies, while Pool D (the combination of Pools B + C) comprised the largest overall dataset, useful for the exploration of rare events. Clinical pharmacology studies were combined in Pool E.

A total of 3,441 subjects were exposed to ozanimod across all patient studies (Pool D), including 3276 subjects treated with ozanimod 1 mg and 1098 subjects treated with ozanimod 0.5 mg. Of these, 2765 subjects (84.4%) in the ozanimod 1 mg group and 938 subjects (85.4%) in the ozanimod 0.5 mg group were exposed for ≥ 12 months, and 1226 subjects (37.4%) in the ozanimod 1 mg group and 395 subjects (36.0%) in the ozanimod 0.5 mg group were exposed for ≥ 24 months. Total cumulative exposure to ozanimod 1 mg or 0.5 mg was 6446.6 and 1628.9 patient-years, respectively.

The Safety Population for Pool A1 included 2659 subjects, of whom 882 subjects received at least 1 dose of ozanimod 1 mg, 892 subjects received at least 1 dose of ozanimod 0.5 mg, and 885 subjects received at least 1 dose of IFN β-1a (Table 21).

Table 21: Extent of Exposure – Pool A1 (Safety population)

Parameter	IFN β-1a 30 µg (N=885)	Ozanimod 0.5 mg (N=892)	Ozanimod 1 mg (N=882)	Total (N=2659)
Exposure interval, n (%)				
≥ 6 months	849 (95.9)	862 (96.6)	854 (96.8)	2565 (96.5)
≥ 12 months	804 (90.8)	820 (91.9)	818 (92.7)	2442 (91.8)
≥ 18 months	408 (46.1)	407 (45.6)	416 (47.2)	1231 (46.3)
≥ 24 months	310 (35.0)	291 (32.6)	299 (33.9)	900 (33.8)
Total duration of exposure (months)				
Mean (SD)	17.752 (6.1633)	17.792 (5.9821)	18.066 (5.9599)	17.870 (6.0351)
Min, max	0.03, 24.49	0.03, 25.09	0.10, 24.56	0.03, 25.09
Cumulative exposure (patient-years)				
Total exposure[a]	1304.8	1318.0	1323.3	3946.1

IFN = interferon; N = number randomized to treatment, n = number receiving treatment for exposure interval.
A Patients-years of exposure was calculated as ([date of last dose – date of first dose]) +1)/365.25
Note Pool A1 includes Studies RC01-201B and RPC01-301

Approximately 92% of subjects in Pool A1 were exposed to ozanimod or IFN β-1a for at least 12 months, and approximately 34% of subjects in Pool A1 were exposed to ozanimod or IFN β-1a for at least 24 months. The total duration of exposure was well-balanced across treatment groups and Pool A1 was most appropriate to focus on for the characterization of the safety profile of ozanimod in the treatment of adult patients with RRMS. Total cumulative exposure to ozanimod 1 mg and 0.5 mg was 1323.3 and 1318.0 patient-years, respectively. Pool B, with 2787 subjects, included 1018 subjects followed for at least 36 months.

The demographic characteristics of subjects in Pool A1 were generally well balanced across the 3 treatment groups. The mean age of the total population was 35.5 years, 66.8% were female, 98.9% were white, 89.7% were from Eastern Europe, and the mean weight was 69.92 kg. For Pool A1, the disease history of subjects was generally well balanced across treatment groups. The mean time since MS symptom onset for the three treatment groups combined was 6.7 years and mean time since diagnosis of MS was 3.7 years (the mean age at diagnosis was 32.1 years). In the 12 and 24 months prior to screening, the mean (median) number of relapses experienced by subjects was 1.3 (1.0) and 1.7 (2.0), respectively. The mean EDSS score at baseline was 2.57. The reported medical history in Pool A1 was consistent with the disease population and known comorbidities of MS and was well-balanced across the 3 treatment groups. The most frequently occurring comorbidities were nervous system disorders (38%), of which optic neuritis was most frequent (26.7%). Other frequently occurring comorbidities were eye disorders (24.2%), musculoskeletal and connective tissue disorders (22.8%), infections and infestations (21.8%), surgical and medical procedures (18.4%), gastrointestinal disorders (15.7%), and vascular disorders (12.0%), primarily hypertension (6.5%). The demographics, baseline disease characteristics, MS treatment history, and concomitant medications for Pool A and for Pool B were consistent with those for Pool A1.

Subjects >55 years of age were excluded from studies contributing to Pool A1. Approx. 8% of subjects in each treatment group in Pool B were 50-59 years of age due to participation in OLE Study RPC01-3001. The only data in subjects aged >60 years derived from Pool C studies with 5 and 52 patients between 60 and 69 years of age in the ozanimod 0.5 mg and 1 mg group and 5 subjects aged 70 to 75 years in the ozanimod 1 mg dose group. The Applicant justified the newly proposed posology wording

("There is limited data available on RRMS patients >55 years of age" ...) with the US FDA 4-months safety update

(cut-off date 31-01-2019) including 161 subjects treated beyond the age of 55 during the study (pool B). Of note, no active comparison is available for safety data of patients > 55 years of age. An additional analysis of clinical safety data of these 161 patients included in Pool B were provided by the Applicant. The limited number of patients >55 years of age generally exhibited a higher incidence of TEAEs in contrast to patients ≤55 years. The Applicant position that the increasing incidence of TEAEs with increasing age categories may be due to a higher reporting rate in older patients was supported by the reporting trend provided by the Applicant. The reporting rate of TEAEs was highest in the first 6 months of treatment and declined thereafter (data have been presented up to 78 months of treatment). TEAEs in patients >55 years of age were qualitatively in line with those reported for patients ≤ 55 years being the more remarkable quantitative differences found for liver function test abnormalities (ALT increased and gamma-glutamyltransferase (GGT) increased) and cardiovascular – related TEAEs (hypertension and orthostatic hypotension). Overall it was agreed that currently available safety data in the elderly did not indicate a worsened safety profile of ozanimod in the elderly that would lead to a different perception of the benefit-risk profile. However, no firm conclusion could be made with regard to long-term safety in the elderly based on the limited number of elderly subjects evaluated in clinical trials as indicated in the section 4.2 of the SmPC.

Adverse events

The overall incidence of AEs was lower in the ozanimod treatment groups compared with IFN β-1a, which was driven by the high rate of influenza-like illness seen with IFN β-1a (Table 23). The incidences of severe and serious TEAEs were low and similar across the 3 treatment groups in Pool A1. Adverse events leading to permanent discontinuation of study drug or to withdrawal from the study were infrequent in all treatment groups and reported at a slightly lower incidence in the ozanimod treatment groups compared with the IFN β-1a group. Adverse events leading to temporary discontinuation or delay of study drug (ie, treatment interruption) were infrequent and reported at a similar incidence in the ozanimod 1 mg and IFN β-1a treatment groups, and at a slightly higher incidence in the ozanimod 0.5 mg treatment group. During the controlled period, there was 1 death in the ozanimod 0.5 mg treatment group; there was 1 additional death in the ozanimod 1 mg treatment group that occurred ~10 months after discontinuation of study drug. Neither death was considered by the investigator of the Sponsor to be related to ozanimod (**Table 22**).

Table 22: Incidence of Treatment-Emergent Adverse Events During the Controlled Period in RMS Pivotal Studies — Pool A1 (Safety Population)

Subject Experiencing:	IFN β-1a 30 µg (N = 885) n (%)	Ozanimod 0.5 mg (N = 892) n (%)	Ozanimod 1 mg (N = 882) n (%)	Total Ozanimod (N = 1774) n (%)
At least 1 TEAE	701 (79.2)	585 (65.6)	592 (67.1)	1177 (66.3)
At least 1 severe TEAE	29 (3.3)	29 (3.3)	22 (2.5)	51 (2.9)
At least 1 serious TEAE	39 (4.4)	47 (5.3)	41 (4.6)	88 (5.0)
Any TEAE leading to temporary discontinuation or delay of study drug	14 (1.6)	25 (2.8)	16 (1.8)	41 (2.3)
At least 1 TEAE leading to permanent discontinuation of study drug	34 (3.8)	21 (2.4)	26 (2.9)	47 (2.6)
Any TEAE leading to study withdrawal[a]	36 (4.1)	20 (2.2)	26 (2.9)	46 (2.6)
Death	0	1 (0.1)	1 (0.1)	2 (0.1)

eCRF = electronic case report form: IFN = interferon; PT = preferred term; TEAE = TEAE = treatment-emergent adverse event
There were 3 (unreconciled) data issues where sites incorrectly completed the question "Was subject terminated from Study due to this AE?" on the AE eCRF. Two subjects in the INF B-1a treatment group have "yes" indicated for termination from study due to the respective AEs but should have "No" indicated for termination from study due to the respective AEs. One subject in the ozanimod 0.5mg group had "No" indicated for termination from study due to the AE of acute hepatitis B (PT) but should have "Yes" indicated for termination from study due to the event. Note: At each level of subject summarization, a subject is counted only once if the subject reported multiple events.

Most Frequently Reported Adverse Events

The system organ classes with the highest proportions of subjects reporting AEs were Infections and Infestations, Nervous System Disorders, and Investigations. Adverse events reported by ≥ 5% of subjects in any treatment group were nasopharyngitis, headache, upper respiratory tract infection, ALT increased, and influenza-like illness (Table 23). The incidence of nasopharyngitis was slightly higher in the ozanimod treatment groups compared with the IFN β-1a treatment group, but no dose effect was observed. The incidences of headache and upper respiratory tract infection were similar across the 3 treatment groups. A greater proportion of subjects in the ozanimod 1 mg treatment groups reported ALT increased as compared to the ozanimod 0.5 mg and IFN β-1a treatment groups. Influenza-like illness and pyrexia are known side effects of IFN β-1a and, as expected, were reported at a higher incidence in IFN β-1a-treated subjects than in ozanimod-treated subjects. The overall higher incidence of AEs in the IFN β-1a treatment group compared with the ozanimod treatment groups could be attributed to the frequency of these events.

Table 23: Incidence of Treatment-emergent Adverse Events Reported for ⩾ 5% of Subjects in Any Treatment Group — Pool A1 (Safety Population)

Preferred Term	IFN β-1a 30 µg (N = 885) n (%)	Ozanimod 0.5 mg (N = 892) n (%)	Ozanimod 1 mg (N = 882) n (%)
Nasopharyngitis	84 (9.5)	103 (11.5)	98 (11.1)
Headache	78 (8.8)	82 (9.2)	78 (8.8)
Upper respiratory tract infection	61 (6.9)	67 (7.5)	52 (5.9)
Alanine aminotransferase increased	28 (3.2)	41 (4.6)	47 (5.3)
Influenza like illness	442 (49.9)	44 (4.9)	44 (5.0)
Pyrexia	56 (6.3)	17 (1.9)	16 (1.8)

IFN = interferon.
Note: Preferred terms are listed in order of decreasing frequency in the ozanimod 1 mg treatment group.

The most frequently reported AEs with ozanimod were defined as those reported in ≥ 2% of subjects in any treatment group and at a ≥ 1% higher incidence in either ozanimod treatment group compared with IFN β-1a (Table 24). Nasopharyngitis was the most frequently reported AE with ozanimod; the incidence was slightly higher in the ozanimod treatment groups compared with the IFN β-1a treatment group, but no dose effect was observed. Other frequently reported infections involved primarily the upper respiratory tract or urinary tract. ALT increased and GGT increased were reported more frequently in the ozanimod treatment groups than the IFN β-1a treatment group, with a modest dose effect observed for the reports of GGT increased. Orthostatic hypotension was reported at a slightly higher incidence in the ozanimod 1 mg, but not in the 0.5 mg treatment group, compared with IFN β-1a. These events occurred at a higher frequency in the first three months of treatment but were not imbalanced across treatment groups during the dose escalation period. Hypertension was reported at a similar incidence in both ozanimod treatment groups, higher than IFN β-1a.

Table 24: Incidence of the Most Frequently Reported Treatment-emergent Adverse Events with Ozanimod (≥ 2% of Subjects in Any Treatment Group and ≥ 1% Higher in Either Ozanimod Treatment Group Versus IFN β-1a) – Pool A1 (Safety Population)

Preferred Term	IFN β-1a 30 µg (N = 885) n (%)	Ozanimod 0.5 mg (N = 892) n (%)	Ozanimod 1 mg (N = 882) n (%)
Nasopharyngitis	84 (9.5)	103 (11.5)	98 (11.1)
Alanine aminotransferase increased	28 (3.2)	41 (4.6)	47 (5.3)
Gamma-glutamyltransferase increased	11 (1.2)	26 (2.9)	40 (4.5)
Orthostatic hypotension	28 (3.2)	32 (3.6)	38 (4.3)
Urinary tract infection	27 (3.1)	30 (3.4)	36 (4.1)
Back pain	23 (2.6)	31 (3.5)	35 (4.0)
Hypertension	18 (2.0)	31 (3.5)	30 (3.4)
Pharyngitis	20 (2.3)	30 (3.4)	28 (3.2)
Respiratory tract infection viral	11 (1.2)	15 (1.7)	21 (2.4)
Abdominal pain upper	9 (1.0)	17 (1.9)	20 (2.3)

IFN = interferon.
Note: Preferred terms are listed in order of decreasing frequency in the ozanimod 1 mg treatment group.

Analysis of Most Frequently Reported Adverse Events by Maximum Severity

The most frequently reported AEs with ozanimod were predominantly mild or moderate in severity across all 3 treatments. The incidence of moderate AEs was lower in the ozanimod treatment groups compared with the IFN β-1a treatment group, largely due to the higher incidence of moderate influenza like illness in the IFN β-1a group. The incidence of severe TEAEs was low and similar across the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups (2.5%, 3.3%, and 3.3%, respectively). The incidence of severe cases of individual AEs was < 1%. Severe AEs reported for >1 ozanimod-treated subject were ALT increased (1 subject [0.1%] on ozanimod 1 mg and 2 subjects [0.2%] on ozanimod 0.5 mg), GGT increased (2 subjects [0.2%] on ozanimod 0.5 mg), and abdominal pain upper (1 subject [0.1%] on ozanimod 1 mg and 1 subject [0.1%] on ozanimod 0.5 mg). Severe AEs reported in >1 subject in the IFN β-1a treatment group were influenza-like illness (8 subjects, 0.9%) and MS relapse (2 subjects, 0.2%).

Analysis of Most Frequently Reported Adverse Events by Time Interval

The overall incidence of AEs was lower in the ozanimod 1 mg and 0.5 mg treatment groups compared with IFN β-1 during Months 0 to 3 (35.9% and 36.4% versus 63.4%, respectively) and was generally similar across the 3 treatment groups during Months 3 to 6 (25.8%, 27.0%, 26.2%, respectively) and Months 6 to 12 (35.0%, 35.1%, 40.6%). The incidence of AEs in the ozanimod treatment groups was similar during each exposure interval.

Among the most frequently reported AEs with ozanimod, the incidence of nasopharyngitis was generally similar across the 3 treatment groups during each exposure interval. The incidence of other infections

was generally similar across exposure intervals, although a higher incidence of respiratory tract infection viral was observed in the ozanimod 1 mg treatment group during Months 0 to 3 compared with the other treatment groups, and a higher incidence of pharyngitis was observed in the ozanimod 0.5 mg treatment group during Months 3 to 6 compared with the other treatment groups.

Long-term Use

Pool B (All RMS Studies) and Pool D (All RMS + IBD Studies) provided the longest duration of exposure to ozanimod; total exposure to the 1 mg and 0.5 mg doses was 5660.5 PY and 1602.3 PY, respectively, for Pool B, and 6446.6 PY and 1628.9 PY, respectively, for Pool D. Approximately 94% of subjects in Pool B were exposed to ozanimod 1 mg or 0.5 mg for at least 12 months, and approximately 65% were exposed to ozanimod 1 mg or 0.5 mg for at least 24 months, the majority of whom were on 1 mg. The pattern and incidence of adverse events was similar for Pools A and B, with the exception of TEAEs of lymphopenia (7.4%), lymphocyte count decreased (5.9%), and leukopenia (1%), which were only reported for ozanimod 1 mg in Pool B (i.e. the dose administered in the open-label studies). These adverse events were not reported in the controlled parts of the studies (Pool A1) in order to keep the investigator blinded. For the most frequently reported PTs in Pool A1 (≥ 5%), the incidences during long-term treatment presented with Pool B data remained within the level of controlled studies or even decreased, with the exceptions of lymphopenia and lymphocyte count decreased (not reported in Pool A1). Among the special safety topics evaluated, there was no observed worsening of the safety profile with longer exposure (up to 68 months). Among the special safety topics evaluated, there was no observed decrement of the safety profile with longer exposure (up to 68 months). Nevertheless, non-serious herpes zoster was reported with longer-term exposure in Pool B, specifically during OLE Study RPC01-3001 (see adverse event of special interest (AESI) section on infections).

A single case of possible PML under ozanimod treatment was reported to have occurred in the ongoing OLE Study RPC01-3001 leading to discontinuation of study drug (reported to EMA on 24-02-2020). Given that no cerebrospinal fluid withdrawal was performed, PML could neither be ruled out nor confirmed for this case.

Collectively, the overall incidence of AEs and severe AEs in the ozanimod treatment groups was not increased compared with IFN β-1a. The study data do not indicate cumulative toxicity of ozanimod, since no significant worsening in the safety profile with prolonged ozanimod exposure has been observed.

Safety Topics of Interest

Based on the known biology of S1P modulators special attention was directed at assessing cardiac effects, hepatic effects, infections, consequences of lymphopenia, macular oedema, malignancies and pulmonary effects. Depression and suicidality were also identified for detailed analysis because of their association with the underlying disease state.

<u>Cardiac Effects</u>

The S1P1 receptor is highly expressed in atrial, septal, and ventricular cardiomyocytes. After initial agonism, continuous dosing results in functional antagonism and down-regulation of S1P. Activation of S1P receptors on cardiac cells provides an explanation for the transient effects on heart rate (bradycardia) and atrioventricular conduction. S1P modulators, initiated at the full dose, result in a transient reduction in heart rate (of 8 bpm) on Day 1 and, less commonly, a temporary delay in atrioventricular (AV) conduction observed in some patients (DiMarco, 2014). High-grade AV conduction abnormalities occurred in some patients, treated with non-selective S1P modulators. First dose effects resulted in the regulatory requirement for first-dose observation when initiating treatment with S1P non-

selective modulators. The S1P1 receptor is expressed on all endothelial and vascular smooth muscle cells, where it appears to contribute to the regulation of endothelial barrier function and peripheral vascular tone. Modulation of S1P1 on these cells may result in blood pressure effects. In adult Relapsing MS controlled clinical trials, patients treated with a non-selective S1P modulators had an average increase over placebo of approximately 3 mm Hg in SBP, and approximately 1 mm Hg in DBP, first detected after approximately 1 month of treatment initiation, and persisting with continued treatment. Hypertension was reported as an adverse event in approx. 6.5% of patients on a non-selective S1P modulator and in approx. 3.3% of patients on placebo.

Subjects with certain pre-existing cardiovascular conditions (e.g., myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnoea) were only eligible to participate in the active-controlled Phase 3 RMS studies if the event occurred more than 6 months prior to screening.

Based on Phase 1 data and experience with S1P modulators, a 7-day dose-escalation approach was implemented in the ozanimod Phase 2 and 3 clinical programs which consisted of treatment with ozanimod 0.25 mg on Days 1 to 4 and ozanimod 0.5 mg on Days 5 to 7. Patients allocated to ozanimod 1mg received the first 1mg on day 8. This dose regimen was shown to be successful in mitigating chronotropic and dromotropic effects observed after initiation at the full (maintenance) dose due to the initial $S1P_1$ agonism. Based on results from study RPC01-1910, a dose interruption for up to 14 days after a 28-day course of treatment is not associated with significant changes in HR upon retreatment (section 4.2 of the SmPC).

First-dose experience and monitoring

Using this approach in the placebo-controlled Phase 2 study, no clinically meaningful HR reductions, conduction abnormalities (24 h Holter monitoring during the dose escalation period), or AE reports of bradycardia with the initial dose escalation regimen on Days 1, 5, and 8 were observed between ozanimod and placebo. Cardiac conduction (measured by ECG and Holter monitoring) was not differentially affected by ozanimod vs. placebo during titration. No second-degree AV blocks type II or higher were reported. Second-degree AV block type 1 (24h-Holter monitoring) was similarly observed in subjects on ozanimod and placebo (almost exclusively on Day 1: 2.3% and 2.4% in subjects on placebo and ozanimod 0.25 mg, respectively).

In the active-controlled Phase 3 studies including approximately 1,774 subjects treated with ozanimod, the 6-hour monitoring data on Day 1 demonstrated that ozanimod was associated with only a modest and not clinically meaningful reduction in mean HR on Day 1 (mean HR reduction from baseline of 1.2 bpm with a nadir at Hour 5, with return towards baseline by Hour 6). Second- or third-degree AV block were not reported in the active-controlled Phase 3 RMS studies and no patient was reported with a HR < 40 bpm. It should be noted that patients with clinically significant cardiovascular history were excluded from these studies as were patients taking medications that reduce HR or affect cardiac conduction.

In the OLE Study RPC01-3001 (ozanimod 1 mg), consistent results were demonstrated at the time of ozanimod dose escalation initiation. A non-clinically meaningful reduction in mean HR (-1.2 bpm) was observed in subjects who switched from IFN β-1a. No conduction abnormalities were identified. Moreover, ozanimod did not affect cardiac repolarization.

'Symptomatic bradycardia' was reported in two subjects belonging to the ozanimod 0.5 mg group during the dose escalation period (with 0.25 mg) in Pool A1. 'Symptomatic bradycardia' was rated an important potential risk to be monitored during post-marketing routine and additional pharmacovigilance activities (ORION Study).

Blood pressure changes were uncommon with first dose administration of ozanimod. Incidence of events of vascular disorders were therefore low and evenly distributed across treatment groups during dose escalation.

Long-term cardiac experience

Chronic treatment with ozanimod resulted in a slightly increased mean HR over baseline level in all treatment groups at Week 24 (phase 2 study) and Month 24 (controlled part of phase 3 trials), respectively (increases of approximately 2 bpm or less). No clinically significant changes in ECG parameters were observed with chronic treatment in either treatment group. Specifically, there were no second- or third-degree AV blocks observed in the phase 3 studies. The Applicant proposed that patients presenting with (or with a history of) second-degree AV block Type II or third-degree AV block must not be treated with ozanimod.

Blood pressure changes were noted with long-term ozanimod treatment: SBP increased by Month 24 across all treatment groups but slightly higher in subjects on ozanimod as compared to IFN ß-1a. The mean increase at Month 3 in SBP was 1.6 mmHg increase over IFN ß-1a, which corresponds to a mean increase in SBP from baseline of 4.1 mmHg for ozanimod 1 mg. A discrete increase in DBP at Month 3 was similarly observed (DBP: 0.9 mmHg increase over IFN ß-1a) corresponding to a mean increase in DBP from baseline of 1.8 mmHg for ozanimod 1 mg. At Month 24, the mean change from baseline for OZA 1 mg was 5.2 mmHg (SBP) and 2.3 mmHg (DBP). Among subjects who entered the OLE, similar small increases in SBP of approximately 4 mm Hg were observed in subjects who switched from IFN β-1a or who continued from an ozanimod parent treatment group. The effect on SBP, DBP and hypertension-related events are adequately reflected in the SmPC Patients with uncontrolled hypertension were not per se excluded from participation in clinical trials with ozanimod. Upon request, the Applicant clarified that for these 124 patients with a post-hoc definition of uncontrolled hypertension (SBP>140 mmHg or DBP>90 mmHg at baseline) a worsening of pre-existing uncontrolled hypertension was not observed. Nevertheless, the Applicant proposed a specific warning to obtain cardiologist advice before initiation of ozanimod in the setting of uncontrolled hypertension, which was agreed by CHMP.

The incidence of specific events from the cardiac disorders SOC (e.g. bradycardia and AV block first-degree) did not substantially increase with longer treatment up to 24 months in Pool A1. However, the incidence of events from the vascular disorders SOC (e.g. orthostatic hypotension and hypertension) was higher in subjects on ozanimod, dose-related (3.4%, 3.5%, and 2.0% in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups, respectively) and in line with cardiac monitoring results described above (discrete increase in SBP and DBP after approx. 3 months). In OLE Study RPC01-3001, the incidence of AEs in the Cardiac Disorders and Vascular Disorders SOCs did not increase with longer-term exposure with ozanimod 1 mg.

Sponsor-designated events of interest (SDEI) included a thorough compilation of events from vital signs and ECG monitoring, cardiac disorder TEAEs and conduction abnormalities. A higher incidence of SDEIs in the ozanimod groups (16.7% and 17% for ozanimod 0.5 mg and 1 mg, compared to 13.6% for IFN ß-1a) is mainly driven by events in line with a reduced HR during the initial 6-hour monitoring on Day 1.

Cardiovascular medical history was found to increase the incidence of cardiac disorders (such as bradycardia and first-degree AV block) in subjects on ozanimod, while such conditions were less affecting the incidence of events in the IFN ß-1a group. Even more pronounced was the occurrence of cardiac disorders in subjects with concomitant cardiovascular medications (all treatment groups) compared to subjects without those medications (with CV medication: IFN ß-1a 2.7%, ozanimod 0.5 mg 10.6%, ozanimod 1 mg 7.5%; without CV medication: IFN ß-1a 2.7%, ozanimod 0.5 mg 2.4%, ozanimod 1 mg 2.7%). Events of vascular disorders (such as hypertension) were more frequently observed in subjects with CV medical history and those with concomitant CV medication. Hypertension and orthostatic hypotension were the TEAEs most frequently reported and thus in line with the safety profile of ozanimod.

Although, these analyses argued for an increased cardiovascular risk in patients with underlying CV conditions and/ or CV medication treated with ozanimod, which was additionally supported by the analysis of SDEIs for CV medical history/risk (yes/no), the Applicant clarified that the numerical imbalance between subjects with and without concomitant cardiovascular medication was mainly driven by events of bradycardia and sinus bradycardia on Day 1 of dosing. Moreover, metabolism and nutrition disorders (such as hypercholesterolemia and obesity) predominated the observed imbalance of TEAEs in ozanimod vs. IFN ß-1a treated patients with/ without cardiovascular history in the cardiac and vascular disorders SOC. Additional analyses of concomitant medical history and concomitant cardiovascular medication were quite reassuring that the imbalances between ozanimod and IFN ß-1a could be attributed to the cardiac safety profile of ozanimod.

Concomitant administration of class Ia or class III antiarrhythmic drugs was not investigated and might worsen the cardiac safety of ozanimod. The Applicant addressed the need for enhanced vigilance on cardiac safety with these medications and thus proposed a warning in section 4.4 to obtain cardiologist advice on treatment initiation/monitoring in patients treated with antiarrhythmics, which was deemed acceptable given that the most critical time for cardiac TEAEs with ozanimod is during treatment initiation. The present data supported the need for additional monitoring during treatment initiation in a number of patients (i.e. those with a HR<45 bpm, HR is the lowest value post-dose (after 6 hours), new onset second-degree or higher AV block at the 6 hour post-dose ECG, and QTc interval≥500 ms) to determine the individual cardiovascular response to ozanimod. In addition, specific conditions (i.e. cardiac history, pre-existing QT interval prolongation, medicinal products that are known to potentiate bradycardia, and antiarrhythmic drugs (class Ia and III) require cardiologist advice prior to treatment initiation to decide on the safe use of ozanimod and monitoring during treatment. This information is reflected in the sections 4.4 and 4.8 of the SmPC. Moreover, the RMP adequately reflects "long-term cardiovascular effects" as missing information to address the need for data with ozanimod treatment in patients suffering from cardiovascular comorbidities. Additional pharmacovigilance activities are proposed to address this issue (besides other long-term safety aspects, i.e. the ORION Study and long-term follow-up of OLE Study RPC01-3001).

Even though long-term experience from clinical trials do not raise significant cardiovascular concerns, it should be stressed that subjects with several pre-existing conditions (as indicated above) were excluded from clinical studies with ozanimod. Despite their exclusion from participation in clinical trials, some patients presented at baseline with a resting HR <55 bpm, with prolonged QTcF interval or additional risks for QT prolongation, as well as with concomitant medication known to impact cardiac conduction (63 patients on ozanimod 1 mg and 42 patients on IFN β-1a). Although, during the dose-escalation period, a slightly higher incidence in bradycardia-related TEAEs (none with a baseline HR<55 bpm) and vascular disorder – related TEAEs (hypotension, orthostatic hypotension) was observed in patients with potentially excluded cardiac conditions as compared to the overall population, the difference was marginal. Based on a summary of maintenance data of these patients, no cardiovascular TEAEs were reported for the subjects on ozanimod 1 mg after initial dose escalation up to Day 90. After Day 90, there was a similar low incidence of TEAEs in patients on ozanimod 1 mg and IFN β-1a in line with the cardiac safety profile of ozanimod. All patients continued treatment with ozanimod. The incidence of cardiac disorder-related TEAEs in subjects with concomitant QT prolonging medication during maintenance treatment (beyond Day 11) was not markedly different from the incidence in the IFN β-1a group. The recommendations on pre-existing cardiac conditions were adequately reflected in section 4.4 of the SmPC taking into account the contraindications on certain relevant cardiac conditions (i.e. patients with history or presence of second-degree AV block Type II or third-degree AV block or sick sinus syndrome unless the patient has a functioning pacemaker) in section 4.3.

Hepatic Effects

Consistent with what has been observed with other S1P receptor modulators, hepatic enzyme elevations, including ALT, AST, and GGT, were seen with ozanimod treatment (**Table 25**).

Table 25: Maximum Postbaseline Elevations in ALT, AST, GGT, and Bilirubin – Pool A1 (Safety Population)

Parameter	IFN β-1a 30 µg (N = 885) n (%)	Ozanimod 0.5 mg (N = 892) n (%)	Ozanimod 1 mg (N = 882) n (%)
ALT			
≥ 3 x ULN	27 (3.1)	34 (3.8)	48 (5.5)
≥ 5 x ULN	11 (1.3)	9 (1.0)	14 (1.6)
≥ 10 x ULN	4 (0.5)	3 (0.3)	4 (0.5)
AST			
≥ 3 x ULN	19 (2.2)	8 (0.9)	9 (1.0)
≥ 5 x ULN	10 (1.1)	3 (0.3)	5 (0.6)
≥ 10 x ULN	2 (0.2)	1 (0.1)	4 (0.5)
GGT			
> 2.5 x ULN	30 (3.4)	55 (6.2)	108 (12.3)
> 5 x ULN	8 (0.9)	20 (2.2)	27 (3.1)
> 20 x ULN	1 (0.1)	0	0
Bilirubin			
> 1.5 x ULN	16 (1.8)	38 (4.3)	41 (4.7)
> 2 x ULN	2 (0.2)	14 (1.6)	14 (1.6)
> 3 x ULN	0	1 (0.1)	3 (0.3)

Number of subjects with an assessment
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; IFN = interferon; ULN = upper limit of normal.
Note: Categories (x ULN) correspond to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 4.03 grading.

No clear trend for a time-dependency could be deduced for ALT (and AST) across Pool A1, but postbaseline GGT abnormalities gradually increased within 24 months of observation. Changes in bilirubin were overall small and occurred more frequently with ozanimod than with IFN β-1a. Small total bilirubin changes appeared to be related to unconjugated (indirect), pre-hepatic bilirubin changes (typically observed with conditions of Gilbert's disease) rather than direct bilirubin changes (typically observed with toxic/ drug-induced liver changes).

Subjects with previous hepatic conditions or baseline liver enzyme abnormalities were generally found to be more susceptible for liver enzyme changes/ postbaseline abnormalities with ozanimod. Comparison with Pool B data did not suggest an increased risk for hepatic enzyme changes beyond 24 months of treatment.

The median time to postbaseline abnormalities in ALT≥3x ULN (and also GGT>2.5x ULN) was 6 months for subjects on ozanimod and recovery to ALT<3x ULN was observed within one month despite continuous treatment (and similarly after drug discontinuation), while normal ALT limits (≤1x ULN) were not achieved within 4 months. AST postbaseline abnormalities occurred less frequently and, in more subjects, IFN β-1a with a later median time to onset (after approx. 9 months) and a more thorough resolution. A median time of 9 months to onset was also observed for postbaseline bilirubin abnormalities in subjects on ozanimod.

The incidence of hepatic-related AEs was evaluated in the SOCs of Hepatobiliary Disorders and Investigations. While there were more reports of elevations of hepatic laboratory abnormalities (Investigations SOC) in the ozanimod treatment groups compared to IFN β-1a, there were no differences

in symptomatic AEs, and few subjects permanently discontinued treatment due to hepatic-related AEs (1.2%, 0.4%, and 0.8% in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups, respectively).

A greater incidence of liver enzymes elevations was observed in males compared to females, which has also been reported with S1P modulators. Although the underlying mechanism is unknown, factors that may explain this different gender response include: higher baseline aminotransferase levels in males versus females; higher baseline weight and BMI in males versus females; and a higher likelihood of fatty liver disease and alcohol consumption (which was not evaluated in these trials) between males and females.

Across the entire ozanimod clinical development program (RMS + IBD studies [Pool D]), there were 10/3441 subjects (0.3%) with concurrent ALT/AST ≥ 3 x ULN and total bilirubin > 2 x ULN suspect of hepatotoxicity (Hy's law). Two subjects were treated with ozanimod 0.5 mg, whereas 8 were on ozanimod 1 mg (from the study entry or switched to 1 mg ozanimod) at the time of concurrent elevation. All 10 subjects had recovery (to < 3 x ULN) or resolution (to ≤ 1 x ULN) of the lab abnormalities either on treatment (n=3 [2 with Gilbert's syndrome, 1 with lab error]) or after study drug discontinuation (n=7). An external expert Hepatic Advisory Board reviewed these cases and concluded that none of the cases met the criteria for Hy's Law on the basis of the presence of comorbid conditions associated with liver function test abnormalities and/or the pattern of laboratory abnormalities (Hepatic Advisory Board minutes).

The findings on hepatic safety were comparable for long-term treatment with ozanimod by comparison of incidence rates between Pool A (controlled RMS studies) and Pool B. The incidence rate of hyperbilirubinaemia was found to increase during long-term treatment with ozanimod 1 mg, most likely caused by patients who switched from a control group to ozanimod 1 mg in the extension studies.

Data from the ozanimod development program seem to be in line with real-world pharmacovigilance data from S1P modulators, which showed a signal for laboratory abnormalities but not for severe hepatic events (Antonazzo, 2018). Ozanimod therapy at a 1 mg or 0.5 mg daily dose is well below the daily dose range (usually greater than 50 mg) of oral medications most often associated with drug-induced liver injury (Lammert, 2008; Yu, 2014).

To conclude, ozanimod treatment leads to increases in hepatic enzymes and might thus worsen pre-existing liver impairment. The extent of worsening remains unknown given that subjects with defined pre-existing hepatic conditions, including chronic hepatic impairment or liver enzymes/ bilirubin ≥1.5x ULN were excluded from clinical studies. Upon request, severe liver impairment (Child-Pugh class C) was listed as a contraindication in section 4.3 of SmPC. The Applicant also updated 4.4 SmPC to provide further details for routine liver monitoring including time intervals, retesting in case of increases above ULN, and stopping rules.

Infections

Infections in the controlled study experience

In Pool A1, no differences were observed between treatment groups in the overall incidence of infections (34 to 35%) and infections that occurred at least 1% higher in the ozanimod groups as compared to IFN β-1a were nonserious and probably seasonal infections of the upper respiratory tract (i.e. nasopharyngitis, pharyngitis, and viral respiratory tract infection) and urinary tract infections. Likewise, no differences in serious infections could be observed (ranging from 0.6 to 1% across groups) and these comprised appendicitis and typical bacterial/ viral infections and resolved without clinical sequelae following standard medical management. Discontinuations due to infections were rare and similar across groups (0.1%). No disseminated or serious opportunistic infections were reported. Opportunistic infections included herpes zoster/ varicella zoster virus infections, and these were slightly higher in

subjects on ozanimod vs. IFN β-1a (0.2%, 0.3%, and 0.6% in subjects on IFN β-1a, ozanimod 0.5 mg, and ozanimod 1 mg). Subjects with zoster infections continued on ozanimod treatment without any clinical consequences.

Long-term risk for infections

Systemic opportunistic infections were not reported with long-term exposure of ozanimod in clinical studies. No cases of PML were identified in the ozanimod clinical program up to the data cut-off (30 June 2019). On 24 February 2020, EMA became aware of a possible first case of PML under ozanimod treatment in the ongoing OLE Study RPC01-3001. A female subject (age 50-60) in the OLE Study RPC01-3001 presented with (partially recovered) disability worsening (worsening of the neurological status), for whom PML cannot be formally excluded. The patient's MRI showed a lesion ('right temporal lobe brain MRI lesion') that was initially treated as MS lesion by the investigator but considered as consistent with the radiographic appearance of PML after being reviewed at the Sponsor's request by external neuroradiologists. The patient presented with only mild lymphopenia [0.89x109/L] on the day of admission. Other lymphocyte count measurements during treatment with ozanimod over 3.5 years in OLE Study RPC01-3001 were consistently in the normal range. Blood tests for JCV were negative for JCV DNA by PCR and positive for JCV antibodies. Given that no cerebrospinal fluid withdrawal was performed, PML could neither be ruled out nor confirmed (possible PML case according to International PML diagnostic criteria). Nevertheless, *'Serious opportunistic infections including PML'* was already included as an important potential risk in the summary of safety concerns proposed for ozanimod. An adequate warning about PML is stated in section 4.4 of the SmPC.

Reports of "candida infections" and "fungal infections" almost exclusively occurred in Pool B. Comparisons of incidence rates between uncontrolled open-label data and controlled parent study data as well as controlled Pool A(A1) and overall Pool B data did not suggest an increased risk of non-serious infections with continued treatment. In contrast, incidence rates of serious infections were slightly higher with extended exposure in subjects who had switched from a parent study with 0.5 mg to open-label 1 mg Ozanimod in OLE Study RPC01-3001, and in Pool B compared to Pool A1, also likely due to switches from placebo or IFN β-1a in a parent study to open-label ozanimod 1 mg.

There was an increase in the incidence of local and manageable herpes zoster infections in the open-label extension (included in Pool B; 30 Jun 2018) compared with the active-controlled studies (Pool A1); however, no further substantial increase in the incidence was observed with longer treatment (Pool B; 31 Jan 2019) (Table 26). None of the reported herpes zoster infections with long-term treatment was serious or led to discontinuation. Section 4.4 includes an adequate recommendation of VZV vaccination in patients without documented immunity to VCV.

In addition, an increased risk for infections is to be expected within 3 months after discontinuation of ozanimod in line with the duration of lymphocyte recovery given the long mean elimination half-life of ozanimod metabolites CC112273 and CC1084037 of ~11days (i.e. lymphocytes recovered in 80 to 90% of subjects on ozanimod 1 mg within 2 to 3 months after stopping treatment). The need for increased surveillance is described in section 4.4 of the SmPC.

The treatment of subjects with severe active infections and active chronic infections (e.g., hepatitis, tuberculosis) with ozanimod is contraindicated (SmPC section 4.3) in line with exclusion criteria set in the phase 3 study protocols and the recommendations stated for other S1P modulators. Additional warning was included in section 4.4 regarding a delay in initiation of therapy until the infection is resolved. Furthermore, patients with prior or concomitant antineoplastic, immunosuppressive, or immune-modulating therapies were generally excluded from clinical studies. The incidence in TEAEs from the infections and infestations SOC in patients with prior DMT treatments (evaluated as 'extrinsic factor') appeared higher as compared to those without prior DMTs in line with ALC abnormalities. However, the differences were small and did not point towards a generally different safety profile in patients with

previous immunomodulating therapy. In order to account for the lack of data in these patients, the Applicant included a general contraindication in section 4.3 of the SmPC for patients with "*immunodeficient state*" encompassing all forms of immunodeficiency (e.g. due to intercurrent illness or as the result of immunosuppressive therapy). Additional warning is included in section 4.4 in line with other S1P modulators and description of possible interaction in section 4.5.

Table 26: Incidence of Infections, Serious Infections, and Herpes Zoster with Increasing Exposure to Ozanimod 1 mg (Safety Population)

	Ozanimod 1 mg Number (%) of Subjects		
	Active-controlled studies up to 24 months	All studies (including OLE) up to 68 months	All studies (including OLE) up to 75 months
Term	Pool A1 Total SY = 1345.4 N = 882	Pool B (30 Jun 2018) Total SY = 5703.4 N = 2631	Pool B (31 Jan 2019) Total SY = 7058.5 N = 2631
Any infection	310 (35.1) IR = 300.5	1120 (42.6) IR = 278.4	1278 (48.6) IR = 270.1
Any serious infection	9 (1.0) IR = 6.7	37 (1.4) IR = 6.5	44 (1.7) IR = 6.3
Herpes zoster infections[a]	5 (0.6) IR = 3.7	29 (1.1) IR = 5.1	37 (1.4) IR = 5.3

IR = incidence rate; OLE = open-label extension; PT = preferred term; SOC = system organ class; SY = subject-years on study; TEAE = treatment-emergent adverse event. a Includes PTs of herpes zoster and Varicella zoster virus infection.

Lymphocyte reduction and risk of infection

Reductions in lymphocyte counts were expectedly reported, based on the mode of action of ozanimod, in nearly all patients in the ozanimod 1 mg group (shift from baseline to low in 94% of patients) compared to the IFN ß-1a group (shift from baseline to low in 24.4% of patients). There was a dose-dependent reduction of peripheral lymphocyte count to approx. 45% of baseline at Month 3, corresponding to a mean blood lymphocyte count of 0.8 x 10^9/L and this reduction was sustained throughout the treatment period. In pool A1, dose-dependent reductions in ALC to values<0.5 x 10^9/L were observed in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups (54.7%, 25.3%, and 1.6% of subjects, respectively). Dose-dependent reductions in ALC to values<0.2 x 10^9/L (grade 4) were also observed in the ozanimod 1 mg and 0.5 mg treatment groups (3.3% and 0.4%, respectively), versus none in the IFN β-1a treatment group. Serious infections including opportunistic infections were not associated with an ALC value of <0.2x 10^9/L in Pool A1.

In the overall pool of RMS subjects treated with ozanimod 1 mg (Pool B, N = 2631), with up to ~75 months of exposure as of 31 Jan 2019, the mean reduction in ALC of ~55% from baseline observed within 3 months was generally maintained through the data cut-off date of FDA 4-months safety update (4MSU) (31 Jan 2019). Despite persistent lymphopenia, there was no increase in the overall incidence of infections, serious infections, or other opportunistic infections with longer exposure.

Using Pool B (the broadest base of safety information in the RMS population), to assess the possible relationship between ALC reduction and the incidence of serious or opportunistic infections, considering ALC was assessed every 3 months, subjects with serious or opportunistic infections were analysed according to the lowest ALC recorded prior to the onset of the first infection and the subsequent measurement. In Pool B, 5.5% of subjects treated with ozanimod 1 mg were reported with an ALC values

<0.2x 10^9/L any time during treatment and except for a single subject with a serious infection of pyelonephritis concurrent with the ALC<0.2 x 10^9/L, none of them had a concurrent serious or opportunistic infection Table 27.

Time to recovery of lymphocyte counts less than 1 x 10^9/L to within normal range took up to 3 months in 90% of patients. Lymphopenia is stated as ADR in section 4.8 of the SmPC.

Table 27: Incidence of Serious or Opportunistic Infections in Subjects with ALC<0.2 x 10^9/L.- Pool B (Safety Population)

Parameter	Ozanimod 0.5 mg N = 1033 n (%)	Ozanimod 1 mg N = 2631 n (%)
Subjects with a postbaseline ALC assessment	1031	2621
Subjects with ALC < 0.2 x 10^9/L	4 (0.4)	143 (5.5)
Proportion who had a serious infection at any time	0/4	1/143 (0.7)
Concurrent[a] serious infection	0/4	1/143 (0.7)[b]
Proportion who had an opportunistic infection at any time	1/4 (25.0)	10/143 (7.0)[c]
Concurrent[a] opportunistic infection	0/4	0/143
Proportion without any serious or opportunistic infection	3/4 (75.0)	132/143 (92.3)

ALC = absolute lymphocyte count.
a Concurrent defined as an ALC ≤ 0.2 x 109/L recorded at the laboratory visit prior to the onset of the first infection or at the subsequent assessment (visits were spaced up to 3 months apart).
b The concurrent serious infection was pyelonephritis.
c Includes 10 subjects with herpetic infections (herpes zoster, herpes simplex, oral herpes, or ophthalmic herpes simplex) and 1 subject with a genital Candida infection (all nonserious).

Malignancies

Malignancies were examined due to the potential effects of ozanimod as an immunomodulatory agent. In Pool A1, the incidence of AEs in the SOC of Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps) was similar across treatment groups (21 [2.4%] subjects, ozanimod 1 mg; 19 [2.1%] subjects, ozanimod 0.5 mg; 24 [2.7%] subjects, IFN β-1a). To confirm the characterization of an event as a malignancy, medical review of individual events identified by a comprehensive Standardized MedDRA Query search was undertaken.

Subjects with a history of malignancies (other than treated basal cell carcinoma) were excluded from the Phase 3 RMS studies. In the pool A1, there were 12 total malignancies. Of the 10 total malignancies in the ozanimod groups, 5 were cutaneous (3 basal cell carcinoma, one keratoacanthoma and one malignant melanoma in situ[retrospectively determined to be pre-existing by the Sponsor]) and 5 were non-cutaneous (3 breast cancer, 1 testicular seminoma and 1 medulloblastoma[retrospectively determined to be pre-existing by the Sponsor]) (Table 28). There were 2 malignancies in the IFN β-1a treatment group, a basal cell carcinoma and chronic lymphocytic leukemia. The extent of safety follow-up in Pool A1 was 1326.88 person-years (PY) for IFN β-1a and 2686.82 PY for the ozanimod groups combined. The incidence of any malignancies in the active-controlled Phase 3 RMS studies (Pool A1) was low (0.6%, 0.6%, and 0.2% in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups, respectively), which corresponded to study duration-adjusted incidence rates (IR) per 100,000 person-years (PY) of 372.2, 373.6, and 150.8, respectively (Table 28). To allow for more meaningful comparisons with established reference sources, malignancies were further classified by the exclusion of nonmelanoma skin cancers (NMSC) as well as subjects whose malignancy, upon Sponsor review, was

assessed to have been pre-existing (Table 28). A post hoc Fisher's exact test failed to show a statistically significant association between the incidence of malignancy (any or any excluding pre-existing malignancies) and treatment with either ozanimod 1 mg or 0.5 mg versus IFN β-1a. The incidence rates per 100,000 PY (95% CI) for malignancies (excluding NMSC) and for malignancies (excluding NMSC and preexisting) in the ozanimod groups combined (223.5 [82.0, 486.4] and 148.9 [40.6, 381.4], respectively) were similar to the rate of 202.7 (201.4, 204.1) for the comparable age range (20 to 54 years) in the general US population in 2014 based on a Surveillance, Epidemiology and End Results (SEER) database analysis (which excludes NMSC) (SEER, 2017). The incidence rate per 100,000 PY (95% CI) for any malignancies (including pre-existing cases) in the ozanimod groups combined (372.9 [178.8, 685.7]) did not show an increased risk relative to the estimated background rates of any malignancies in MS patients which have been reported: approximately 370 per 100,000 PY in the British Columbia MS study (Kingwell, 2012) and approximately 673 per 100,000 PY according to the Danish MS register (Nielsen, 2006).

Table 28: Incidence of Malignancies – Pool A1 (Safety Population)

Malignancy Preferred Term	**IFN β-1a 30 µg (N = 885) (PY = 1326.88) n (%)**	**OZA 0.5 mg (N = 892) (PY = 1341.45) n (%)**	**OZA 1 mg (N = 882) (PY = 1345.37) n (%)**	**Total Ozanimod (N = 1774) (PY = 4013.70) n (%)**
Any malignancies	2 (0.2) IR = 150.8	5 (0.6) IR = 373.6	5 (0.6) IR = 372.2	10 (0.6) IR = 372.9
Cutaneous Malignancy	1 (0.1)	3 (0.3)	2 (0.2)	5 (0.3)
Basal cell carcinoma	1 (0.1)	2 (0.2)	1 (0.1)	3 (0.2)
Keratoacanthoma	0	0	1 (0.1)	1 (< 0.1)
Malignant melanoma in situ[a]	0	1 (0.1)	0	1 (< 0.1)
Noncutaneous Malignancy	1 (0.1)	2 (0.2)	3 (0.3)	5 (0.3)
Invasive breast carcinoma	0	1 (0.1)	1 (0.1)	2 (0.1)
Breast cancer	0	0	1 (0.1)	1 (< 0.1)
Medulloblastoma[a]	0	1 (0.1)	0	1 (< 0.1)
Testicular seminoma (pure) stage I	0	0	1 (0.1)	1 (< 0.1)
Chronic lymphocytic leukaemia	1 (0.1)	0	0	0
Malignancies excluding pre-existing malignancies[a]	2 (0.2) IR =150.8	3 (0.3) IR =224.0	5 (0.6) IR =372.2	8 (0.4) IR =298.2
Malignancies excluding NMSC	1 (0.1) IR =75.4	3 (0.3) IR =223.8	3 (0.3) IR =223.2	6 (0.3) IR =223.5
Malignancies excluding NMSC and pre-existing malignancies	1 (0.1) IR =75.4	1 (0.1) IR =74.6	3 (0.3) IR =223.2	4 (0.2) IR =148.9
Malignancies of NMSC	1 (0.1) IR = 75.4	2 (0.2) IR =149.3	2 (0.2) IR =148.7	4 (0.2) IR =149.0

IFN = interferon; IR = incidence rate (per 100,000 person-years); NMSC = nonmelanoma skin cancer; PT = preferred term; SDEI = Sponsor-defined event of interest; PY = person-years.

[a]One event of malignant melanoma in situ and 1 event of medulloblastoma (both in the ozanimod 0.5 mg group) were determined retrospectively to be pre-existing. The subject with medulloblastoma had a history of optic neuritis and documented multiple sclerosis for 7 years prior to randomization. Note: Incidence rate per 100,000 PY is calculated as number of subjects / PY x 100,000 for specific malignancy SDEI category. For a subject in a particular category, the time on study is calculated based on the date the subject first meets an SDEI criterion within the category (date first criterion is met - first dose date of study drug + 1)/ 365.25; for subjects who don't meet an SDEI criterion in the category, the time on study is the study duration (last date on study - first dose date of study drug +1)/365.25;

A comprehensive review of DMT that have received marketing authorization for MS did not suggest an increased cancer risk with these agents (Lebrun, 2018). The incidence rates per 100,000 PY (95% CI) for any malignancies with ozanimod 1 mg (372.2 [120.8, 868.5]) and 0.5 mg (373.6 [121.3, 871.8]) were at the low end of the range of what has been reported for any malignancies in controlled Phase 3 clinical trials of recently approved DMTs in patients with RMS (range, 352 to 1200 per 100,000 PY) (Mavenclad EPAR, 2017; Gilenya CDER medical review, 2010; Tecfidera CDER medical review, 2013; Aubagio CDER medical review, 2012). Furthermore, ozanimod malignancy rates were 0.6% in both the 1 mg and 0.5 mg groups in Pool A1. Similar incidences were reported in a recent meta-analysis of 11 Phase 3 trials (with a similar overall duration of exposure as Pool A1) with DMTs registered for use in MS (dimethyl fumarate, fingolimod, teriflunomide, natalizumab, alemtuzumab, and glatiramer acetate). The combined malignancy incidence rates in this meta-analysis were 0.6% for the active treatment groups and 1.2% for the placebo groups (Pakpoor, 2015). The incidence rate per 100,000 PY of nonmelanoma skin cancers (including basal cell carcinoma and keratoacanthoma) in the ozanimod groups combined was 149.0 (95% CI: 40.6, 381.6), which compares with reported rates of 146 to 422/100,000 PY for a US population (Minnesota and Hawaii, respectively) (Chuang, 1990; Reizner, 1993).

Long-term risk for malignancies

Long-term treatment with ozanimod (based on Pool B data) was not associated with an increase in malignancies beyond Pool A1. Overall, incidence rates per 100,000 PY were essentially similar or even lower as compared to those in Pool A1 for any malignancy but also after exclusion of pre-existing malignancies and/or NMSC. For Pool B (all RMS studies), the incidence rate per 100,000 PY (95% CI) for malignancies (excluding nonmelanoma skin cancer) was 191.6 (104.8, 321.5); with the exclusion of pre-existing malignancies as well as nonmelanoma skin cancer, the incidence rate was 164.2 (84.9, 286.9) per 100,000 PY. These incidence rates compared favourably with the rates observed in Pool A1 (223.5 and 148.9 per 100,000 PY, respectively), indicating that, with longer exposure, the incidence of malignancies in the RMS studies did not increase. Malignancies during long-term treatment not reported in Pool A1 included squamous cell carcinoma (of skin), cervix carcinoma, clear renal cell carcinoma, glioblastoma, metastasis, pancreatic carcinoma, papillary thyroid cancer, and uterine cancer, which were reported in a single subject each. Cutaneous malignancies were similarly observed in subjects with IBD and subjects with RMS. Noncutaneous malignancies in Pool C were different in IBD studies and in line with the underlying disease. Pool D (all RMS + Inflammatory bowel disease (IBD) studies) rates for all malignancies 368.9 (248.9, 526.7) and for those that excluded nonmelanoma skin cancer and pre-existing malignancies 196.3 (112.2, 318.8) did not show meaningful differences in the exposure rates when compared with Pool A1; confidence intervals overlapped with rates from SEER. There were no reports of lymphoma (typical for immunosuppression) in the ozanimod clinical program.

Four cases of breast cancer (PTs of breast cancer and invasive breast carcinoma) were reported in Pool B, including 3 during the active-controlled studies (Pool A1). Although, this appears striking, only one additional case was reported in the OLE Study RPC01-3001 despite an approximately 3-times higher patient-years of exposure in Pool B. Breast cancer seemed not to increase with longer ozanimod treatment duration. This frequency is within the expected incidence over the treatment period of 4.86 events of breast cancer, calculated by applying the SEER incidence rate for breast cancer in an age-matched (20- to 54-year-old) female population (92.4/100,000) to female subjects' exposure to ozanimod in Pool B (5256.7 SY). Using these data, the standardized incidence rate (SIR) for breast cancer in Pool B is estimated to be 0.82 (95% CI: 0.22, 2.11) (data on file). By comparison, the SIR of breast cancer in the MS population has been estimated to range between 0.94 (0.77, 1.31) and 1.21 (1.05, 1.39) across 4 different population-based studies (Kyritsis, 2016). The risk for breast cancer might be increased in females with multiple sclerosis although etiology is unclear. Furthermore, two-thirds of the MS patients studied were female. In contrast, no breast cancer was reported in the IBD program with ozanimod, where 60% of all ozanimod-treated patients were male.

During the procedure, the Applicant provided additional data (6-months of additional data) derived from FDA 4MSU. Overall, four more malignancy events were reported within the time period of the 4MSU (31 January 2019), i.e. one additional case of breast cancer (PT breast neoplasm), one case of bile duct cancer (later not confirmed as malignancy but hydatid cyst), and two additional cases of basal cell carcinoma (not further addressed by the Applicant). The total of 5 breast cancer cases (all in RMS subjects) remained within the expected incidence of breast cancer over the treatment period of 5.79 events, calculated by applying the SEER incidence rate for breast cancer in an age-matched (20- to 54-year-old) female population (92.4/100,000) to all female subjects' exposure to ozanimod in Pool D (6269.9 PY [4MSU]). Using these data, the SIR for breast cancer in ozanimod-treated female subjects is estimated to be 0.86 (95% CI: 0.28, 2.01), which compares with the SIR reported in the MAA of 0.82 (95% CI: 0.22, 2.11). It was acknowledged that the additional case of breast cancer did not change the previously reported incidence rate. Reported malignancies up to 31 Jan 2019 (4MSU) are provided for Pool B (ozanimod RMS subjects) in **Table 29**. In particular, the incidence rates of nonmelanoma skin cancers and also rates of other malignancies, including breast cancer, were not increased with longer exposure to ozanimod at the time of the 4MSU and remained within expectations for the general population and the age-matched MS population in the SEER cancer registry. Malignancies, such as lymphomas, that have been commonly observed with broader immunosuppressive therapies, have not been reported.

Table 29: Comparison Between the MAA and 4MSU Data Cuts of the Incidence of SDEIs of Malignancy — Pool B (Safety Population)

	MAA Data Cut (30 Jun 2018)		4MSU Data Cut (31 Jan 2019)	
Malignancy Preferred Term	Ozanimod 1 mg (N = 2631) (Total PY = 5690.6)	Total Ozanimod (N = 2787) (Total PY = 7312.2)	Ozanimod 1 mg (N = 2631) (Total PY = 7045.6)	Total Ozanimod (N = 2787) (Total PY = 8667.3)
	n (%)	n (%)	n (%)	n (%)
Any malignancy	18 (0.7) IR = 317.0	23 (0.8) IR = 315.4	22 (0.8) IR = 313.1	27 (1.0) IR = 312.5
Cutaneous Malignancy	8 (0.3)	11 (0.4)	10 (0.4)	13 (0.5)
Noncutaneous Malignancy	10 (0.4)	12 (0.4)	12 (0.5)	14 (0.5)
Malignancies excluding pre-existing malignancies[a]	18 (0.7) IR = 317.0	21 (0.8) IR = 287.9	22 (0.8) IR = 313.1	25 (0.9) IR = 289.3
Breast cancers[e]	3 (0.2) IR = 79.0	4 (0.2) IR = 81.6	4 (0.2) IR = 85.1	5 (0.3) IR = 86.4
Malignancies excluding NMSC[f] and pre-existing malignancies	11 (0.4) IR = 193.5	12 (0.4) IR = 164.2	13 (0.5) IR = 184.7	14 (0.5) IR = 161.7
Malignancies excluding NMSC[f]	11 (0.4) IR = 193.5	14 (0.5) IR = 191.6	13 (0.5) IR = 184.7	16 (0.6) IR = 184.8
Malignancies of NMSC[f]	7 (0.3) IR = 123.2	9 (0.3) IR = 123.3	9 (0.3) IR = 128.0	11 (0.4) IR = 127.2

MAA = marketing authorization application; 4MSU = 4-months safety update data; IR = incidence rate (per 100,000 person-years); NMSC = nonmelanoma skin cancer.

To conclude, although, numerically there were more malignancies reported with ozanimod than with IFN β-1a, the incidence rates, with wide confidence intervals, did not appear to indicate an increased overall risk of malignancies or an incidence rate that increases with greater exposure duration. The malignancies reported did not demonstrate any specific pattern and were also not typical of those observed in an

immunosuppressed population (e.g., no cases of lymphoma were seen). Upon review of the provided incidences of cutaneous and non-cutaneous malignancies in Pool A1 (the basis for inclusion of adverse drug reactions (ADRs) in SmPC section 4.8) and in consideration of the 4MSU, it was agreed with the Applicant that no specific type of cancer could be retrieved, which would qualify as a designated ADR in section 4.8. Longer follow-up with larger numbers of exposed patients are required to make a robust assessment regarding risk of malignancy associated with ozanimod treatment.

In the awareness of the potential risk of skin neoplasm formation with S1P modulators, patients treated with ozanimod should be cautioned against exposure to sunlight without protection. Upon request, the Applicant included a warning on the section 4.4 of the SmPC so patients treated with ozanimod should be cautioned against exposure to sunlight without protection and should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy. In addition, skin neoplasms were eminent in patients after marketing authorisation of S1P modulators prompting recent risk minimisation measures (see EMA/688187/2015 and EMA/82227145/2017). Adequate risk minimisation measures were aligned with the currently approved SmPC of S1P modulators. Available (long-term) data for ozanimod did not suggest that the risk for malignancies is different to S1P modulators and as such, the same warnings and measures are applicable, e.g. warning on immunosuppressive effects that could lead to an increased risk for developing cancer in line with the outcome of EMEA/H/C/PSUSA/00001393/201702. Given the imbalance in malignancies observed with IFN β-1a and ozanimod, *"malignancy"* was included as a potential risk in the RMP. Additional pharmacovigilance activities were proposed to further address the long-term risk for malignancies (ORION Study and long-term follow-up of OLE Study RPC01-3001). Moreover, and in line with S1P modulators, ozanimod is contraindicated in patients with known active malignancies.

Macular Oedema

Macular oedema was examined closely because of the effect of S1P receptor modulation on vascular endothelial cells. In the ozanimod RMS program, OCT was used as a standard screening tool to identify subjects for further ophthalmologic examination. The OCT was evaluated at baseline and Months 6, 12, and (in Study RPC01-201B) 24 in the controlled studies, at the end of the 6-month Study RPC01-201A Extension, and every 12 months in the OLE Study RPC01-3001. If an OCT abnormality was identified, or if visual signs or symptoms of ME observed, an ophthalmological examination was performed by an ophthalmologist (preferably a retina specialist), including eye history, visual acuity, and dilated ophthalmoscopy, to confirm the diagnosis of macular oedema and/or to identify other ophthalmic abnormalities. An assessment of macular oedema was conducted by an expert panel (Macular Edema Review Panel (MERP)) who reviewed all AEs of macular oedema and AE preferred terms that could be associated with macular oedema, as well as OCT findings potentially suggestive of macular oedema (regardless of whether an macular oedema-related AE was reported), and ophthalmic examinations. The MERP was comprised of 3 neuro-ophthalmologists and a retina specialist who were blinded to study treatment throughout all panel reviews.

Minor mean increases in central foveal thickness were observed across treatment groups but lacking a dose-dependency or a time effect. Abnormal values in subjects with normal values at baseline were highest around Month 6 in any group not exceeding an incidence of 5%.The incidence of confirmed macular oedema cases in the controlled Phase 3 RMS studies (Pool A1) was 1/882 (0.1%) in the ozanimod 1 mg treatment group and 3/892 (0.3%) in the ozanimod 0.5 mg treatment group (there were none in the IFN β-1a treatment group). An additional 3 confirmed cases were identified in the OLE Study RPC01-3001, for a total of 7/2787 (0.3%) in the RMS clinical program. Two confirmed cases were identified in the IBD program. Overall (Pool D), there were 9/3441 (0.3%) confirmed cases of macular oedema reported in the entire ozanimod program (Pool D: 0.2% for ozanimod 1 mg, 0.3% for ozanimod 0.5 mg), of which 4 cases derived from Pool A1 (0.1% for ozanimod 1 mg, 0.3% for ozanimod 0.5 mg). Cases of macular oedema in the controlled studies did not occur before 6 months of treatment with

variable time to onset from baseline. However, amongst the five cases from open-label experience with ozanimod, two happened within 2 months of starting ozanimod (while treatment in the parent studies was placebo or IFN β-1a). Therefore, regular ophthalmologic evaluation for all patients might not be useful given the lack of a clear time-dependence.

All cases of macular oedema were identified with OCT findings consistent with macular oedema and all cases were associated with pre-existing risk factors or comorbid conditions that are known to cause macular oedema. Eight of the 9 subjects recovered following discontinuation of study drug; the remaining case (secondary to ocular trauma) was reported to be stable as of the last available follow-up. Clinical signs associated with macular oedema, such as visual acuity defect or complications such as retinal detachment, were not indicated in these patients. However, in three patients from the open-label studies, the narratives indicated symptoms of decreased visual acuity, decreased vision, and vision blurred. The incidence of macular oedema in the ozanimod clinical program (0.3%) was lower than the reported incidence of 0.6% with placebo in a meta-analysis of controlled studies with S1P modulators, (Pul, 2016). At present, no increased risk for macular oedema can be deduced from available long-term data compared to controlled studies.

To conclude, no confirmed case of macular oedema was reported in a control group and macular oedema has thus been added as an ADRs SmPC section 4.8. Patients with a history of uveitis and diabetes mellitus type I or uncontrolled diabetes mellitus type II have an increased risk for developing macular oedema and were thus not eligible for study inclusion, which is adequately reflected in SmPC section 4.4. Besides an initial ophthalmologic evaluation before commencing therapy with ozanimod, follow-up evaluations on-treatment in patients with risk factors (such as history of uveitis and diabetes mellitus) need to be implemented. Patients who present with confirmed macular oedema should have treatment discontinued. A decision on whether or not ozanimod therapy should be re-initiated after resolution of macular oedema needs to take into account the potential benefits and risks for the individual patient as indicated in section 4.4 of the SmPC. Additional pharmacovigilance activities are proposed for this important potential safety concern (ORION Study and long-term follow-up of OLE Study RPC01-3001), which is adequate.

Pulmonary Effects

The pharmacodynamic effect of S1P receptor modulators on bronchial smooth muscle cells could potentially lead to a worsening of pre-existing pulmonary conditions in patients with MS.

Minor mean and median reductions from baseline over time were observed in PFT (including FEV_1, FVC, FEV_1/FVC ratio, and diffusing capacity for carbon monoxide (D_{LCO})), which were slightly higher in subjects on ozanimod 1 mg as compared to ozanimod 0.5 mg or IFN β-1a. These changes were not clinically meaningful and were primarily driven by changes during the first 3 months. These early small changes for the 1 mg ozanimod dose relative to 0.5 mg ozanimod dose or IFN β-1a were not progressive through 12 months. An examination of the FEV1 and FVC from Month 12 through 24 using just the Study RPC01-201B, which was controlled through 24 months, showed similar, small changes from Month 12 through 24 in all treatment groups which were not meaningfully different. The absolute changes at any given time point for FEV_1 or FVC were unlikely to be of clinical significance. The median change from baseline for FEV_1 and FVC at Month 12 and Month 24 with ozanimod 1 mg was approx. 100 ml. The variability in the estimates (standard error of the mean [SEM]) over time results in a significant overlap across the treatment groups suggested for lack of any meaningful difference. Examination of the subjects with outlier values below 80% or 60% on 2 or more consecutive assessments, or with their last value below the 80% or 60% threshold, respectively, indicated no differences across the treatment groups. In order to look for subjects with potential pulmonary changes related specifically to lung volume restriction an examination of subjects with concurrent decreases from baseline (< 80%) in both D_{LCO} and FVC was done. Eight subjects (2 in ozanimod 1 mg, 4 in the ozanimod 0.5 mg, and 2 in IFN β-1a) were identified and all continued in the trial without respiratory AEs that were serious or led to discontinuation. Five of

these 8 subjects came from 1 investigator site. It is notable that of the 8 subjects with concurrent decreases in FVC and D_{LCO}, the baseline % predicted FVC was greater than 100 in 7 out of 8 with the 2 highest likely representing erroneous and/or unphysiological values. Collectively, the declines in FVC in these subjects may represent regression to the mean or learning effect rather than a clinically significant reduction in lung function. Importantly, the lack of association of PFT findings to related AEs suggested that these observed small changes at the ozanimod 1 mg dose were not clinically meaningful. Respiratory AEs in the active-controlled Phase 3 RMS studies were similar across treatment groups with few SAEs and no AEs that led to discontinuation. The totality of the pulmonary data indicated that mild reductions in FEV_1 and D_{LCO} occurred early in treatment with ozanimod 1 mg but were not clinically meaningful and did not progress. Furthermore, the data did not demonstrate an increased incidence of respiratory-related AEs in comparison to IFN β-1a.

Data from Pool B for a total of 24 months of controlled treatment with ozanimod 1 mg indicate small reductions in FEV_1 and FVC (expressed as median percent reductions from baseline) mainly at Month 3 and no further significant reductions were noted at later time points up to Month 24 (FEV_1 Month 3: -1.8%, Month 24: -3.4%). Percent changes in median FVC values from baseline up to 24 months considerably fluctuated.

At present, there is no evidence for an increase in the (long-term) incidence of respiratory adverse events (such as asthma, dyspnea and other obstructive events) with ozanimod treatment as compared to IFN β-1a. However, PFT-related adverse events (i.e. FEV_1 decreased) were almost exclusively reported for ozanimod 1 mg in Pool A1 (0.7%) and Pool B (0.5%) in the summary of SDEIs. Summary of PFT abnormality PTs revealed a slightly higher incidence of subjects with any reported PFT abnormalities in the ozanimod 1 mg group (1.7%) compared with the IFN β-1a group (0.8%). The difference in incidences between these two groups mainly derives from FVC decreased and FEV_1 decreased. Therefore, 'pulmonary function test abnormal' was added as ADR to SmPC section 4.8 with more detailed explanation given in the subsection of 'Description of selected adverse reactions' on the respiratory system.

Patients were excluded from studies if they had clinically relevant pulmonary disease or PTFs indicating FEV_1 or FVC <70% of predicted values at screening. For S1P modulators, caution is advised in patients with severe respiratory disease, pulmonary fibrosis and COPD). A discussion was presented on pulmonary function parameters in ozanimod-treated patients, who are at risk for worsening of pulmonary function. Of note, patients with conditions like asthma or COPD were not excluded from clinical trials despite those with a screening FEV_1 or FVC <70% of predicted values. However, a total of 11 patients presented with such values at baseline. Of these, only a single subject (on ozanimod 1 mg) had an outlier result. For current smokers with <80% of baseline PFT for two consecutive post-baseline visits or on the last post-baseline visit, outlier analyses of FEV_1 and FVC showed more patients affected on ozanimod as compared to IFN β-1a, while the overall percentage was low. At least for those with FVC outliers, no concomitant adverse events or actions on the measurements have been reported. It is acknowledged that no firm conclusion can be drawn based on the limited number of subjects with more pronounced pulmonary conditions like COPD. However, regarding patients with a medical history of asthma, outliers were solely reported in the ozanimod 1 mg group. More subjects with baseline FEV_1 % predicted or FVC % predicted <80% had an outlier result after being treated with ozanimod as compared to IFN β-1a. Given the limited data on patients treated in clinical ozanimod studies with a medical history of respiratory function impairment and given the above results, a general warning statement in Section 4.4 with regard to caution for patients with specific underlying respiratory conditions has been included.

Other Safety Topics

Depression and Suicidal Ideation or Behavior

S1P receptor modulators are not known to increase the risk of depression or suicidality. Ozanimod seems not to induce depression, suicide and suicide-related events, all of which occurred in a low and similar number of subjects across treatment groups throughout clinical studies. In the only placebo-controlled study of ozanimod in MS patients (Study RPC01-201A), no signal of increased risk of depression over placebo was identified for ozanimod with the incidence of depression for the ozanimod 1 mg group not differing from that reported for the placebo group (1 case each, 1.2% versus 1.1%, for ozanimod 1 mg and placebo, respectively.

Two suicidal attempts were mentioned in the RMS program (one in Study RPC01-201B another in the OLE Study RPC01-3001). Upon request, the Applicant provided additional evidence about available SAEs in line with suicidal actions, including (serious) events of intentional overdose. In total, four subjects on ozanimod were reported to either have had a TEAE of suicide attempt (one subject) or intentional overdose (2 subjects) or both, suicide attempt and intentional overdose (one subject on ozanimod 0.5 mg), three of which had a history of depression. Neither of these cases was found related to study drug. The overall assessment of suicidality does not give rise to a concern that ozanimod triggers suicidality. Moreover, one case reporting craniocerebral injuries resulting from traumatic-mechanic event was evaluated and conclusion by the investigator was that this did not represent suicidal intent.

Overdose with Ozanimod

One subject who had been receiving ozanimod 1 mg for approximately 1 year in OLE Study RPC01-3001 intentionally ingested more than 100 pills of prescription medications, including ozanimod. This event was recorded as an intentional overdose by the investigator. The patient experienced no symptoms related to overdose. Abnormalities in the Columbia Suicide Severity Rating Scale were present at baseline prior to initiation of ozanimod.

Abuse Potential

Ozanimod and CC112273 did not show potential for abuse liability based upon assessment in a rat self-administration study. Across the ozanimod clinical development program, there was no evidence for drug abuse, misuse, withdrawal symptoms, or dependence on ozanimod. There was no evidence for ozanimod having the potential for abuse based on a comprehensive review of AE reports.

Rebound and Withdrawal Effects

Rebound in MS has been defined as exceptionally high disease activity with a severe increase in disability and multiple new MRI brain lesions following discontinuation of therapy (Evangelopoulos, 2018; Hatcher, 2016). There is no evidence for this type of rebound effect associated with the cessation of ozanimod.

A post hoc analysis of ARR in subjects who discontinued study drug was conducted to assess the potential for disease rebound following the cessation of treatment. The active-controlled Phase 3 RMS studies included a 28-day post-treatment follow-up visit. An assessment of relapses occurring during the 28-day posttreatment follow-up was conducted in subjects who 1) permanently discontinued study drug in the treatment period of the parent studies, or 2) following completion of the treatment period and prior to the first dose of study drug in the OLE Study RPC01-3001. The subject-years on study was short as the majority of subjects continued in the OLE and the time before enrolment into the OLE was generally ≤2 weeks. A total of 6 relapses were reported during this period: 1 subject in the ozanimod 1 mg dose group, 1 subject in the ozanimod 0.5 mg dose group, and 4 subjects in the IFN β-1a group, resulting in lower relapse rates in the ozanimod dose groups (unadjusted ARRs of 0.058 and 0.056 for ozanimod 1 mg and 0.5 mg respectively) compared with the IFN β-1a group (unadjusted ARR of 0.235). The subject in the ozanimod 1 mg group discontinued study drug prematurely due to an AE of irritability and reported a relapse 19 days after stopping ozanimod. The relapse was reported as nonserious, moderate in severity, and partially recovered. There was no evidence that this event represented a worsening from baseline.

Withdrawal effects were evaluated by an analysis of AEs with onset after the last dose, in particular those that occurred in at least 2 subjects and: 1) had the potential to reflect signs and symptoms indicating activity of the treated disease after study discontinuation, or 2) are potentially life threatening. There were no AEs indicative of withdrawal reported in the active-controlled Phase 3 RMS studies.

There was no evidence of rebound or withdrawal in the active-controlled Phase 3 RMS studies. Nevertheless, phase 3 studies routinely observed patients for 28 days after drug discontinuation, which may not have been sufficient to observe effects following withdrawal of ozanimod considering the long half-life of the active metabolites CC112273 and CC1084037 which may mitigate the potential for rebound or withdrawal effect. Therefore, additional wording on "Return of disease activity (rebound) after ozanimod discontinuation" has been included in SmPC section 4.4 to reflect this concern together with the class effect known for S1P receptor modulators. Moreover, the Applicant correctly classified "Effects following withdrawal of drug' as 'missing information", for which post-marketing additional pharmacovigilance activities are planned using long-term studies/ extension study data from ORION and OLE Study RPC01-3001 to further evaluate possible rebound effects in relation to MS disease state recrudescence, full recovery from lymphopenia and carry over effects to subsequent MS therapy.

Method for Defining Adverse Drug Reactions in Product Information

A thorough justification of ADRs to be included in section 4.8 of the SmPC was provided by the Applicant. ADRs were selected based on the incidence of reports (≥ 2% overall and ≥ 1% higher than IFN β-1a during the controlled Phase 3 studies, and in consideration of AEs reported in the placebo-controlled Phase 1 and 2 studies) and medical assessment (including a causality determination by use of the Bradford-Hill criteria, and in consideration of the mechanism of action of ozanimod and possible class effects).

All AEs reported in the ozanimod clinical development program were considered in the selection of ADRs, including a review of both placebo-controlled and active-controlled studies in consideration of the known safety profile of IFN β-1a. Each ADR is categorized by frequency (ie, very common, common, uncommon, or rare) based on the subject incidence reported in the ozanimod 1 mg group in Pool A1 (N=882). This method is consistent with the European Commission's guidance on the estimation of frequency of adverse reactions [A Guideline on Summary of Product Characteristics, Rev. 2, September 2009] and the Council for International Organizations of Medical Sciences' Guidelines for Preparing Core Clinical-Safety Information on Drugs, 2nd Edition (CIOMS, 1999).

There were 19 AEs reported in the controlled Phase 3 RMS studies (Studies RPC01-301 and RPC01-201B [Pool A1]) with a frequency ≥ 2% of subjects in the total ozanimod group: rhinitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, respiratory tract infection viral bronchitis, urinary tract infection, ALT increased, GGT increased, insomnia, depression, headache, fatigue, arthralgia, influenza like illness, hypertension, orthostatic hypotension, back pain and abdominal pain upper. Ten of these 19 AEs were reported at an incidence ≥ 1% higher in any ozanimod dose group than in the IFN β-1a group: nasopharyngitis, pharyngitis, respiratory tract infection viral, urinary tract infection, ALT increased, GGT increased, hypertension, orthostatic hypotension, back pain, and abdominal pain upper. Two of these 10 AEs were rejected as ADRs because the evidence did not support a causal relationship to ozanimod treatment (i.e. back pain and abdominal pain upper). The remaining 8 preferred terms provided enough evidence for an association to ozanimod treatment as ADRs. These included nasopharyngitis, pharyngitis, respiratory tract infection viral, urinary tract infection, ALT increased, GGT increased, hypertension and orthostatic hypotension.

In addition, events that were assessed as causally related to ozanimod treatment but less frequently than 2% included bradycardia, hypersensitivity (including rash and urticaria) and herpes zoster.

Lymphopenia is an expected pharmacologic effect of ozanimod and is included as an ADR.

In the course of this procedure, further events have been classified as adverse drug reactions, including macular oedema, blood bilirubin increased and pulmonary function test abnormal based on the aforementioned criteria.

As pharmacovigilance activities, two studies were planned to address most proposed concerns:

- ORION study, a post authorization, multinational, long-term noninterventional study to evaluate the long-term safety profile of ozanimod in the real-world setting.
- Long-term follow-up of OLE Study RPC01-3001 to characterise the long-term safety of ozanimod in patients with relapsing MS.

No additional risk minimisation measures for any concern other than routine measures are proposed or deemed necessary.

Serious adverse event/deaths/other significant events

Serious Adverse Events

In Pool A1, the incidence of SAEs was very low and similar across treatment groups (4.6%, 5.3% and 4.4% in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups, respectively), with most SAE terms reported in single subjects. No discernible trends in any type of SAE were noted across the treatment groups, and no dose-related effects were observed (**Table 30**).

Table 30: Incidence of Serious Treatment-emergent Adverse Events Reported in ⩾ 2 Subjects in Any Treatment Group – Pool A1 (Safety Population)

Preferred Term	IFN β-1a 30 µg (N = 885) n (%)	Ozanimod 0.5 mg (N = 892) n (%)	Ozanimod 1 mg (N = 882) n (%)
Appendicitis	2 (0.2)	1 (0.1)	3 (0.3)
Intervertebral disc disorder	1 (0.1)	0	2 (0.2)
Ovarian cyst	0	0	2 (0.2)
Pyelonephritis acute	2 (0.2)	0	1 (0.1)
Cervical radiculopathy	0	2 (0.2)	0
Atrial fibrillation	0	2 (0.2)	0
Sinus tachycardia	0	2 (0.2)	0
Ankle fracture	0	2 (0.2)	0
Multiple sclerosis relapse	3 (0.3)	1 (0.1)	0

In Pool B, long-term exposure to ozanimod of up to 68 months revealed a slightly higher incidence of SAEs for patients in the ozanimod 1 mg group (Pool B) as compared to Pool A1 (7.2% vs. 4.6%). An increase in the incidence of SAEs from Pool A1 to B was noted for the infections and infestations system organ class (SOC) with ozanimod 1 mg (Pool A1: 1%; Pool B: 1.4%), obviously driven by continuous dosing of 1 mg, whereas SAEs were less frequently reported in patients on 0.5 mg or "switchers" from 0.5 mg to 1 mg (1.7% vs. 0.6% and 0.8%). No accumulation of specific types of serious infections was found.

Deaths

Seven deaths, all in subjects on ozanimod, were reported up to the data cut-off on 30 Jun 2018 in the ozanimod clinical program. Five deaths occurred in RMS subjects, including 2 that occurred during the controlled Phase 3 studies (Pool A1) and 2 that occurred during the OLE (Study RPC01-3001). None of these deaths were considered to be related to study drug by the investigator or the Sponsor. Two deaths occurred in the IBD program, 1 in the UC program and 1 in the CD program. These deaths were considered to be related to study drug by the investigator and unrelated to study drug by the Sponsor.

The events surrounding each death were summarized below:

Two deaths in the Controlled Phase 3 RMS Studies (Pool A1)

On Study

- A young female (age ranging 20-30 years) subject who received ozanimod 0.5 mg for approximately 21 months in Study RPC01-201B, died from accidental drowning on Study Day 637. There was no medical or family history of depression or suicide. An autopsy was not performed, and a death certificate was not provided. The event was considered to be unrelated to study drug by the investigator.

Off Study

- A young female (age ranging 20-30 years) subject who received ozanimod 1 mg for approximately 11 months in Study RPC01-201B before discontinuing study drug due to Guillain-Barré syndrome on Study Day 332 and PRES. The subject died approximately 10 months after the last dose of ozanimod as a result of chronic kidney failure. Relevant past medical history included toxic hepatitis. The event of chronic kidney failure was considered to be unrelated to study drug by the investigator.

Three deaths during the RMS OLE Study RPC01-3001

- A young female (age ranging 20-30 years) subject who received ozanimod 0.5 mg for approximately 12 months in Study RPC01-301 and at least 1 dose of ozanimod (0.25 mg) in OLE Study RPC01-3001 (last dose date unknown), died in the hospital on Study Day 69 (449 days from the first dose of ozanimod) from multiple craniocerebral injuries resulting from traumatic-mechanic event. The subject did not have a medical history of suicidal ideation or depression, and the investigator indicated that there was no evidence of depression or suicidality during the study. Relevant medical history included prior concussion, abdominal cavity injury, cervical polyps (removed), bradycardia, and metabolic cardiomyopathy. The event was considered to be unrelated to study drug by the investigator.
- A middle-aged male (age ranging 40-50 years) subject who received ozanimod 1 mg for approximately 12 months in Study RPC01-301 and for approximately 13 months in OLE Study RPC01-3001, died on Study Day 404 due to a pulmonary embolism after a 38-day hospitalization due to a surgical repair of a lower limb fracture. The subject's last dose of ozanimod 1 mg was on Day 395. No treatment was reported for the event. The investigator considered the event unrelated to study medication.
- In addition to the subjects above, the Sponsor is aware of the death of another subject ~~424-1001,~~ which occurred more than 28 days after discontinuation from OLE Study RPC01-3001. This subject had SAE of metastatic pancreatic carcinoma on Study Day 124 (1,135 days after the first dose of ozanimod) that was considered unlikely to be related to study drug by the investigator and Sponsor. The investigator was not able to attribute the death as an outcome of this SAE, and the death was not recorded as an on-study event.

Two deaths during the IBD Studies:

- A middle-aged female (age ranging 40-50 years) subject with UC who received ozanimod 0.5 mg for approximately 32 weeks in Study RPC01-202 and ozanimod 1 mg for approximately 863 days in RP01-202OLP, discontinued study drug due to adenocarcinoma. On study ALC levels were <0.5 x 10^9/L on Study Day 830. The subject died in the hospital from mucinous adenocarcinoma (of gastric, pancreatic, bilial, or endometrial [intestinal type] origin) on open-label extension Study Day 911. The event was considered to be possibly related to study drug by the investigator. The Sponsor considered the event to be unrelated to study drug.
- A young female (age ranging 20-30 years) subject with CD who received ozanimod 1 mg for approximately 11 months in Study RPC01-2201, discontinued study drug to allow initiation of high-dose corticosteroid for treatment of worsening Crohn's disease on Study Day 330. The subject was hospitalized due to the worsening Crohn's disease on Study Day 338 and died in the hospital from complications of worsening Crohn's disease (duodenal fistula, sepsis) on Study Day 361. Even though the SDEI was stated as serious or opportunistic infection, this could not have been confirmed in retrospect. The event was considered to be possibly related to study drug by the investigator. The Sponsor considered the event to be unrelated to study drug.

Note for the purpose of the PPD protection, ranges of ages were included in the EPAR instead of individual ages of subjects.

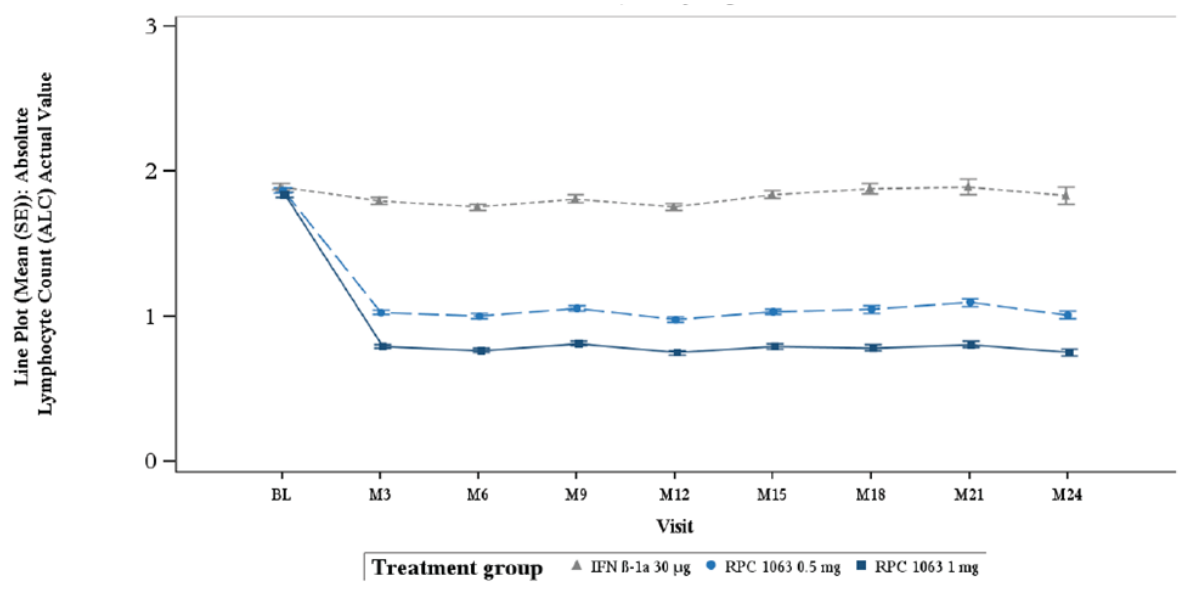
To conclude, two cases are suspect of a suicidal context, two cases might involve immunosuppressant properties of ozanimod leading to infections, and two cases of death were reported in the context of malignancies. Although, no common pattern of adverse events of special interest known for ozanimod could be derived from the seven death cases, at least a contribution of ozanimod could not be ruled out.

Laboratory findings

Absolute Lymphocyte Count

A dose-dependent reduction in ALC from baseline of approximately 50% to 70% is associated with clinical efficacy in RMS (Subei, 2015). The lymphocyte count was reduced as early as from Week 4 in the phase 2 study on, reaching a maximum decrease at Month 3 after treatment initiation. Mean ALC reductions from baseline were 53.5% to 57.4% for subjects on ozanimod 1 mg and 40.9% to 45.8% for subjects on ozanimod 0.5 mg in Pool A1. Mean actual ALC values were (and remained) below lower limit of normal starting at Month 3 (Figure 10).

Figure 10: Mean (SE) Absolute Lymphocyte Count by Visit – Pool A1 (Safety Population)



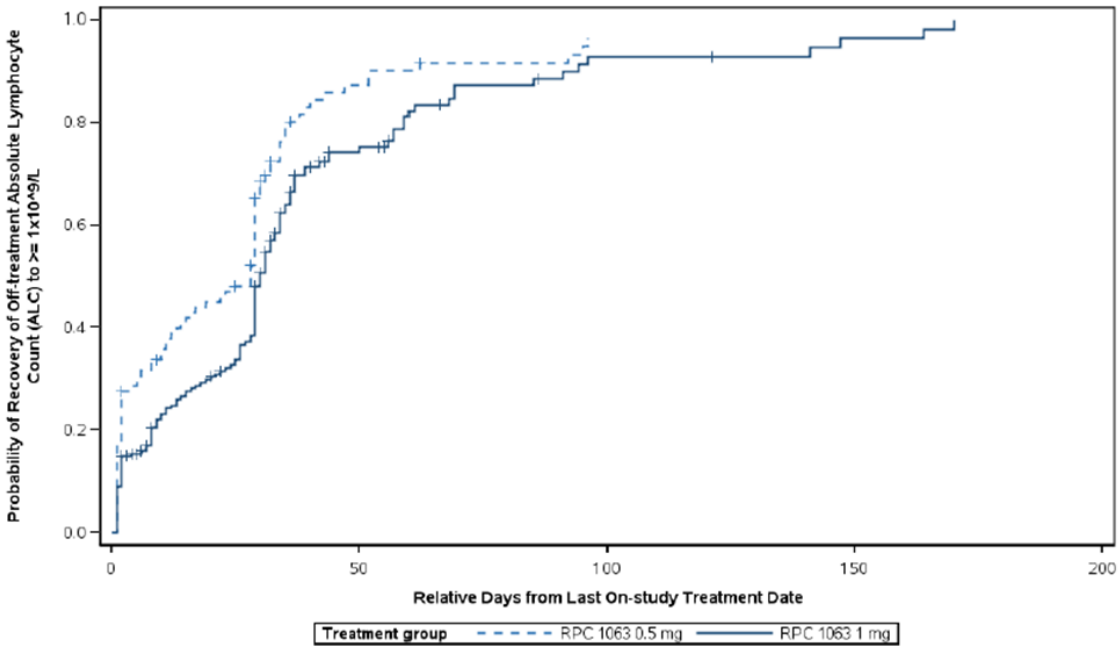
IFN ß-1a 30 µg	885	874	845	833	823	625	434	386	375
RPC 1063 0.5 mg	892	885	865	853	831	623	444	386	370
RPC 1063 1 mg	882	868	856	843	827	629	453	395	381

ALC = Absolute lymphocyte count; BL = baseline, IFN = interferon; M = month; RCP 1063 = ozanimod HCl; SE = standard error

The number of subjects with an ALC <0.2 x 10^9/L was higher in the 1 mg ozanimod group (n=29, 3.3%) than in the ozanimod 0.5 mg group (n=4, 0.4%) and the IFN β-1a group (0) in Pool A1 (5.5% of patients treated with ozanimod 1 mg in Pool B). The majority of these subjects (22/29 [75.9%] in the ozanimod 1 mg group and 3/4 [75%] in the ozanimod 0.5 mg group) recovered to levels ≥0.2 x 10^9/L while on treatment. As indicated in the AESI section on "infections", ALC values of <0.2 x 10^9/L were not associated with serious infections. Adequate warning wording has been included in SmPC section 4.4 (*"infections"*) to reflect threshold ALC values to prompt therapeutic action as well as precautionary measures. Nevertheless, it cannot be ruled out that prolonged lymphocyte count decreases will translate into an increased risk for acquiring serious or opportunistic infections in rare cases.

Lymphocyte counts collected from approximately 200 subjects following discontinuation of study drug allowed for a post hoc assessment of off-treatment recovery of ALC. Based on the KM estimate, the median time to recovery of ALC to the normal range (≥ 1 x 10^9/L) was 30 days after treatment discontinuation in the ozanimod 1 mg treatment group and 28 days after treatment discontinuation in the ozanimod 0.5 mg treatment group (Figure 11).

Figure 11: Kaplan Meier Plot of Time to ALC Recovery to Lower Limit of Normal Range (≥ 1 x 10^9/L) – Pool B



ALC = Absolute lymphocyte count, RPC 1063 = Ozanimod.

In the ozanimod 1 mg treatment group, approximately 80% of subjects recovered to the normal range 2 months after treatment discontinuation and approximately 90% recovered to the normal range 3 months after treatment discontinuation. In the ozanimod 0.5 mg treatment group, approximately 80% of subjects recovered to the normal range approximately 35 days after treatment discontinuation and approximately 90% of subjects recovered to the normal range 2 months after treatment discontinuation

Liver Function Tests (see section on Hepatic effects)

Other Clinical Laboratory Evaluations

Despite dose-dependent mean decreases in leukocytes (in line with decreases in lymphocyte counts) and basophiles as well as mean increases in monocytes and respective abnormalities in pre-defined threshold values for these parameters, no other concerns emerged on haematology values. The incidence of AEs related to haematology parameters was overall low. None was serious or led to discontinuation of the drug.

Modest, dose-dependent, non-progressive increases from baseline in total cholesterol and low-density lipoprotein levels were observed at Month 3 with ozanimod 1 mg and 0.5 mg relative to IFN β-1a. These changes were accompanied by corresponding increases in high-density lipoprotein and no meaningful changes in triglyceride levels. No concomitant increases in cardiac-related AEs were noted with cholesterol changes.

No clinically meaningful trends in changes from baseline in other chemistry parameters or urinalysis parameters were observed for any treatment group.

Safety in special populations

The effects of age, sex, race, region, BMI, smoking status and prior use of DMT on the incidence of AEs and SAEs were examined for subjects in Pool A1. The overall incidence and type of AEs for ozanimod

versus IFN β-1a within each subgroup were generally consistent with those of the overall population and did not reveal any clinically relevant concerns in any subgroup.

Age

In each treatment group, the ratio of subjects≤ 40 years old versus > 40 years old was approximately 2:1 (ozanimod 1 mg: 621 versus 261; ozanimod 0.5 mg: 615 versus 277; IFN β-1a: 614 versus 271). The incidence of AEs was similar in subjects ≤ 40 years of age and subjects > 40 years of age in all 3 treatment groups (ozanimod 1 mg: 65.1% versus 72.0%; ozanimod 0.5 mg: 64.4% versus 68.2%; IFN β-1a: 79.6% versus 78.2%) and did not reveal any clinically relevant concerns with ozanimod treatment. In both age subgroups, the predominant SOCs were infections and infestations and nervous system disorders.

There was a higher incidence of SAEs in subjects > 40 years of age than subjects ≤ 40 years of age in all 3 treatment groups (ozanimod 1 mg: 6.5% versus 3.9%; ozanimod 0.5 mg: 7.9% versus 4.1%; IFN β-1a: 7.4% versus 3.1%). This difference was not attributable to any particular SOC(s).

Within age subgroups, the overall incidence of TEAEs and SAEs was similar across the treatment groups. A higher incidence of hepatic SDEIs was observed among subjects > 40 years old in the ozanimod 1 mg and 0.5 mg treatment groups, relative to IFN β-1a (13.8%, 11.2%, 5.2%, respectively), than among subjects ≤ 40 years of age (10.1%, 8.0%, 6.2%, respectively). Reductions in ALC to < 0.2 x 109/L were more frequently observed in subjects > 40 years old than ≤ 40 years old in the ozanimod 1 mg treatment group (6.5% versus 1.9%, respectively), but not the ozanimod 0.5 mg treatment group (0.7% and 0.3%, respectively) or IFN β-1a treatment group (no cases in either subgroup).

Subjects >55 years of age were excluded from studies contributing to Pool A1. As reported before, an additional analysis of clinical safety data of these 161 patients included in Pool B were provided by the Applicant. The limited number of patients >55 years of age generally exhibited a higher incidence of TEAEs in contrast to patients ≤55 years. The most remarkable differences were found for liver function test abnormalities (ALT increased and GGT increased) and cardiovascular – related TEAEs (hypertension and orthostatic hypotension).

Sex

Population PK analysis showed that CC112273 steady-state exposure in males was approximately 35% lower compared to females. In each treatment group, the ratio of female subjects to male subjects was approximately 2:1 (ozanimod 1 mg: 576 to 306; ozanimod 0.5 mg: 598 versus 294; IFN β-1a: 602 versus 283).

There was a higher incidence of AEs among female subjects compared to male subjects in the ozanimod 1 mg and IFN β-1a treatment groups (Table 31), which was attributable to events in the psychiatric disorders, nervous system disorders, and gastrointestinal disorders SOCs. The incidence of AEs was similar between female and male subjects in the ozanimod 0.5 mg treatment group. Within the subgroups of female and male subjects, the relative differences across treatment groups in the incidence of AEs were similar. Imbalances between gender subgroups were likely due to the natural history of specific AEs or to a chance finding from rare AEs.

Table 31: Incidences of Frequently reported TEAEs, Frequently reported SAEs and SDEIs by sex – Pool A1

Parameter	Female			Male		
	IFN β-1a N = 602 n (%)	Ozanimod 0.5 mg N = 598 n (%)	Ozanimod 1 mg N = 576 n (%)	IFN β-1a N = 283 n (%)	Ozanimod 0.5 mg N = 294 n (%)	Ozanimod 1 mg N = 306 n (%)
TEAEs Reported at Overall Incidence ≥ 5% in Any Treatment Group						
Any TEAE	488 (81.1)	397 (66.4)	403 (70.0)	213 (75.3)	188 (63.9)	189 (61.8)
Nasopharyngitis	58 (9.6)	72 (12.0)	69 (12.0)	26 (9.2)	31 (10.5)	29 (9.5)
Headache	59 (9.8)	64 (10.7)	55 (9.5)	19 (6.7)	18 (6.1)	23 (7.5)
Upper respiratory tract infection	41 (6.8)	46 (7.7)	41 (7.1)	20 (7.1)	21 (7.1)	11 (3.6)
Alanine aminotransferase increased	18 (3.0)	18 (3.0)	21 (3.6)	10 (3.5)	23 (7.8)	26 (8.5)
Influenza like illness	309 (51.3)	36 (6.0)	34 (5.9)	133 (47.0)	8 (2.7)	10 (3.3)
Pyrexia	40 (6.6)	12 (2.0)	14 (2.4)	16 (5.7)	5 (1.7)	2 (0.7)
SAEs Reported at Overall Incidence ≥ 2 Subjects in Any Treatment Group						
Any SAE	28 (4.7)	29 (4.8)	29 (5.0)	11 (3.9)	18 (6.1)	12 (3.9)
Appendicitis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.4)	0	2 (0.7)
Intervertebral disc disorder	1 (0.2)	0	0	0	0	2 (0.7)
Ovarian cyst	0	0	2 (0.3)	0	0	0
Pyelonephritis acute	2 (0.3)	0	1 (0.2)	0	0	0
Cervical radiculopathy	0	1 (0.2)	0	0	1(0.3)	0
Atrial fibrillation	0	0	0	0	2 (0.7)	0
Sinus tachycardia	0	1 (0.2)	0	0	1 (0.3)	0
Ankle fracture	0	1(0.2)	0	0	1 (0.3)	0
Multiple sclerosis relapse	1 (0.2)	1 (0.2)	0	2 (0.7)	0	0
SDEIs						
Any serious or opportunistic infections SDEI	20 (3.3)	17 (2.8)	18 (3.1)	6 (2.1)	7 (2.4)	7 (2.3)
Herpes zoster	1 (0.2)	3 (0.5)	4 (0.7)	1 (0.4)	0	0
Varicella zoster virus infection	0	0	1 (0.2)	0	0	0
Any malignancy SDEI	2 (0.3)	5 (0.8)	4 (0.7)	0	0	1 (0.3)
Any cardiac SDEI	82 (13.6)	97 (16.2)	95 (16.5)	38 (13.4)	52 (17.7)	55 (18.0)
Any pulmonary SDEI	110 (18.3)	96 (16.1)	129 (22.4)	32 (11.3)	61 (20.7)	60 (19.6)
Pulmonary function tests	106 (17.6)	93 (15.6)	123 (21.4)	31 (11.0)	59 (20.1)	57 (18.6)
Pulmonary AEs	7 (1.2)	4 (0.7)	11 (1.9)	2 (0.7)	2 (0.7)	4 (1.3)
Any macular edema SDEI	0	2 (0.3)	1 (0.2)	0	1 (0.3)	0
Any hepatic SDEI	32 (5.3)	38 (6.4)	49 (8.5)	20 (7.1)	42 (14.3)	50 (16.3)
Hepatic chemistry	10 (1.7)	4 (0.7)	9 (1.6)	4 (1.4)	9 (3.1)	13 (4.2)
Hepatic AEs	31 (5.1)	37 (6.2)	48 (8.3)	20 (7.1)	39 (13.3)	49 (16.0)
Any postbaseline ALC < 0.2 x 10^9/L	0	4 (0.7)	23 (4.0)	0	0	6 (2.0)

AE = Adverse event, ALC = Absolute lymphocyte count, IFN = Interferon, TEAE = Treatment-emergent adverse event, SAE = Serious adverse event, SDEI Sponsor-designated events of interest

The incidence of SAEs was low and slightly higher among female than male subjects in the ozanimod 1 mg and the IFN β-1a group, while for subjects in the ozanimod 0.5 mg group, the incidence of SAEs was lower in female subjects than in male subjects. Among the SDEIs, the incidence of serious and opportunistic infections were generally comparable across the treatment groups in both male and female subjects (Table 32). All cases of herpes zoster or Varicella zoster virus infection in the ozanimod treatment groups occurred in female subjects; however, this is consistent with the epidemiologic literature (Fleming, 2003). All malignancies (except 1 case of testicular seminoma [pure] stage I) were reported in female subjects. The overall low incidence of malignancies and the disproportionate gender distribution in clinical MS studies did not allow a meaningful conclusion. ALC reductions to <0.2 x 10^9/L

occurred predominantly in females. Pulmonary SDEIs in the ozanimod treatment groups occurred at a higher incidence relative to IFN β-1a in male subjects as compared to female subjects. This was driven mainly by PFT abnormalities.

The incidence of liver enzyme elevations, primarily ALT and GGT, as well as the incidence of hepatic SDEIs was significantly higher in males (twice as high) as compared to females as discussed in previous section.

Race

For Pool A1, the vast majority of subjects were white (approximately 99%); therefore, due to the small sample size of the non-white subgroup, no conclusions can be drawn regarding the difference in the overall incidence of AEs between the white and non-white race groups.

Region

No reliable conclusions can be drawn for TEAE incidences in different regions given that 90% of patients were from Eastern Europe and only 10% from countries included in the group of rest-of-the world.

Body Mass Index

The vast majority (~90%) of subjects had a BMI < 30 kg/m2 as compared to ≥ 30 kg/m2 in all 3 treatment groups (ozanimod 1 mg: 784 versus 97; ozanimod 0.5 mg: 812 versus 79; IFN β-1a: 788 versus 97). Comparisons between BMI subgroups should be interpreted with caution due to the relatively smaller population of subjects with BMI ≥ 30 kg/m2.

The incidence of AEs was higher in subjects with a BMI ≥ 30 kg/m2 than in subjects with a BMI < 30 kg/m2 in the ozanimod treatment groups (ozanimod 1 mg: 82.5% versus 65.2%; ozanimod 0.5 mg: 78.5% versus 64.3%) and was similar between the BMI subgroups in the IFN β-1a treatment group (79.4% versus 79.2%). There were no differences in the incidence of AEs between the ozanimod treatment groups within either BMI category.

Overall, the pattern of AEs reported by BMI subgroup was generally consistent with the overall population and did not reveal any clinically relevant concerns with ozanimod treatment. Ozanimod-treated subjects with a BMI ≥ 30 kg/m2 had a higher incidence of orthostatic hypotension (both treatment groups) and hypertension (ozanimod 1 mg only) compared with subjects with BMI <30 kg/m2. The incidence of orthostatic hypotension was 8.2% and 11.4% for subjects with BMI ≥30 kg/m2 in the ozanimod 1 mg and ozanimod 0.5 mg groups, respectively, compared with 3.8% and 2.8%, respectively, for subjects with BMI < 30 kg/m2. This increase was not observed for subjects in the IFN β-1a group (1.0% for BMI ≥30 kg/m2 and 3.4% for BMI <30 kg/m2). The incidence of hypertension in the ozanimod 1 mg treatment group was 12.4% in subjects with BMI ≥ 30 kg/m2 and 2.3% in subjects with BMI <30 kg/m2. Such an increase was not observed for subjects in the ozanimod 0.5 mg treatment group (2.5% for BMI ≥30 kg/m2 and 3.6% for BMI <30 kg/m2) or the IFN β-1a group (3.1% for BMI ≥30 kg/m2 and 1.9% for BMI <30 kg/m2).

The incidence of SAEs among subjects with BMI ≥ 30 kg/m2 was lowest in the ozanimod 1 mg treatment group (3.1% versus 5.1% and 5.2% in the ozanimod 0.5 mg and IFN β-1a treatment groups, respectively) and was similar across the treatment groups among subjects with BMI <30 kg/m2 (4.8%, 5.3%, and 4.3%, respectively).

Smoking Status

The overall incidence and type of AEs and SAEs for ozanimod versus IFN β-1a among current and not current smokers were generally consistent with those of the overall population and did not reveal any clinically relevant concerns with ozanimod treatment.

Prior Disease-modifying Therapy

Approximately 30% of subjects in each treatment group had a history of prior DMT use, most commonly glatiramer acetate, IFN β-1a, or IFN β-1b.

The overall incidence and type of AEs and SAEs for ozanimod versus IFN β-1a for subjects with prior DMT use was generally consistent with the overall population and did not reveal any clinically relevant concerns with ozanimod treatment. There was a slightly higher incidence of Infections and Infestations AEs in ozanimod-treated subjects with prior DMT use compared with DMT-naïve subjects (1 mg: 39.7% versus 33.3%, respectively; 0.5 mg: 39.2% versus 31.6%, respectively) but not in the IFN β-1a treatment group (33.3% versus 35.0%, respectively). These differences were not driven by serious or opportunistic infections. This finding is also in line with data from S1P modulators leading to specific warnings in the respective SmPC on prior immunosuppressive treatments. Nearly all evaluated ALC abnormalities or adverse events deriving thereof for ozanimod 1 mg showed a numerical difference in their occurrence at the expense of patients with prior DMT treatment reported. The difference, however, was small and did not point towards a generally different safety profile in patients with previous immunomodulating therapy.

Hepatic Impairment Study

Study RPC01-1904 was a Phase 1, open-label, parallel-group study to characterize the PK and safety of a single 0.25 mg dose of ozanimod in 16 subjects with mild (n=8) or moderate (n=8) hepatic impairment and 15 healthy matched subjects with normal hepatic function.

No dose adjustment is deemed necessary for patients with mild or moderate hepatic impairment (Child-Pugh class A and B) based on a total of 16 subjects (8 with mild and 8 with moderate impairment) treated with a single 0.25 mg dose of ozanimod and compared to 15 healthy matched controls from study RPC01-1904. The exposure in this study is much lower than the recommended therapeutic dose of 1 mg daily. Nevertheless, a single-dose PK study using 0.25 mg ozanimod to evaluate the effect of hepatic impairment is adequate to extrapolate to the recommended 1 mg once-daily maintenance dose as per the CHMP "Guideline on The Evaluation of The Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function" (CPMP/EWP/2339/02). Even though, based on this limited data, it could not be excluded that patients with mild to moderate liver impairment treated with therapeutic doses of ozanimod could have more frequent or more severe adverse events with long-term exposure, risk mitigation with the addition of routine monitoring of transaminase and bilirubin levels is thought to mitigate the risk in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Moreover, *'Severe liver impairment (Child-Pugh class C)'* is listed as a contraindication given that ozanimod was not studied in this subpopulation.

Renal Impairment Study

Study RPC01-1906 (Renal Impairment) was a Phase 1, open-label study to characterize the PK and safety of a single 0.25 mg dose of ozanimod in 8 subjects with ESRD with or without haemodialysis and 8 matched healthy subjects with normal renal function. Subjects with normal renal function were matched by body weight (± 20%) and age (± 10 years) to subjects with ESRD.

There were no clinically meaningful differences in systemic exposures of ozanimod and CC112273 in subjects with ESRD compared with their matched healthy subjects. Subjects were followed for 4 days, with a follow-up phone call 6 days after discharge. Two subjects (25.0%) with ESRD reported a total of 6 AEs and 1 subject (12.5%) with normal renal function reported 1 AE. The most frequently reported AEs were headache and nausea, each reported in 2 subjects with ESRD. There were no AEs leading to death, SAEs, or AEs resulting in discontinuation of the study or study drug. Based on this trial, renal impairment had no clinically important effects on pharmacokinetics of ozanimod or its main metabolite CC112273. No dose adjustment is needed in patients with renal impairment.

Use in Pregnancy and Lactation

Fertility study assessments in the rat had a NOEL of 30 mg/kg/day, corresponding to > 240 times the exposure at the MRHD for ozanimod and the active metabolites (across species). In the embryo-foetal development study, findings at higher dose levels included embryo-foetal death, abnormal/delayed ossification, and abnormalities of the viscera and large blood vessels. Pre- and post-natal effects of ozanimod evaluated in rats induced no abnormalities in either the parental females of F1 generation.

Ozanimod is excreted in the milk of ozanimod-treated rats.

Of note, during the entire clinical program, 48 pregnancies (38 subject pregnancies and 10 partner pregnancies) were reported as of the cut-off date (30 Jun 2018). All pregnancy exposures for study subjects occurred during the first trimester and subjects discontinued study medication promptly, with the exception that some subjects who elected termination and did not discontinue study medication. Of the 38 subject pregnancies, 23 resulted in a live birth of healthy infants (1 with late intrauterine growth retardation with subsequent normal progress), 5 resulted in spontaneous early loss, 8 subjects underwent elective abortion, and 2 subjects had not yet delivered. The incidence of spontaneous early loss (5/38 [~13%]) is within the known rate of miscarriage in the general population (García-Enguídanos, 2002).

Contraindication for the use of ozanimod during pregnancy and in women of childbearing potential not using effective contraception was added in section 4.3 of the SmPC. With reference to the non-clinical consideration and experience with the related S1P modulator fingolimod (EMEA/H/C/2202-PSUSA/00001393/201902), sections 4.4 and 4.6 of the SmPC and corresponding sections of the PL were reviewed.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

In study RPC01-1902, **itraconazole** as a strong inhibitor of CYP3A4 resulted in no clinically meaningful changes in exposure of ozanimod, CC112273 and CC1084037 and decreased the exposure to RP101075 by approximately 25%. **Rifampin** (strong inducer of CYP3A and moderate inducer of CYP2C8) resulted in minor effects on the AUCs of ozanimod but reduced the exposure for ozanimod, CC112273, and CC1084037 by approximately 24%, 60%, and 55%, respectively. Reduction in exposure to the two main active metabolites CC112273 and CC1084037 is due to CYP2C8 induction effect. A single subject was reported with second-degree AV block while being treated with a single dose of ozanimod 1 mg. Adverse events reported in this trial were in line with adverse events reported with a single ozanimod 1 mg dose (i.e. AV block) and did not suggest an increased risk following CYP3A4 inhibition/ induction.

In study RPC01-1903, **ciclosporin** as strong inhibitor of P-gp and BCRP was found to increase exposure of precursor metabolites of the two main active metabolites. Thus, an increase in exposure to the active metabolites could not be excluded. Although, no specific safety concerns were noted with coadministration of single doses of ciclosporin and ozanimod, the theoretical risk of increased exposure was included in SmPC section 4.5.

Oral contraceptives are frequently prescribed in female MS patients. In a dedicated DDI study (RPC01-1907), co-administration of ozanimod with a single oral contraceptive dose (combined ethinylestradiol and norethindrone), did not alter the PK of either component. Thus, the efficacy of the oral contraceptive is not expected to be altered with ozanimod treatment.

Interactions with cardiac drugs were evaluated using steady-state beta blocker **propranolol** and calcium channel clocker **diltiazem** (RPC01-1908). No clinically meaningful changes in the PK of ozanimod, RP101988, and RP101075 were observed when a single dose of ozanimod 0.25 mg was coadministered with steady-state propranolol or diltiazem. No meaningful changes were observed in cardiac parameters (i.e. heart rate or PR interval) compared to either drug alone. No cardiac-related AEs were reported. Study RPC01-1912 was conducted to evaluate the effect of inhibitors or inducers of CYP2C8 or CYP3A on the exposure of CC112273 and CC1084037. **Gemfibrozil**, a strong inhibitor of CYP2C8, had no effect on the exposure of ozanimod while it increased the exposure (AUC_{last}) of CC112273 and CC1084037 by approximately 47% and 69%, respectively. No cardiac-related or other significant AEs were reported from coadministration of a single **pseudoephedrine** dose with repeated ozanimod doses in study RPC01-1914. Co-administration of ozanimod QD over 30 days with a single dose of pseudoephedrine 60 mg on Day 30 did not potentiate the pseudoephedrine-induced BP response. However, ozanimod increased a pseudoephedrine-induced HR change by approximately 3 bpm, which is adequately reflected in section 4.5 of the SmPC.

The two main active metabolites CC112273 and CC1084037 are selective inhibitors of MAO-B; therefore, DDI are to be expected after simultaneous administration of ozanimod with serotonergic (i.e. selective serotonin reuptake inhibitors (SSRI), serotonin–norepinephrine reuptake inhibitors (SNRI), etc.) or sympathomimetic medications. Inhibition of MAO-B increases serotonin in the synaptic cleft, which sets the patient at risk for potentially life-threatening serotonin syndrome. Standardised MedDRA queries (based on neuroleptic malignant syndrome as SMQ) based on Pool D data did not reveal cases of serotonin syndrome; by application of a broader search strategy, 5 of 6 subjects had such SAEs in a timely context to initiation of serotonergic medication. When restricted to concomitant use of SSRI / SNRI (Pool A1), an increased incidence of TEAEs (driven by hypertension) in subjects on ozanimod compared to IFN β-1a, was reported after initiation of these drugs. Further analyses in Pool D found no significant difference on the incidence of serotonin syndrome extended broad SMQ TEAEs in patients treated with ozanimod after initialization of SSRI or SNRI concomitant medications (and without such medication). This finding was supported by clinical pharmacology studies and preclinical studies.

No specific concerns are to be raised on concomitantly administered sympathomimetic medications, cardiovascular medications, and steroid treatment, based on overall TEAE reporting rates after initiation of these drugs compared to IFN β-1a.

Discontinuation due to adverse events

The incidence of discontinuations from study drug due to AEs was low in Pool A1 with slightly more subjects having discontinued from IFN β-1a as compared to ozanimod (3.8% IFN β-1a, 2.4% ozanimod 0.5 mg, 2.9% ozanimod 1 mg). This was due to events of influenza like illness (1.4% of subjects on IFN β-1a vs. none in the ozanimod groups). The incidence of AESIs leading to discontinuation of ozanimod was low and included ≤3 subjects per treatment group with hepatic enzyme elevations (*ALT increased, GGT increased, liver function test abnormal, AST increased*), single cases of macular oedema (≤ 3 subjects per group) and bradycardia (2 subjects on ozanimod 0.5 mg only). The pattern and incidences of TEAEs leading to discontinuation did not change with longer-term exposure to ozanimod (Pool B). Pool C differed from what has been reported for the RMS studies in that the underlying IBD dominated the reasons for drug discontinuations.

More patients on IFN β-1a withdrew from study as compared to patients in either ozanimod group (4.1% vs. 2.6% total ozanimod). There was no SOCs or PTs for ozanimod that was significantly affected by study withdrawals as compared to IFN β-1a (influenza-like illness). No changes in the pattern and incidence of TEAEs leading to study withdrawal could be deduced from Pool B.

Dose interruptions due to TEAEs were infrequently reported for all treatment groups and highest for ozanimod 0.5 mg (2.8%), while ALT and AST increased were the most frequently reported reasons.

Post marketing experience

N/A

2.7.1. Discussion on clinical safety

Zeposia (ozanimod), an $S1P_1$ and $S1P_5$ agonist, was evaluated for the treatment of adult patients with RRMS with a recommended daily dosage of 1 mg. Experience with other S1P receptor modulators led to give particular attention to prespecified AEs of special interest that represent potential safety concerns and to an initial dose escalation regimen of ozanimod, which was actually successful in decreasing potential first-dose chronotropic and dromotropic effects.

The safety profile of ozanimod has been examined in a clinical development program including a subject population of more than 3,400 with over 8000 person-years of follow-up in RMS and IBD, including 2,765 subjects treated with ozanimod 1 mg for more than 1 year, 1,226 treated for more than 2 years, and 613 treated for more than 3 years. Only 88 patients from phase 2 Study RPC01-201A were exposed to placebo and 65 patients from the IBD Study RPC01-202, thus limiting comparative conclusions.

Available data suggested that the overall safety profile of ozanimod initiated with a dose titration regimen was at least not worse when compared to other S1P receptor modulators without initial dose escalation regimen, including the short and long-term cardiovascular effects. Overall the safety database seemed to be adequate for the proposed target population of patients with RRMS. Nevertheless, safety data for patients over 55 years, pregnant and lactating women, patients with hepatic impairment as well as for the paediatric population was limited or even missing.

Specifically, no controlled safety data was available for RMS patients >55 years of age, which was depicted in the posology section 4.2 of the SmPC. However, the rate of TEAEs in subjects >40 years of age was consistently higher as compared to <40 years, while the group of subjects >40 years was restricted to subjects up to 55 years of age based on study inclusion criteria; the susceptibility for AEs could be expected to be higher in older subjects. As of the 31 Jan 2019 safety data cut-off date for the US FDA 4MSU, there were 161 subjects who had turned >55 years of age during the study (Pool B). The limited additional safety data for subjects > 55 years did not indicate a worse safety profile of ozanimod in the elderly that would lead to a different perception of the benefit-risk profile. However, no firm conclusion could be made with regard to long-term safety in the elderly based on the limited number of elderly subjects being evaluated in clinical trials so far. This is reflected in the posology section of the SmPC.

Embryofoetal toxicity in exposed pregnant women is an important potential risk supported by the established role of the $S1P_1$ receptor in vasculogenesis (Ben Shoham *et al*., 2012; Pyne, 2017) and cases of abnormal foetal development in the post-marketing setting of the related S1P modulator fingolimod (Karlsson *et al*., 2014). In reproduction toxicity studies with ozanimod, embryolethality and teratogenicity were evident in rats and rabbits at exposures similar or below those in humans administered 1 mg ozanimod. Pregnant and lactating women were excluded from the study population throughout the clinical development program. Therefore, section 4.6 of the SmPC was updated to state that women of childbearing potential should have a negative pregnancy test before starting treatment to ensure that they are not pregnant and must use effective contraception during treatment and for 3 months after stopping ozanimod, which was considered adequate. The CHMP also agreed to the proposed educational materials for healthcare professionals (HCPs) and a patient wallet card that will be distributed

by HCPs to females of childbearing potential as additional risk minimisation measures. Experience in the post-marketing setting for both proposed ORION study and from spontaneous reporting will provide further long-term sources of information. Although it could be accepted the explanation to keep the safety concern *"Embryofoetal toxicity in exposed pregnant females"* as important potential risk in the RMP, essentially due to the lack of clinical data, CHMP was of the opinion that in order to further minimize the safety concern of *'embryofoetal toxicity'* the administration of ozanimod during pregnancy and in women of child-bearing potential not using effective contraception needed to be reflected as a contraindication in section 4.3 of the SmPC**.** Additionally, whilst ozanimod and metabolites are excreted in animal milk, it is not known whether excretion occurs in human milk, albeit it is expected. The human neonate might therefore be exposed to ozanimod and susceptible to the adverse effect profile observed in adults or unspecified developmental effects. For this reason, the Applicant proposed to not recommend use in breast-feeding women. Nonetheless, in accordance with the currently approved instructions of the S1P modulator fingolimod (EMEA/H/C/2202/II/53), a more restrictive wording was finally included in section 4.6: "Zeposia should not be used during breast-feeding". Additionally, The Applicant will provide any reports of neonatal exposure in the post-marketing setting in the periodic safety update report (PSUR).

Ozanimod was well tolerated, with a low rate of discontinuation and a similar incidence of SAEs in the Phase 3 RMS program across treatment groups (4.6%, 5.3%, and 4.4% in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a groups, respectively). There was no evidence of cumulative toxicity with ozanimod. The adverse events (based on PT), which were reported more frequently with ozanimod than IFN β-1a (defined as more than a 1% difference) occurred dose-related for *ALT increased, GGT increased, orthostatic hypotension, urinary tract infection, back pain, respiratory tract infection viral, and abdominal pain upper*. In general, the pattern and incidences of AEs leading to discontinuation did not change with long-term exposure to ozanimod. The pattern and incidence of adverse events was similar for Pools A and B, with the exception of TEAEs of lymphopenia (7.4%), lymphocyte count decreased (5.9%), and leukopenia (1%), which were only reported for ozanimod 1 mg in Pool B (i.e. the dose administered in the open-label studies). These adverse events were not reported in the controlled parts of the studies (Pool A1) in order to keep the investigator blinded. Moreover, symptomatic lymphopenia was not reported in the phase 3 studies. The overall safety profile of the 2 tested doses of ozanimod was similar with the exception of: frequency of ALC<0.2 x 10^9/L, which was greater for the 1 mg versus the 0.5 mg dose (3.3% versus 0.4 %), and increased frequency of liver function test elevations (>3 x ULN for ALT) with the 1 mg versus the 0.5 mg (5.5% versus 3.8%).

The approach of defining adverse drug reactions in order to inform section 4.8 of the SmPC was deemed acceptable and further complemented by ADRs as requested during the course of this procedure. The following ADRs have been defined:

- Very common: nasopharyngitis, lymphopenia
- Common: pharyngitis, respiratory tract infection viral, urinary tract infection, bradycardia, hypertension, orthostatic hypotension, alanine aminotransferase increased, gamma-glutamyl transferase increased, blood bilirubin increased, pulmonary function test abnormal
- Uncommon: Herpes zoster, hypersensitivity (including rash and urticaria), macular oedema

Overall, treatment initiation of ozanimod without post-dose observation was supported to be safe in patients with normal cardiac status. With dose escalation at initiation of ozanimod treatment, a minimal reduction in mean HR with a nadir at Hour 5, with return towards baseline by Hour 6 was associated with Ozanimod. Second-degree AV blocks type I were solely reported in the phase 2 study by 24-h Holter monitoring and similar in subjects on placebo and ozanimod 0.25 mg on Day 1. No second-degree AV block type II or higher was reported in clinical RMS studies with ozanimod. No additional effects on heart rate or AV conduction were observed with chronic ozanimod dosing. TEAEs reported on Day 1 of dose

escalation (bradycardias in 0.5% of subjects on ozanimod vs. 0 on IFN β-1a) subsided thereafter. SDEI including cardiac monitoring abnormalities as well as cardiac-related TEAEs were driven by a reduced HR during the initial 6 hours of monitoring on Day 1. No effects on QT interval were identified in preclinical and clinical studies, including a designated TQT study

Subjects with certain pre-existing cardiovascular conditions were only eligible to participate in the active-controlled Phase 3 RMS studies if the event occurred more than 6 months prior to screening. Additionally, patients with HR< 55 bpm at screening were not eligible and the use of concomitant treatment with medications with a known impact on the cardiac conduction system was not permitted during the study. During the procedure, the Applicant clarified that a limited number of patients entered the Phase 3 controlled studies with a pre-existing cardiovascular condition, baseline HR < 55 bpm, prolonged baseline QTcF or medications known to impact cardiac conduction. Based on this post hoc analysis, while these patients had a higher incidence of first-dose bradycardias, an increase in cardiac events and QT prolongation during maintenance treatment was not observed. Overall, the CHMP concluded that in patients with underlying cardiac disease or concomitant medication affecting heart rhythm and/or conduction, a more cautious approach was needed. As stated in section 4.4 of SmPC, first dose monitoring and/or additional 6 hours post-dose observation period on Day 1 was recommended for these patients. Moreover, cardiologist advice was required for some pre-existing cardiac conditions, as well as for patients concomitantly treated with antiarrhythmic drugs. Specifically, concomitant administration of class Ia or class III antiarrhythmics was not investigated and might worsen the cardiac safety of ozanimod (see section 4.4 of SmPC). Moreover, patients with MI (myocardial infarction), unstable angina, stroke, transitory ischemic attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure during 6 months prior to ozanimod initiation as well as patients with history or presence of second-degree AV block Type II or third-degree AV block or sick sinus syndrome severe untreated sleep apnea should not receive ozanimod in line with contraindication stated in section 4.3 of SmPC.

Also, in line with known class effects, small increases in SBP and DBP were noted during treatment with ozanimod starting approximately after 3 months of treatment, which remained roughly constant over 24 months of observation in Pool A1. The increase in blood pressure was reflected by more TEAEs of hypertension in the ozanimod 1 mg group compared to IFN β-1a group (4.5% vs. 2.3%). A warning on blood pressure changes was included in section 4.4 of the SmPC. Moreover, subjects with post-hoc defined uncontrolled hypertension were not observed to have had worsening of hypertension during ozanimod treatment (6 patients were treated for 3 to 5 years).

Prior to initiation of therapy it is recommended to obtain baseline liver function tests. While elevations in hepatic tests were common, these were generally asymptomatic and resolved with continued treatment. TEAEs from the hepatobiliary disorders SOC were mainly driven by liver enzyme increases; however, (non-serious) events of hepatitis and hepatitis toxic were reported in 6 subjects on ozanimod and in only one subject on IFN β-1a. Almost all of these subjects had a history of hepatic disorder or baseline liver enzyme abnormalities. No patient developed liver failure. Ten patients were suspect of having met Hy's law criteria for hepatotoxicity during treatment with ozanimod (Pool D), but hepatic experts did not confirm Hy's law after review. During the procedure, the Applicant proposed routine liver monitoring, including time intervals, retesting and thresholds for treatment discontinuation to prevent significant drug-induced liver injury based on clinical trials' protocols and results. The incidence of liver enzyme elevations, primarily ALT and GGT, as well as the incidence of hepatic SDEIs was significantly higher in males (twice as high) as compared to females, an effect known for S1P receptor modulators. Regarding patients with hepatic impairment, no dose adjustment was deemed necessary for patients with mild or moderate hepatic impairment (Child-Pugh class A and B) based on a total of 16 subjects (8 with mild and 8 with moderate impairment) treated with a single 0.25 mg dose of ozanimod and compared to 15 healthy matched controls. However, the absence of adverse effects after a single

0.25 mg dose in the hepatic impairment study RPC01-1904 in subjects with Child-Pugh class A and B is not reassuring for the absence of a risk with the higher 1 mg maintenance dose in clinical practice. The extent of worsening in patients with pre-existing liver impairment remains unknown given that subjects with defined pre-existing hepatic conditions, including chronic hepatic impairment or liver enzymes/ bilirubin ≥1.5x ULN that were excluded from clinical studies. The use of ozanimod in patients with severe hepatic impairment (i.e. Child-Pugh class C) was added as a contraindication in section 4.3 of the SmPC.

The decrease in ALC due to ozanimod is dose-dependent and may increase susceptibility to infections. Clinical trials revealed that in the recommended dose of 1 mg of ozanimod, ALC values $<0.5x10^9$/L and $<0.2 \times 10^9$/L were found in 54.7% and in 3.3% of subjects versus 1.6% and none in IFN β-1a, respectively. There was no difference either in the incidence of infection TEAEs, serious infections, infections leading to discontinuation and serious or opportunistic infections reported in the context of SDEI between ozanimod and IFN β-1a in Pool A1. Although serious or opportunistic infections were generally not associated with concurrent ALC values $<0.2 \times 10^9$/L, the long-term risk under real-world treatment conditions cannot be predicted. Section 4.4 has been amended to reflect precautionary measures as well as threshold ALC values prompting therapeutic action.

Slightly more Herpes zoster infections/ varicella zoster virus infections occurred in subjects on ozanimod (0.4% for total ozanimod) compared to IFN β-1a (0.2%) in Pool A1 and tended to increase with longer treatment duration in Pool B (1.2% for total ozanimod). The SmPC adequately informs on the recommendation for a Varicella Zoster Virus (VZV) vaccination in patients without documented immunity to VZV before initiation of ozanimod.

No case of systemic opportunistic infections including PML was reported with ozanimod treatment up to 68 months. However, absence of systemic opportunistic infections should be interpreted with caution given the short-term exposure of a limited number of patients in the ozanimod program. As such, EMA has been informed by the Applicant about a possible first case of PML under ozanimod treatment on 24 February 2020. This communication has been shared with the Rapporteurs as previously described. Even though the clinical course was stated to be unusual for PML, it could not be ruled out by cerebrospinal fluid testing given that the patient refused to undergo under lumbar puncture. Follow-up of this case evolved with significant recovery of signs and symptoms, which is very uncommon in PML, even with immunoreconstitution. Notwithstanding, to account for the slightly altered perception of the PML risk with ozanimod treatment, the Applicant proactively proposed changes in the subsection on PML, which was considered acceptable. In this line, *'Serious opportunistic infections including PML'* was included as important potential risk in the RMP

Considering cases of PML and cryptococcal infections occurred with other S1P receptor modulators during the post-authorisation phase, PML belongs to the potential risks associated with S1P receptor modulators. Patients should be observed for signs and symptoms of infections during therapy and for up to 3 months after discontinuation, given the long mean elimination half-life of the active ozanimod metabolites. Suspension of ozanimod dosing is warranted should serious infections occur. A warning in Section 4.4 that immunosuppressive effects predisposes patients to an infection risk, including opportunistic infections was also added. Finally, the presence of severe active infections, active chronic infections (hepatitis and tuberculosis) and 'Immunodeficient state' which comprise patients with prior or concomitant use of anti-neoplastic, immunosuppressive or immune-modulating therapies that were generally excluded from clinical studies were included as contraindication in section 4.3 of SmPC.

Up to ~75 months of exposure as of 31 Jan 2019 generally maintained the mean reduction in ALC (of ~55%) from baseline. While the overall incidence of infections and of serious or opportunistic infections was similar between the ozanimod 1 mg and IFN β-1a treatment groups in active-controlled studies, the incidence of local and manageable herpes zoster infections increased with duration of exposure but appeared to be roughly stable up to longest duration of exposure so far. Despite persistent lymphopenia,

there was no increase in the overall incidence of infections, serious infections, or other opportunistic infections with longer exposure.

Malignancies were reported more frequently in the ozanimod groups as compared to IFN β-1a in Pool A1 (0.6% for 0.5 mg and 1 mg ozanimod each vs. 0.2% on IFN β-1a) with an incidence rate of 373.6, 372.2, and 150.8 per 100,000 person-years. A similar number of cutaneous (3 *basal cell carcinoma*, one *keratoacanthoma*, one *malignant melanoma in situ*) and noncutaneous malignancies (3 cases of *breast cancer*, one *medulloblastoma*, and one *testicular seminoma (pure) stage I*) was reported in the ozanimod groups. *Basal cell carcinoma and chronic lymphocytic leukemia* occurred in the IFN β-1a group. Given the imbalance in malignancies observed with IFN β-1a and ozanimod, *"malignancy"* was included as potential risk in the RMP. Review of the incidences of cutaneous and non-cutaneous malignancies in Pool A1 (the basis for inclusion of ADRs in section 4.8 of the SmPC) revealed no specific type of cancer to be increased with ozanimod treatment (including data of the 4-months FDA safety update), which would qualify as an ADR in section 4.8. Active malignancies were added as contraindication in section 4.3 of SmPC. Pharmacovigilance activities to further address the long-term risk of malignancies comprise evaluation in a real-world long-term safety study (ORION) and long-term follow-up of OLE Study RPC01-3001. Given that S1P receptor modulators and ozanimod share the same mode of action, the same potential risks with immunosuppression observed in the postmarketing setting for S1P receptor modulators apply to ozanimod including the risk of skin neoplasms. Upon request, the Applicant included a warning on the section 4.4 of SmPC so patients treated with ozanimod should be cautioned against exposure to sunlight without protection and should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy. Moreover, adequate risk minimisation measures were aligned with the currently approved SmPC of S1P modulators regarding skin neoplasm.

Macular oedema is a well-known class effect and was reported in 0.3% and 0.1% of subjects on ozanimod 0.5 mg and 1 mg, respectively, upon confirmation by an expert panel on retinopathies, after at least 6 months of treatment. Most cases were non-serious and improved or resolved spontaneously after stopping ozanimod. The risk of and necessary control for macular oedema in patients with risk factors (e.g. diabetes and uveitis) was sufficiently described in the SmPC (section 4.4) and macular oedema has been added as an ADRs in section 4.8 of SmPC. Discontinuation of ozanimod is recommended in patients developing macular oedema (section 4.4). Additional pharmacovigilance activities were proposed for this important potential safety concern (ORION Study and long-term follow-up of OLE Study RPC01-3001).

PFT revealed mild reductions in FEV_1, FVC, FEV_1/FVC ratio, and D_{LCO}, in subjects on ozanimod 1 mg relative to ozanimod 0.5 mg and IFN β-1a. Long-term data in Pool B confirmed these to occur from baseline to Month 3 with only small additional reductions up to Month 24. Abnormal PFT results were the driver for an increased incidence of SDEI in the ozanimod 1 mg group but not accompanied by symptomatic AEs. PFT abnormalities have been summarized and reported in section 4.8 of the SmPC (as an ADR). Changes in FEV_1 and FVC from baseline have been described in the "Description of selected adverse reactions" subsection. In few patients with abnormal baseline PFTs <70% (normal at screening) and in smokers, no deterioration of their baseline condition has been reported despite small increases in PFT outlier results compared to IFN β-1a. However, it still remains unknown if ozanimod worsens pre-existing respiratory function impairment like asthma or COPD based on the limited number of patients treated in clinical trials with such conditions. A warning statement has thus been included in section 4.4.

Ozanimod was not found to induce depression, suicidality or abuse potential. There was no evidence of rebound or withdrawal in the active-controlled Phase 3 RMS studies. Nevertheless, phase 3 studies routinely observed patients for 28 days after drug discontinuation, which may not have been sufficient to observe effects following withdrawal of ozanimod considering the long half-life of the active metabolites. Therefore, the Applicant included a warning on potential rebound upon discontinuation of ozanimod in section 4.4 in line with other S1P receptor modulators and correctly classified 'Effects

following withdrawal of drug' as 'missing information', for which post-marketing additional pharmacovigilance activities are planned to further evaluate this aspect.

DDI are to be expected based on the extensive metabolism of ozanimod leading to formation of active metabolite with a long elimination half-life of ~ 11 days each. Wording in regard to the uneventful outcome of these studies is adequately depicted in the SmPC. However, since the two main active metabolites CC112273 and CC1084037 are selective inhibitors of MAO-B, DDIs are to be expected at least with serotonergic drugs and a discretely increased rate of TEAEs in the ozanimod group was reported in subjects with concomitant SSRI/SNRI administration in Pool A1, further analyses for Pool D were requested, which did not demonstrate difference in the incidence of serotonin syndrome extended broad SMQ TEAEs in patients treated with ozanimod after concomitant SSRI/SNRI administration.

Taken into consideration the post-marketing experience with a non-selective S1P modulator and uncertainties about long-term risks derived from chronic immunosuppression which may last up to 3 months after discontinuation, the CHMP thoroughly discussed the safety profile of ozanimod as a key aspect to determine whether the benefit-risk balance should be positive for the broad indication of RRMS patients as requested by the Applicant or whether a restriction for highly active RRMS patients would be more appropriate. In order to bring crucial perspectives from physicians and patients to the discussions on this particular aspect, the CHMP agreed to convey a scientific advisory group for neurology (SAG-N).

Additional expert consultations

The Applicant of Zeposia (ozanimod) considers the benefit-risk balance of Ozanimod positive in the broad RRMS population, i.e., independent of disease activity (proposed indication: '*Ozanimod is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis'*). In reply to the CHMP questions, the Applicant has discussed the evidence for efficacy in patients with highly active and in those with "regular" active RRMS and has compared the overall safety profile to other sphingosine 1-phosphate modulators.

The following questions were posed to a SAG-N Experts:

1. **The SAG Experts are kindly asked to elaborate on the evolution of the clinical management of RRMS in recent years. Are the experts aware of highly effective disease modifying therapies (DMTs) - including fingolimod- being used in patients without highly active disease? If so, which criteria are used in clinical practice to make treatment decisions?**

The SAG experts acknowledged that there is a trend towards an earlier use of highly effective DMT including Fingolimod in the early stages of RMS to attain a more favourable outcome in patients. The present reimbursement rules however prevent early use of Fingolimod in several member countries. In this regard, the evolution of the clinical management could favour a broad indication of Ozanimod.

According to SAG experts, there is use of highly effective DMT in patients without highly active disease in Europe, but this use is not homogeneous across Europe. It was also noted that criteria of defining highly active MS is not standardized and some of the current definitions may be difficult to take in the clinical setting. The fingolimod label, as an example, allows using fingolimod in "patients that have a "rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI." However, with current and 2017 revised MS diagnostic criteria, MS is mostly diagnosed after the first relapse, and in some circumstances, it appears not reasonable to wait for a second disabling relapse prior to using a compound with proven high efficacy as compared to e.g. the interferons. New expected MS criteria for defining the MS course (an updated version of defining the clinical course of multiple sclerosis by Lublin) may help to unify this use, but so

far none is well established. In some countries, prescribers stick to the escalation algorithm. By opposite, interpretation of the guidelines is more flexible in other countries. Most of the SAG experts expressed their preference for using highly active DMT in a more liberal scenario, which is currently not feasible, mostly due to reimbursement restrictions. Specifically, a SAG expert commented that S1P modulators could be used as first-line therapy as they are highly effective and safety concerns are manageable using risk minimization measures as implemented in the clinical practice for Fingolimod. It was also noted that the risk of rebound was perceived as a potential limitation for using of Ozanimod as first line therapy considering the experience with Fingolimod. Albeit available data on Ozanimod do not confirm this risk, this may be due to the fact that only a very limited number (exact numbers could not be provided to the SAG by the company) of patients with "highly active MS" have stopped the treatment and have closely been followed since.

The SAG experts agreed that MRI activity, particularly the number of gadolinium enhancing (GdE) lesions and T2 lesion burden (number of lesions) and location (spinal cord) and severity of relapses and are the leading factors for selecting highly efficacious DMTs as first-line therapy in the clinical practice. According to SAG experts, other factors to be considered include the presence of oligoclonal bands in the cerebrospinal fluid. Several SAG experts confirmed that highly efficacious DMTs are currently off-label used after one disabling relapse in RRMS, and also after one not-disabling relapse in combination with other negative prognostic factors such high lesion burden or spinal cord lesions on MRI.

Conclusion: The SAG experts acknowledged that there is a trend towards an earlier use of highly effective DMT in RRMS. There is use of these drugs in patients without highly active disease in Europe, although it was noted that this use is not homogeneous across Europe. This is likely due to lack of standardized criteria for defining active RRMS and reimbursement restrictions due to current labelling of some of DMT including Fingolimod. Overall, the SAG experts expressed their preference for using highly active DMT, for early stages (not as second-line therapy) based on currently knowledge on effect of early treatment on MS and experience gathered in clinical practice. Overall, SAG experts agreed that MRI-derived findings including the number of T2 and GdE lesion burden (number of lesions) and location (spinal cord) together with severity of relapse are leading factors for selecting highly effective DMT as first-line therapy in the clinical practice while other factors (oligoclonal bands) should be also considered.

2. **Based on the known safety profile of sphingosine 1-phosphate modulators, the SAG experts are kindly asked to clarify how the long-term risks (i.e. "AIDS-like" adverse events, namely infections, neoplasms and lymphopenia) are monitored in clinical practice and whether the risks are considered well manageable. Additionally, the CHMP is interested in the patients' perception and acceptance of these risks and their impact on quality of life.**

In the clinical practice, lymphopenia is easily and routinely monitored using blood tests. One SAG expert expressed that a more favourable profile could be expected in Ozanimod compared to Fingolimod regarding risk of lymphopenia.

The SAG experts agreed that main safety concerns are long-term risks, particularly malignancies with a specific mention to skin neoplasms. They considered also pregnancy-related adverse events. For the target population (pregnancy and use in women of childbearing potential not using effective contraception are contraindications), the risk of infection was not neglected but the main emphasis was put on the risk of malignancies particularly considering the recent findings of an epidemiological study based on data from a Swedish MS register that suggests that risk of malignancies is higher for Fingolimod than for other DMT (namely Natalizumab and Rituximab) in MS (Alping et al., Ann Neurol 2020;00:1-12).

Overall, the SAG experts agreed that long-term risks are expected to be similar to the ones reported in other immunosuppressant therapies and particularly in Fingolimod. However, they expect that measures that are currently in place for other highly effective DMT such as Fingolimod could be also considered for Ozanimod to minimize and monitor these risks.

Regarding these safety concerns, patients' representatives expressed the view that, as a general position (not specifically linked to Ozanimod), patients will likely be willing to assume these risks provided they are well-balanced with the expected efficacy. The uncertainty about long-term safety profile was expressed by one patient representative who further expressed also a concern about an uncertain future therapeutic strategy if ozanimod needed to be discontinued due to efficacy failure or safety concerns. Potential answers received from the SAG experts were other DMT with a different mechanism of action or bone marrow transplantation. Another SAG expert noted that most patients will likely accept short-term risk but caution action should be considered with regards to necessary information due to long-term risks (mainly malignancies).

Conclusion: Safety concerns are expected to be similar to the ones reported in other immune-suppressant therapies. The SAG experts put the emphasis on uncertainties regarding the long-term risk of malignancy. The SAG experts agreed that risks cannot be neglected but are manageable in the clinical practice using similar measures to the ones implemented for other highly efficacy drugs including Fingolimod. Patient's representatives expressed the view that, as a general position, patients will likely be willing to assume these risks provided they are well balanced with the expected efficacy, and they receive a sincere information regarding long-term use risks.

3. Do the SAG experts consider that a restriction of the target population would be justified based on the known safety profile of sphingosine 1-phosphate receptor modulators overall, and ozanimod in particular, alongside with the current clinical management of these patients?

The SAG experts agreed that a restriction of the target population for highly active RRMS is not justified based on safety concerns that are considered to be manageable. Nevertheless, they also reminded that such broad indication should also weight the real importance of therapeutic benefit against the severity of risks, even the rare one. It was noted that although benefit of Ozanimod has been established on some outcomes (such annualized relapse rate and lesion burden), the benefit on CDP-3M and CDP-6M was not demonstrated.

Based on the population included in the trial, the SAG experts agreed that Ozanimod should be indicated only for active RRMS to reinforce that it should not be used for stable/non-active MS patients under well-tolerated treatment. Switching from other drugs to ozanimod should be allowed despite no clear indication of active disease, for example in patients with side effects or intolerability issues.

It was considered that the definition of an active MS could be approximated from the inclusion criteria of the pivotal trials. However, there was no agreement about whether these inclusion criteria should be directly added in the wording of the indication of Ozanimod, the judgement of clinicians for each case appearing more appropriate. As noted by some SAG experts, the inclusion criteria used in pivotal trials do not appear in the indication section of SmPC of some DMT recently approved by EMA for RRMS/RMS (e.g. Tecfidera and Ocrevus).

One SAG expert even considered that ozanimod use as first treatment option in a woman childbearing potential could be justified if patients are willing to adhere to efficient contraception, and if they are well educated about pregnancy-related adverse events such as the teratogenicity of the drug. The risk of rebound activation after ozanimod cessation could be managed for example by well-planned bridging therapy before pregnancy initiation.

Conclusion: The SAG experts agreed that a restriction of the target population for highly active RRMS based on safety profile is not justified. Overall, the SAG experts expressed the view that a broad indication could be considered for Ozanimod, but only for active forms of RRMS, i.e. patients who have experienced relapse activity during the previous year, or who have had signs of inflammatory activity in the MR during the previous year.

4. In case a broader indication is envisaged,

a) Are the SAG experts aware of possible drug-drug interactions to occur in the broad RRMS population further affecting patients' safety?

If a broader indication is granted for RRMS, the SAG experts did not consider that drug-drug interactions could further impact safety in this population. If broad indication is granted, it is expected that Ozanimod will be indicated for RRMS in an earlier phase of the MS course when the presence of comorbidities among RRMS patients is an unusual finding.

b) What kind of post-authorization data could the Applicant be requested to generate in order to support the clinical safety in the unrestricted (regular and highly active) indication?

In addition to the described risks included in the RMP, the SAG experts did not identify any other risk. As such, the SAG expert considered that measures for gathering post-authorization data currently proposed by the Applicant to be acceptable. However, the SAG experts emphasized that post-authorization data for informing safety during pregnancy and risk of long-term malignancy should be a priority. Additional post-authorization studies for obtaining safety data for those with absolute lymphocyte count below 200 109/L and for those with low BMI/low body weight should be recommended. The SAG experts also considered adequate the 10-year length of duration of post-marketing experience as provided by the Applicant. One SAG expert proposed that safety information could also be gathered through some European Registries.

Conclusion:

a) If a broader indication is granted for RRMS, the SAG experts did not consider that drug-drug interactions could further impact safety in this population

b) Overall the SAG experts agreed with the strategies currently proposed by the Applicant to provide long-term safety data but emphasized the need for gathering data on safety profile during pregnancy and risk of long-term malignancy.

2.7.2. Conclusions on the clinical safety

The main safety issues identified in the clinical program were small and transient decreases in HR, mainly during titration and symptomatic in few cases only (bradyarrhythmia), macular oedemas, reversible mainly asymptomatic increases in liver enzymes and reversible (within three months of treatment cessation) decreases in ALC (lymphopenia), an increased risk of herpes zoster infections with long-term treatment and a disproportionately higher incidence in malignancies with ozanimod vs. IFN β-1a.

The long-term risk for serious or opportunistic infections and malignancies could not sufficiently be characterised within the limited period of clinical MS studies and thus prompts pharmacovigilance activity post-marketing.

Despite its more targeted selectivity for S1P receptor subtypes, the overall safety profile of ozanimod, based on the presented clinical data in RMS patients, appeared qualitatively similar to S1P receptor

modulators except for cardiac effects during the first days of treatment for which the dose titration is considered to have favoured a lower effect on HR and AV conduction. Moreover, the pharmacokinetics of ozanimod need to be taken into account for any claim on quantitative differences. Despite a comparatively lower mean terminal elimination half-life of ozanimod vs. other S1P receptor modulators (~ 22 hours vs. ~ 200 hours), two main active metabolites were reported at a rather late time point in the ozanimod clinical program (i.e. CC112273 and CC1084037). Both accounted for approx. 88% of the circulating total active drug exposure and exhibited a mean elimination half-life of approx. 11 days each. Thus, drug effects of ozanimod might be present for as long as 45 days after discontinuation and thus quantitatively comparable to other S1P receptor modulators ($t_{1/2}$ 200 hours; steady state after 1 to 2 months). This should be considered regarding the risk of infections after discontinuation of treatment and potential drug-drug interactions. It is therefore concluded, that several risks observed with ozanimod were also quantitatively similar to the ones of other S1P receptor modulators.

The Applicant's position that tolerability and safety of ozanimod is independent of disease activity was acknowledged. However, no controlled safety and pharmacokinetic data were available for RMS patients >55 years of age, which also depicts a relevant MS population. Risks derived from the long-term immunosuppression due to maintained reduction in peripheral lymphocyte count were thoroughly discussed during the procedure and were also discussed by the SAG-N experts.

Available evidence including a follow-up up to 75 months did not show an increase in the incidence of adverse events such as increased (opportunistic) infections or malignancies. Furthermore, the Applicant complied with the required risk minimisation measures to cover any remaining uncertainties taking into consideration the broad RRMS indication applied for.

At present, the clinical safety profile of ozanimod based on the available short- and long-term study data was considered manageable by applying the proposed risk minimisation measures in the product information together with the long-term safety data collection in post-marketing clinical trials.

2.8. Risk Management Plan

Safety concerns

Table 32: Table of summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Symptomatic bradycardia Severe liver injury Serious opportunistic infections including PML Macular oedema Malignancy Posterior reversible encephalopathy syndrome Embryofoetal toxicity in exposed pregnant females
Missing information	Long-term cardiovascular effects Effects following withdrawal of drug Use in patients over 55 years

Pharmacovigilance plan

Table 33: 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 authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
ORION Planned	To evaluate the long-term safety profile of ozanimod in the real-world setting.	Symptomatic bradycardia, severe liver injury, serious opportunistic infections including PML[a], macular oedema, malignancy, PRES, embryofoetal toxicity in exposed pregnant females, long-term cardiovascular effects, effects following withdrawal of drug, use in patients over 55 years old.	Study to start after the EC Decision. Protocol submission Interim study reports at 3 years and 5 years after study initiation. Final study report expected 11 years after study start. Status updates	 December 2020 December 2023 December 2025 December 2031 With PSURs
Long-term follow up of Study RPC01-3001 Ongoing	To characterise the long-term safety of ozanimod in patients with relapsing MS.	Severe liver injury, serious opportunistic infections[a], macular oedema, malignancy, PRES, embryofoetal toxicity in exposed pregnant females, long-term cardiovascular effects, effects following withdrawal of drug, use in patients over 55 years old.	Study closure 2022. Final study report Status updates	 June 2023 With PSURs

[a] Note ORION and long-term follow-up of Study OLE RPC01-3001 are not powered to assess PML

Risk minimisation measures

Table 34: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
None		
Important Potential Risks		
Symptomatic bradycardia	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1. PL Sections 2, 3 and 4. Ozanimod is contraindicated in patients at risk of symptomatic bradycardia (SmPC Section 4.3, PL section 2). Initial dose escalation regimen for ozanimod and advice regarding re-initiation of therapy following treatment interruption is described in SmPC Section 4.2 and PL Section 3. Recommendation that an ECG in all patients should be obtained prior to treatment initiation with ozanimod to determine whether any pre-existing cardiac abnormalities are present is included in SmPC Section 4.4 and PL Section 2. Warning that ozanimod may result in transient reductions in HR is included in SmPC Sections 4.4 and 5.1. Initiation pack covering dosing for the first 7 days, or in the case of resuming treatment following treatment interruption. **Additional risk minimisation measures:** – Healthcare Professional checklist. – Patient/caregiver's guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** ORION study.
Severe liver injury	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2. PL Sections 2 and 4. Ozanimod is contraindicated in patients with severe hepatic impairment (SmPC Section 4.3, PL section 2). Recommendations to measure transaminase and bilirubin levels before treatment initiation, for liver function monitoring and treatment discontinuation if significant liver injury is confirmed, are included in SmPC Section 4.4 and PL Section 2. **Additional risk minimisation measures:** – Healthcare Professional checklist. – Patient/caregiver's guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** ORION study. Long-term follow-up of Study RPC01-3001.
Serious opportunistic infections including PML	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, and 4.8. PL Sections 2 and 4. Ozanimod is contraindicated in patients with severe active infections, active chronic infections such as hepatitis and tuberculosis (SmPC Section 4.3, PL section 2). Recommendation that discontinuation of ozanimod be considered in case of opportunistic infection is included in SmPC Section 4.4. Recommendations to measure blood cell counts prior to and during treatment with ozanimod, advice to monitor patients at	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Adverse drug reaction follow-up form for PML (see Annex 4). External expert review of potential PML cases.

	risk of infection, clinical symptoms or MRI findings that physicians should be vigilant for as suggestive of PML, treatment instructions in cases suggestive of PML and treatment discontinuation if PML is confirmed are provided in SmPC Section 4.4 and PL Section 2. **Additional risk minimisation measures:** – Healthcare Professional checklist. – Patient/caregiver's guide.	**Additional pharmacovigilance activities:** ORION study. [a] Long-term follow-up of Study RPC01-3001. [a]
Macular oedema	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8. PL Sections 2 and 4. Recommendations for treatment of patients with risk factors for macular oedema (SmPC section 4.4 and PL section 2) and treatment discontinuation if significant macular oedema is confirmed are described in SmPC Section 4.4. **Additional risk minimisation measures:** – Healthcare Professional checklist. – Patient/caregiver's guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** ORION study. Long-term follow-up of Study RPC01-3001.
Malignancy	**Routine risk minimisation measures:** SmPC Sections 4.3 and 4.4. PL Section 2. Ozanimod is contraindicated in patients with active malignancies (SmPC Section 4.3, PL Section 2). Advice regarding monitoring of patients with concurrent conditions or known factors, such as previous immunosuppressive therapy, is included in SmPC Section 4.4. Recommendation that patients treated with ozanimod should be cautioned against exposure to sunlight without protection. Warning that patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy (SmPC Section 4.4, PL Section 2). **Additional risk minimisation measures:** – Healthcare Professional checklist. – Patient/caregiver's guide.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** ORION study. Long-term follow-up of Study RPC01-3001.
Posterior reversible encephalopathy syndrome (PRES)	**Routine risk minimisation measures:** SmPC Section 4.4. PL Section 2. Recommendation to discontinue ozanimod if PRES is suspected is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** ORION study. Long-term follow-up of Study RPC01-3001.
Embryofoetal toxicity in exposed pregnant females	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, 4.6 and 5.3. PL Section 2. Advice for women of childbearing potential to use effective contraception during treatment, and for at least 3 months after ozanimod treatment discontinuation is included in SmPC Sections 4.4 and 4.6, and PL Section 2. Ozanimod is contraindicated during pregnancy and in women of	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Adverse drug reaction follow-up form for pregnancy (see Annex 4).

	childbearing potential not using effective contraception, a negative pregnancy test must be available in women of childbearing potential before starting treatment, and counselling information regarding the serious risk to the foetus (SmPC Sections 4.4 and 4.6 and PL Section 2) and ultrasonography examinations should be provided (SmPC Section 4.6 and PL Section 2). Instruction not to use ozanimod during pregnancy, or in women of childbearing potential not using effective contraception, and advice for women of childbearing potential, are provided in PL Section 2. If a woman becomes pregnant during treatment, treatment should be discontinued, and the woman should receive pre-natal monitoring (SmPC section 4.6 and PL section 2). **Additional risk minimisation measures:** – Healthcare Professional checklist. – Patient/caregiver's guide. – Pregnancy-specific patient reminder card.	**Additional pharmacovigilance activities:** ORION study. Long-term follow-up of Study RPC01-3001.
Missing Information		
Long-term cardiovascular effects	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** ORION study. Long-term follow-up of Study RPC01-3001.
Effects following withdrawal of drug	**Routine risk minimisation measures:** SmPC Section 4.4. PL Sections 2 and 3. Warning regarding the potential for severe exacerbation of disease after ozanimod discontinuation and advice on monitoring and treatment is included in SmPC Section 4.4 and PL Sections 2 and 3. Advice to monitor patients for infections for up to 3 months after ozanimod discontinuation is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** ORION study. Follow-up after discontinuation in study RPC01-3001.
Use in patients over 55 years	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** ORION study. Long-term follow-up of Study RPC01-3001.

[a] Note ORION and long-term follow-up of Study RPC01-3001 are not powered to assess PML.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.9. 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 request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.12.2010. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. New Active Substance

The Applicant compared the structure of ozanimod 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 ozanimod hydrochloride to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.11.2. Labelling exemptions

A request to omit certain particulars from the labelling has been submitted by the Applicant and has been found partially acceptable by the Quality Review of Documents (QRD) Group for the following reasons:

The QRD Group requested to print at least the INN in English on the blister foil taking into account the pack configuration (wallet presentation) for the treatment initiation pack (4 x 0.23 mg, 3 x 0.46 mg).

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.11.3. Quick Response (QR) code

A request to include a QR code in the labelling for the purpose of accessing the most up to date version of the package leaflet has been submitted by the Applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: approved package leaflet

2.11.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zeposia (ozanimod) 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

The proposed indication is:

- Zeposia is indicated for the treatment of adult patients with Relapsing-Remitting Multiple Sclerosis (RRMS) with active disease as defined by clinical or imaging features.

MS is a chronic immune-mediated and neurodegenerative disease of the CNS characterized by inflammation, demyelination, neuro-axonal injury leading to irreversible deficits in physical and cognitive functions that impair quality of life. RRMS is the most common form of MS, representing approximately 85% of patients at diagnosis.

There is no cure available for MS. Therapies for MS include treatment for relapses (e.g. steroids), symptomatic treatments (e.g. drugs for stabilization of nerve conduction or dealing with pain) and those that alter the course of the disease (DMTs). The goal of treating RRMS with DMTs is to modify the natural course of disease by reducing the rate of relapses and MRI focal inflammatory activity to delay disability worsening.

The aim of ozanimod is to decrease focal inflammatory activity through inhibition of lymphocyte migration into the CNS. In the natural history of MS there is a relation between the number / frequency of relapses and focal inflammatory MRI lesions, and accumulation of sustained disability. However, not all DMT agents have demonstrated a concomitant reduction of disability along with a reduction in relapses in the phase 3 pivotal trials. This is the case for Ozanimod a demonstration of decrease in disability progression is lacking.

3.1.2. Available therapies and unmet medical need

In addition to substances approved for the treatment of MS symptoms and for the treatment of relapses there are currently more than 10 DMTs approved for use in patients with RRMS and/or other forms of

RMS in the EU. In a clinical setting, early treatment of relapsing MS usually starts with a substance from the IFN β class, glatiramer acetate, dimethyl fumarate or teriflunomide, which are of rather moderate clinical efficacy and are therefore usually used in subjects without high disease activity. The monoclonal DMTs (alemtuzumab, natalizumab or ocrelizumab) and cladribine are restricted to subjects with highly active disease due to less favourable safety profiles.

Fingolimod is the only S1P receptor modulator approved for RRMS. It is considered highly effective and has proven higher efficacy compared to the active comparator IFN β-1a with regard to annualised relapse rate as well as a beneficial effect regarding disability progression in one placebo-controlled trial. Notwithstanding, the therapeutic indication has been restricted to highly active RRMS patients due to safety concerns which includes cardiac effects at initiation of treatment, infections including herpes and cryptococcus, progressive multifocal encephalopathy, cutaneous malignancies, lymphoma, macular oedema, posterior reversible encephalopathy, respiratory effects, increased liver enzymes and the risk of rebound after stopping the treatment.

Despite the availability of several medications for the treatment of RRMS, there remains a need for a highly effective oral agent with a favourable benefit, safety and tolerability profiles. Ozanimod offers an alternative of an effective therapy with acceptable safety and tolerability profile and a dose escalation regimen that does not require first dose observation in a majority of patients apart from those with certain pre-existing cardiac conditions.

3.1.3. Main clinical studies

Two similarly designed pivotal Phase 3 studies of ozanimod in RMS have been submitted (Studies RPC01-301 and Study RPC01-201B). Both studies consisted of a 7-day dose-escalation period followed by a randomized, double-blind, double-dummy, active-controlled, parallel-group treatment period. The main difference between the 2 studies was the duration of the treatment period. In Study RPC01-301 (12+ month study), the treatment period lasted until the last enrolled subject was treated for 12 months, and in Study RPC01-201B (24-month study), the treatment period lasted for 2 years.

Study population were MS diagnosed pts (Mc Donald 2010 criteria), with RMS and MRI brain lesions typical of MS, between 18 and 55 years of age, with evidence of disease activity in the recent past (one relapse in the past year or one relapse in the past 2 years and sign of disease activity in MRI). The proposed main studies provided single and pooled data for efficacy assessment for patients with RMS from low to high disease activity

3.2. Favourable effects

In both adequately designed pivotal studies, the primary objective, i.e. demonstration of superiority over IFN β-1a with regard to adjusted ARR was met for ozanimod HC 1mg, the recommended dose, using pre-specified primary analysis which resulted in a reduction in ARR of 37.7% and 48.2% compared with IFN β-1a during the 24 and 12 months duration of Study RPC01-201B and Study RPC01-301, respectively. Results of the PP analyses and of several pre-specified sensitivity analyses of the primary endpoint (using the negative binomial regression model instead of the Poisson regression model and evaluating only confirmed relapses or confirmed and unconfirmed relapses for both models) were highly consistent with those of the primary analysis in the respective pivotal studies. Upon request, the Applicant provided the results of an additional analysis method using a treatment policy strategy for the intercurrent event treatment discontinuation based on the assumption of the absence of a treatment effect after treatment discontinuation. Hence, multiple imputation analyses were provided using a J2R and CR approaches showing similar results.

Results of the key secondary MRI endpoints for Ozanimod 1mg were consistent with the primary endpoint in both studies. A statistically significant reduction in the total adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan was demonstrated with ozanimod 1 mg compared to IFN β-1a corresponding to a 42.35% and 48.33% reduction over 24 and 12 months in Study RPC01-201B and Study RPC01-301, respectively. Similarly, a statistically significant reduction in the adjusted mean number of GdE brain MRI lesions was demonstrated with ozanimod 1 mg compared to IFN β-1a corresponding to 52.94% and 62.97% reduction at Month 24 and 12 in in Study RPC01-201B and Study RPC01-301, respectively. The sensitivity analyses of the key secondary MRI endpoints resulted in consistently, nominally significantly greater reductions in the ozanimod vs. IFN β-1a groups in both studies. In both pivotal studies, the mean percentage change in normalised whole-brain volume change were lower with ozanimod 1 mg compared to IFN β-1a using pre-defined primary analyses as well as *post hoc* sensitivity analysis based on log-transformed and back transformed data.

In both individual pivotal studies, results of the pre-specified subgroup analyses (including but not limited to analyses by baseline EDSS score, presence of Gd-enhancing lesions, prior treatment status and number of relapses in the past 12 months) of the primary endpoint were generally consistent with the overall results for the 1 mg dose vs. IFN β-1a (all resulting ARR ratios favoured 1 mg ozanimod over IFN β-1a, and for most subgroups, the upper limit of the 95% CI was below 1). Additional sensitivity subgroup analyses (of the single as well as the pooled phase 3 studies) based on a negative binomial model with and without using a J2R approach for treatment discontinuation produced rather consistent results. Similarly, in the provided subgroup analyses of the pooled pivotal studies, in which additional subgroups e.g. based on disease activity were investigated, a consistent treatment effect was found with regard to 1 mg ozanimod vs. IFN β-1a. All pooled subgroup analyses were indicative of nominally statistical significance, except for the small number of treatment naïve subjects (i.e. subjects without any previous MS treatment including corticosteroids). Of particular relevance was the finding of treatment effect in favour of ozanimod 1mg versus INF IFN β-1a observed for patients with and without highly active RMS. Additionally, requested subgroup analyses also showed that subjects with and without prior IFN β-1a treatment benefitted from ozanimod treatment.

The selection of the study centres, favouring Eastern Europe could have negatively impacted extrapolability of benefit-risk towards an EU population. However, the Applicant further explored B/R in subgroups of EU and non-EU population and found that differences between EU and non-EU population did not modify the B/R balance from the response as compared between IFN β-1a and ozanimod. Therefore, applicability of study results from non-EU countries to EU countries was considered sufficiently justified.

While the final recommended dose is 1mg ozanimod, 0.5 mg and 1 mg ozanimod doses were evaluated in both pivotal studies, as well as in the supportive Study RPC01-201A (including the dose blinded Study RPC01-201A Extension). Compared to the 0.5 mg ozanimod dose, the 1 mg dose showed a consistently greater benefit with regard to relapses as well as related MRI findings in the individual studies as well as in the pooled data. Regarding primary and key secondary efficacy endpoints, results from the pivotal Study RPC01-201B and Study RPC01-301 were consistent. As such, dose-response effects and consistency between pivotal studies were considered as favourable effects for this application.

Consistency was also noted between results from the ozanimod drug development program and experience with other S1P receptor modulator in a relapsing population regarding treatment effects on measures of focal inflammatory activity.

In the OLE Study RPC01-3001 (as of cut-off date of 30 June 2018), results regarding unadjusted as well as adjusted ARR in the subgroup of subjects, who were already treated with ozanimod 1 mg during the main study parts of the pivotal studies, appeared stable (and even tended to improve with unadjusted ARR of 0.164 during OLE compared to 0.174 in parent study, and adjusted ARR of 0.133 during OLE

compared to 0.153 during main part). Additional analyses of ARR on a yearly basis appeared to support these findings. The overall drop-out rate during OLE (6.9%) as well as drop-out due to a lack of efficacy (1.0%) were low in this study.

3.3. Uncertainties and limitations about favourable effects

For blinding purposes, a dual assessor approach was used in both pivotal studies, and as per protocol, treatment assignment was neither to be disclosed to the treating nor to the independent efficacy evaluator. Further total WBC and all differential WBC counts were blinded information for all site staff including the treating investigator, subjects were instructed not to disclose symptoms related to their treatment regimen to the efficacy evaluator, and injection sites were to be covered. Upon request, the Applicant provided further clarification about measures to avoid deblinding during relapse assessment that were considered appropriate. While some degree of unblinding resulting from different AE- and effect profiles of the investigational products could be assumed, the potentially resulting bias was considered limited based on the following considerations: treating physicians were guided by a template questionnaire in determining whether an unscheduled relapse assessment was to be scheduled when they were informed by the patients of onset of a possible relapse. Confirmation of a relapse required a pre-specified worsening in EDSS score as evaluated by the independent (blinded) efficacy investigator. Further, the proportion of relapses that were confirmed by the treating investigator was consistently high (>90%) across all treatment groups in both phase 3 studies. In this context, subgroup analyses using principal strata analyses were provided for the subgroup of subjects with or without flu-like symptoms, since flu-like symptoms were post-baseline measurements influenced by treatment. The Applicant provided a principal strata analysis for the stratum of subjects that would obtain flu-like symptoms under IFN β-1a and those who would not obtain flu-like symptoms under IFN β-1a, as well as the corresponding analyses regarding the flu-like symptoms obtained under Ozanimod. Results were rather consistent across the different analyses showing different effect sizes for subjects with flu-like symptoms as compared to those without. Considering subjects that would obtain flu-like symptoms under IFN β-1a as subjects for which treatment allocation (to IFN β-1a) could have been guessed by the investigator, the difference in the treatment effect size between subjects that were potentially unblinded and those who were not was estimated by a principal stratum analysis to approximately 10 %, suggesting an increase from a 37% reduction to a reported 47% reduction in the effect due to potential unblinding. Although the influence of unblinding and that of a different population could not be disentangled, the real effect on the primary endpoint (ARR) might be smaller without the effect of potential unblinding. Nevertheless, further reassurance for efficacy was considered to be provided by the results of the MRI-derived key secondary endpoints, which were largely in line with the ARR results, as MRIs were read centrally and blinded, i.e. by further independent blinded readers who were also locally separated from other treating/efficacy investigators.

Regarding disability progression (CDP-3M, CDP-6M), which was pre-specified as one of the key secondary endpoints based on the pooled phase 3 study data, no statistically significant differences between ozanimod and IFN β-1a were shown. A low and similar percentage of subjects experienced disability progression in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a treatment groups, with CDP-3M percentages progressed of 7.6%, 6.5%, and 7.8%, respectively, and CDP-6M percentages progressed of 5.8%, 4.8%, and 4.0%, respectively. The HR (95%CI) of 1 mg ozanimod vs. IFN β-1a was 0.950 (0.679, 1.330) for CDP-3M and 1.413 (0.922, 2.165) for CDP-6M. The pre-specified sensitivity analyses consistently favoured ozanimod over IFN β-1a regarding CDP-3M (at least numerically). Regarding CDP-6M, some sensitivity analyses favoured ozanimod over IFN β-1a (at least numerically) some analyses favoured IFN β-1a, however, none of the comparisons that numerically favoured IFN β-1a were (nominally) statistically significant. Results from a *post-hoc* sensitivity analyses using tentative progressors with confirmation during OLE Study RPC01-3001 as used in in the ocrelizumab pivotal

studies (EPAR Ocrevus MA/790835/2017) showed very similar risks for CDP-6M in the 1 mg ozanimod group compared to IFN β-1a (HR (95%CI): 1.040 (0.730, 1.482).

The failed demonstration of a benefit compared to IFN β-1a with regard to disease progression could be explained by a couple of key aspects of the study design in the pivotal trials. First, an abbreviated too short study duration, particularly for Study RPC01-301 for which only patients who experienced a severe relapse without complete recovery (tentative disability progression) within the first 6 months could potentially show CDP-6M by the end of the trial at 12 months. Considering the anticipated latency of therapeutic response and duration of studies, a very low rate of progressors was expected in the pivotal studies. Second, disability progression in patients with RRMS is mainly due to lack of complete recovery from severe relapses. In this extend, the level of baseline inflammatory activity plays a key role on the probability of CDP as an event. The included patient population had a rather low disease activity with regard to number of relapses prior to inclusion in the study (mean number of 1.3 in the past year in both studies, mean number of 1.7 (Study RPC01-301) and 1.8 (in Study RPC01-201B), respectively in the past two years). It is however noted that the proportion of subjects with high disease activity as measured by combined relapse and MRI criteria (as specified for subgroup analyses of the pooled phase 3 study data) appeared not to be lower in the ozanimod trials compared to trials with other S1P receptor modulators (approx. 23% and 18%, respectively). This latter comparison should be interpreted with caution, as there are no uniform definitions of high disease activity, and definitions varied across trials of different drugs. These aspects may explain the low rate of CDP-3M and CDP-6M events in the ozanimod drug development program. In settings with low event rates, absolute differences between estimated probabilities may better reflect clinically meaningful differences, while estimated HR may numerically distort the magnitude of differences. The additional analyses of the absolute difference between the KM estimates for CDP-6M for ozanimod 1mg compared to IFN β-1a using the pre-specified primary analysis provided by the Applicant are therefore considered to allow for a reasonable evaluation of CDP-6M. According to these analyses, no statistically significant difference for CDP-6M outcomes was found between both treatment groups, while an approx. 4% higher CDP-6M rate after 2 years of ozanimod treatment could not be excluded. However, the Applicant additionally provided a Bayesian analysis which estimated the probability of a 4% (or greater) difference in CDP-6M to be low (5.4%), further formal testing to evaluate a true difference of at least 4% yielded a p-value of 0.948.

In regards of an effect on other disability outcomes, results of the MSFC (with or without LCLA) and physical QOL-54 and (at least) numerically favoured the ozanimod groups over IFN β-1a. With regard to SDMT, used as cognitive MSFC component in Study RPC01-301, there was indication of a beneficial effect of ozanimod on processing speed, as nominally significant differences in means (95%CI) vs. IFN β-1a were found for ozanimod 1 mg group (0.111 [0.039, 0.182]; p=0.0024). However, in contrast, in Study RPC01-201B, PASAT was used as cognitive component, which measures other aspects of cognition beyond processing speed, and the resulting difference from baseline was not numerically better in the 1 mg ozanimod group compared to IFN β-1a. As SDMT was not used in Study RPC01-201B, the positive effect on processing speed found in Study RPC01-301 could not be replicated, further it is still unclear whether processing speed sufficiently covers overall cognitive function in MS as discussed during qualification SA of Multiple sclerosis clinical outcome assessment (MSCOA) (EMA/CHMP/SAWP/336445/2019).

Whereas 760 subjects were constantly treated with 1 mg ozanimod throughout parent studies and OLE Study RPC01-3001, of which 398 were at least treated for 3 years, the number of subjects treated for at least 4 years was low as of data cut-off for MAA (30 Jun 2018) (n=44). During OLE Study RPC01-3001, the overall proportion of subjects with CDP in the OLE mITT population continued to be low and was 7.0% (CDP-3M), and 5.1% (CDP-6M). Neither the median time to CDP-3M or CDP-6M, nor the time to the 25% percentile could be estimated due to the low event rate. However, as mentioned in the MS Guideline, the course of multiple sclerosis with respect to disability is slow and therefore even longer

follow-up might be needed. As of data cut-off for MAA (30 Jun 2018) the retention rate in OLE Study RPC01-3001 was > 90% with a high number of subjects still participating in the study (N=2,323). The final study results after all subjects will have been exposed to 1 mg ozanimod for a minimum of 5 years are scheduled to be available in 2022.

3.4. Unfavourable effects

The safety profile of ozanimod has been examined in a comprehensive clinical development program with more than 3,400 having been exposed to ozanimod and over 8,000 person-years of follow-up in RMS and IBD. Ozanimod was well tolerated, with a low rate of discontinuation and a lower incidence of SAEs.

Initiation of ozanimod treatment using dose titration over 7 days is mechanistically based on the successive desensitization of G-protein-coupled inwardly rectifying potassium channels via down-modulation of $S1P_1$ receptors and was associated with a transient reduction in HR in most patients (mean decline of 1.2 bpm in mean sitting/ supine pulse on Day 1 with a 0.25 mg dose of ozanimod), which was not associated with clinically significant bradycardia or conduction abnormalities (i.e. second- or third-degree AV block). Bradycardia (incl. sinus bradycardia) was reported in 1.2% of patients on total ozanimod in Pool A1 and 2 subjects reported symptomatic bradycardia in the ozanimod 0.5 mg group in Pool A1. No HR <40 bpm was observed. Symptomatic bradycardia was included as important potential risk in the RMP. First-degree AV block was reported as TEAE in 0.2% of subjects on IFN β-1a and in 0.6% of subjects on ozanimod 1 mg. Any other conduction abnormalities were similarly observed in all treatment groups.

Treatment with ozanimod resulted in an average increase of 1-2 mmHg in SBP and a smaller average increase of 1 mmHg in DBP over IFN β-1a corresponding to approx. 4.1 mmHg and 1.8 mmHg from baseline, approx. 3 months after treatment initiation with only small increases thereafter up to Month 24. Hypertension-related events (combined terms) were reported as ADRs in 4.5% of patients on ozanimod 1 mg and in 2.4% of patients on IFN β-1a in Pool A1, while the incidence did not substantially increase with long-term exposure. Hypertension was included as ADR in the section 4.8 of SmPC.

Ozanimod causes elevations of liver enzymes, especially ALT and GGT increases, but also small increases in bilirubin, which were mainly related to indirect bilirubin. Mean values were found elevated starting from Week 4 (in the phase 2 study) and mainly increased between Month 3 and Month in the Pool A1. Abnormalities in liver enzymes, typically ALT ≥3x ULN and GGT>2.5x ULN, were reported in 5.5% and 12.3% of patients treated with ozanimod 1 mg and in ~3% each for IFN β-1a, with a median time to onset of approx. 6 months after treatment initiation. Following study drug discontinuation, ALT abnormalities ≥3x ULN returned to <3x ULN within one month and to near baseline values within 4 months. Liver enzyme increases were generally not associated with hepatic TEAEs; however, "hepatitis toxic" was reported in 4 subjects on ozanimod. Up to ~1% of subjects discontinued due to hepatic TEAEs. None of the patients treated with ozanimod met the criteria for Hy's law. Patients with severe hepatic impairment (Child-Pugh class C) were not studied and treatment with ozanimod is thus contraindicated. Severe liver injury is a potential risk in the RMP.

Reductions in lymphocyte counts have expectedly been reported, based on the mode of action of ozanimod, in nearly all patients in the ozanimod 1 mg group (shift from baseline to low in 94% of patients) compared to the IFN β-1a group (shift from baseline to low in 24.4% of patients). There was a dose-dependent reduction of peripheral lymphocyte count to approximately 45% of baseline at Month 3, corresponding to a mean blood lymphocyte count of 0.8 x 10^9/L and this reduction was sustained throughout the treatment period. Grade 4 lymphocyte count reductions (<0.2 x 10^9/L) were observed in 3.3% and 0.4% of patients in the ozanimod 1 mg and 0.5 mg group and in no patient on IFN β-1a in

Pool A1 and in 5.5% of subjects on ozanimod 1 mg in Pool B. Time to recovery of lymphocyte counts less than 1 x 10^9/L to within normal range took up to 3 months in 90% of patients. Lymphopenia was included as ADR in section 4.8 of the SmPC.

The decrease in ALC due to ozanimod may increase susceptibility to infections. The overall rate of infections in controlled studies was comparable for the ozanimod 1 mg and IFN β-1a group (35.1% and 34.5%). No disseminated or serious opportunistic infections, including PML, were reported up to 75 months of treatment with ozanimod.

On 24 February 2020, EMA became aware of a possible first case of PML under ozanimod treatment in the ongoing OLE Study RPC01-3001. Even though the clinical course was stated to be unusual for PML, it could not be ruled out given that no cerebrospinal fluid withdrawal was performed, PML could neither be ruled out nor confirmed. Follow-up of this case evolved with significant recovery of signs and symptoms, which is very uncommon in PML, even with immunoreconstitution. Notwithstanding, to account for the slightly altered perception of the PML risk with ozanimod treatment, the Applicant proactively proposed changes in the subsection on PML, which was considered acceptable. Serious opportunistic infections including PML was already included as important potential risk in the RMP considering experience with other DMT. Serious infections including opportunistic infections were not associated with an ALC value of <0.2x 10^9/L in Pool A1. Non-serious Herpes Zoster infections (including VZV infection) occurred in 0.2%, 0.3%, and 0.6% of subjects on IFN β-1a, ozanimod 0.5 mg, and Ozanimod 1 mg in Pool A1, and the incidence increased with long-term treatment (Pool B: ozanimod 1 mg 1.1%, Pool B; 30 Jun 2018), but the incidence rate remained stable thereafter (using the Pool B data cut-off 31 Jan 2019). None of the Herpes Zoster infections was serious or led to discontinuation of study drug. Overall, persistent lymphopenia with longer exposure did not increase the overall incidence of infections, serious infections, or other opportunistic infections. These data should be interpreted in the light of the knowledge of the known safety profile of S1P modulators

Malignancies occurred in 0.6% of subjects on ozanimod (both doses) compared to 0.2% of subjects on IFN β-1a in Pool A1. The incidence of noncutaneous (predominantly breast cancer) and cutaneous malignancies (predominantly basal cell carcinoma) was balanced with ozanimod. The incidence rates and types of malignancies (i.e. nonmelanoma skin cancers and noncutaneous malignancies like breast cancer) remained stable with up to 75 months' exposure to ozanimod 1 mg. Malignancies typically observed with broader immunosuppressive therapies, such as lymphomas, have not been reported. Given the imbalance in malignancies observed with IFN β-1a and ozanimod, *"malignancy"* was included as potential risk in the RMP. Active malignancies were added as contraindication in section 4.3 of SmPC. An increased risk of skin malignancies is labelled for S1P receptor modulators. As such, a dedicated section for Cutaneous neoplasms was included in section 4.4 of SmPC.

Macular oedema, a well-known class effect, was confirmed for 4 patients (0.2%) on ozanimod versus no patient on IFN β-1a in Pool A1 and in an additional 5 patients in uncontrolled studies (including IBD studies). All cases happened in the context of other risk factors or confounding conditions and most cases were non-serious and improved or resolved spontaneously after stopping ozanimod. Cases of macular oedema in the controlled studies did not occur before 6 months of treatment with variable time to onset from baseline, while two subjects had an earlier onset of macular oedema (within 2 months after treatment initiation with ozanimod in open-label studies). As stated in section 4.4, patients with a history of uveitis and diabetes mellitus type I or uncontrolled diabetes mellitus type II have an increased risk for macular oedema, and thus require ophthalmologic assessment before and during therapy with ozanimod. Continuation of ozanimod in patients with macular oedema has not been evaluated. Macular oedema is stated as an ADR in section 4.8 of the SmPC.

Small reductions in PFT (mainly FEV_1, FVC, and D_{LCO}) were noted from Month 3 on in all treatment groups but higher with ozanimod as compared to IFN β-1a. The median change from baseline for FEV_1 and FVC

at Month 12 and Month 24 with ozanimod 1 mg was approx. 100 ml. These changes were not associated with related adverse events. Although no deterioration in PTF was observed in few patients with abnormal baseline PFTs <70% (normal at screening) and in smokers, ozanimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (COPD) as stated in section 4.4 of SmPC. Pulmonary function test abnormal is stated as an ADR in section 4.8 of the SmPC.

One case of PRES was reported in a patient in the context of Guillain-Barré syndrome and autonomic instability. PRES was also found related with S1P receptor modulators treatment. As such, PRES was included as a potential risk for ozanimod. This subject had a fatal event of chronic kidney disease. None of the 7 deaths that occurred during the clinical program was considered related to the study drug by the Sponsor, although two deaths in the IBD program were considered to be related to study drug by the investigator and unrelated to study drug by the Sponsor.

Animal studies showed embryo-lethality and teratogenicity in two animal species. 21 live births in the RMS program (a total of 23 live births including IBD studies) resulted in healthy infants upon delivery. Considering the lack of any safety margins, the established role of the $S1P_1$ receptor in vascular development and the experience gained with S1P receptor modulators, the administration of ozanimod during pregnancy and in women of child-bearing potential not using effective contraception was included as contraindication in section 4.3 of the SmPC**.**

3.5. Uncertainties and limitations about unfavourable effects

In contrast to the predominance and persistence of the major active human metabolites CC112273 and CC1084037, which represent the main pharmacological activity in humans (73% and 15% of the total active drug exposure in humans, respectively), their clearance was enhanced in animals leading to clearly lower and insufficient exposure levels compared to humans receiving the proposed clinical ozanimod therapy. Consequently, no relevant safety margins of CC112273 and CC1084037 were obtained in animals. Attempts to increase the exposure by direct oral administration of CC112273 failed, because of the extensive bacterial degradation by the gut microflora. In addition, the poor aqueous solubility of CC112273 and CC1084037 prevented the maximization of systemic exposure by intravenous administration. For this reason, the whole toxicology program of ozanimod is inconclusive and cannot reliably support the safety of ozanimod in humans, which should be considered for the clinical risk assessment.

Uncertainty was raised on whether the totality of patients with pre-existing cardiac conditions or concomitant CV medication that were excluded from participation in the clinical RMS trials can safely be treated with ozanimod. Although, a vast majority of these conditions was included as contraindication in the SmPC, some were not, for example patients with a resting HR<55 bpm, those with prolonged QTcF interval or additional risks for QT prolongation as well as those with concomitant medication known to impact cardiac conduction. A post-hoc analysis of cardiovascular TEAE evaluation stratified by cardiovascular medical history and cardiovascular concomitant medication showed an increase in the incidence of events (such as bradycardia, first-degree AV block, hypertension and orthostatic hypotension) in subjects treated with ozanimod compared to those with IFN β-1a treatment. Upon further clarification, it was found that the numerical imbalance could be attributed to TEAEs related to treatment initiation with ozanimod (e.g., asymptomatic bradycardia and sinus bradycardia on dosing Day 1) and to its vascular safety (e.g., hypertension and orthostatic hypotension). Concomitant administration of class Ia or class III antiarrhythmic drugs were not investigated and might worsen the cardiac safety of ozanimod. Appropriate wording was included in section 4.4 of the SmPC to recommend observed treatment initiation and further monitoring on patients as well as cardiologist advice on treatment initiation/monitoring in patients with certain pre-existing conditions and those treated with

antiarrhythmics. Nevertheless, it remained unclear whether cardiac safety during maintenance treatment in these patients was impacted. Consequently, the RMP adequately reflects "long-term cardiovascular effects" as missing information to address the need for data with ozanimod treatment in patients suffering from cardiovascular comorbidities. Small increases in SBP and DBP were reported in patients treated with ozanimod along with a difference in hypertension-related TEAEs between ozanimod and IFN β-1a. Although the Applicant clarified that a worsening of pre-existing uncontrolled hypertension (defined post-hoc) was not observed, a specific warning to obtain cardiologist advice before initiation of ozanimod in the setting of uncontrolled hypertension was included in section 4.4 of SmPC.

At present, no increased risk for drug-induced liver injury with ozanimod could be deduced from clinical trial data. However, ozanimod unequivocally dose-related increased hepatic enzymes including slight increases in bilirubin over time, which justified the inclusion of routine liver monitoring and adequate warnings in section 4.4 of SmPC. Given that subjects with a number of pre-existing hepatic conditions, including chronic hepatic impairment or liver enzymes/ bilirubin ≥ 1.5x ULN were excluded from clinical studies, the effect of ozanimod in these subjects remains unknown. In this line, a majority of the 8 subjects (10 subjects) suspect of drug-induced liver injury in the clinical phase 3 RMS (RMS + IBD) studies had pre-existing conditions that made them more susceptible for the observed liver enzyme changes. As such, severe liver injury as potential important risk was included in the RMP. No clinically relevant effects were deduced from a phase 1 study in patients with mild to moderate hepatic impairment and extrapolation of a single 0.25 mg dose used in this study to a maintenance dose of 1 mg in subjects with mild to moderate hepatic impairment was considered acceptable. Patients with severe hepatic impairment were neither included in phase 1 or phase 3 pivotal studies of ozanimod. Thus, severe hepatic impairment (Child-Pugh class C)' was added as a contraindication in section 4.3 of SmPC.

The key pharmacodynamic effect of ozanimod is a rapid decline in peripheral blood lymphocytes on treatment initiation. The dose-dependently impaired trafficking of B and T cells reduced the immune response against foreign antigens in animals and has been similarly reported for S1P receptor modulators (Mehling et al., 2008). Bacterial and viral infections including PML were commonly observed during clinical S1P receptor modulators therapy necessitating specific risk minimisation measures (EMA/688187/2015). In particular, an increased risk for infections is to be expected within 3 months after discontinuation of ozanimod based on the long mean elimination half-life of ozanimod metabolites (CC112273 and CC1084037) requiring increased surveillance during this time, which was also described in the SmPC. Although, a clear relationship between peripheral blood lymphocyte count and the occurrence of (non) serious infections was not detected, even in long-term ozanimod treatment, serious and/or opportunistic infections are an expected risk for the class of S1P receptor modulators. Therefore, 'Serious opportunistic infections including PML' was included as important potential risk in the RMP in line with the experience with S1P receptor modulators. Furthermore, the risk for acquiring serious or opportunistic infections in subjects with severe active infections, systemic opportunistic infections (such as PML and cryptococcal meningitis), and active chronic infections (e.g. viral hepatitis, tuberculosis), as well as those with prior or concomitant antineoplastic, immunosuppressive, or immune-modulating therapies, is undetermined as these patients were generally excluded from clinical studies. A post hoc analysis found that subjects with prior DMT treatments had increased incidences of AEs from the infections and infestations SOC as compared to those not previously treated with such drugs. Therefore, immunodeficient state (e.g. due to intercurrent illness or as the result of immunosuppressive therapy), severe active infections and active chronic infections (hepatitis, tuberculosis) were included as contraindications in section 4.3 of SmPC and a warning in regard to patients with prior and concomitant treatment with antineoplastic, immunosuppressive, or immune-modulating therapies added in section 4.4 of SmPC.

In the controlled studies, there was a higher incidence of malignancies with ozanimod as compared to IFN β-1a. Half of the reported malignancies were cutaneous malignancies, mainly basal cell carcinoma.

The incidence and types of malignancies (i.e. nonmelanoma skin cancers and noncutaneous malignancies like breast cancer) remained stable from the original marketing authorization application submission (data cut of 30 Jun 2018; up to 68 months' exposure to ozanimod 1 mg) through the US FDA 4MSU (data cut of 31 Jan 2019; up to 75 months' exposure to ozanimod 1 mg), and remain within expectations for the general population and the age-matched MS population in the SEER cancer registry. Although, cutaneous neoplasms were not found in long-term toxicity and carcinogenicity studies with ozanimod or S1P receptor modulators in animals, ozanimod widely distributes into ocular and cutaneous structures and shows melanin-binding. An increased risk for skin tumours was apparent after marketing authorisation of S1P receptor modulators and resulted in recent mitigation measures to minimise the human risk (see EMA/688187/2015 and EMA/82227145/2017). The overall available data for ozanimod to date did not suggest that the risk for cutaneous and non-cutaneous malignancies may be different from that of other S1P receptor modulators and as such, the same warnings and measures apply including a warning of cutaneous neoplasms in the SmPC. Given the insufficient exposure of animals in carcinogenicity studies and the well-known limitations of clinical studies required for approval, i.e. the restricted number of treated subjects and the duration of follow-up, a firm conclusion on the potential (long-term) risk for malignancies associated with ozanimod treatment could not be made. However, this risk is expected given that immunosurveillance might be compromised with ozanimod and malignancy as an important potential risk in RMP was proposed to be addressed by the long-term studies ORION and the follow-up of OLE Study RPC01-3001.

All cases of macular oedema, a well-known class effect, happened in the context of other risk factors or confounding conditions and were overall non-serious and improved/resolved after stopping ozanimod. Macular oedema was added as an ADR in section 4.8 and a warning was added in section 4.4 of SmPC. Additional pharmacovigilance activities were proposed for this important potential risk in the RMP.

The predominant toxicity across in all animal species was pronounced lung oedema and histiocytosis which was also observed with another S1P receptor modulator in rats, dogs and monkeys and is mechanistically related to the breakdown of the endothelial barrier in the lungs by $S1P_1$ receptor modulation (Shea *et al*., 2010; Oo *et al*., 2011). There is no evidence for an increased incidence of respiratory events with continuous ozanimod treatment in the long-term Pool B following the discrete decline in PFT. This risk was described in the SmPC and decreases in PFTs (pertaining to the sum of several preferred terms in line with decreases in PFT) were included as an ADR for ozanimod. Moreover, uncertainty was raised to which extent patients with risk factors like smoking, asthma or COPD, which themselves cause abnormal PFTs, can safely be treated with ozanimod over time. While current smokers on ozanimod were not found to have been differentially impaired in their respiratory function compared to those being treated with IFN β-1a, only limited data are available to substantiate a risk in those being affected by asthma or COPD. Therefore, a warning statement in section 4.4 of the SmPC has been implemented to account for a cautious use of S1P receptor modulators in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (COPD).

DDI were reported in line with the extensive metabolism of ozanimod. After initiation of concomitant SSRI/ SNRI medication, an increased incidence of TEAEs (driven by hypertension) was noted in subjects on ozanimod compared to IFN β-1a in Pool A1, which was not observed in Pool D.

The safety profile of ozanimod in the treatment of subjects with RMS has been sufficiently evaluated up to an age cut-off of 55 years. No (controlled) safety data are available for paediatric subjects (<18 years of age) and elderly subjects (> 55 years of age). Limited data for those with a screening age of 55 in the phase 3 trials and subsequently treated in extension studies (n=161 patients in Pool B including the US FDA 4MSU) did not indicate a worse safety profile of ozanimod. However, no firm conclusion could be made with regard to long-term safety in the elderly based on the available data. The posology section has been amended, accordingly. Safety data for pregnant and lactating women is limited.

As indicated above, ozanimod is contraindicated during pregnancy and in women of child-bearing potential not using effective contraception. However, some off-label use can be expected and as such, embryofoetal toxicity in exposed pregnant females was included as a potential important risk for which additional pharmacovigilance activities were proposed.

Information on the effects following withdrawal of ozanimod is lacking, which is caused by the insufficient follow-up time due to the prolonged half-life of ozanimod active metabolites. This was included as missing information and considered to be addressed in a post-marketing setting using long-term studies/ extension study data from ORION and OLE Study RPC01-3001.

3.6. Effects Table

Table 35: Effects Table for Ozanimod in MS (data cut-off 31 January 2019)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ARR	Number of confirmed relapses per year				% reduction Mostly treatment naïve pts	
RPC01-301	… over treatment period (12+ months)	Rate (95% CI)	0.181 (0.140, 0.236)	0.350 (0.279, 0.440)	48% over 12+ months	
RPC01-201B	… over 24 months	Rate (95% CI)	0.172 (0.142, 0.208)	0.276 (0.234, 0.324)	38% over 24 months	
Relapse-free rate	% of subjects who remained relapse-free				Results consistent with ARR analysis	
RPC01-301	KM estimates at Month 18	%	78%	66%	p = 0.0002 (log-rank test)	
RPC01-201B	KM estimates at Month 24	%	76%	64%	p = 0.0012 (log-rank test)	
T2 lesions	# of new or enlarging hyperintense T2-weighted brain MRI lesions				% reduction Mostly treatment naïve pts	
RPC01-301	… over 12 months	Adjusted mean (95% CI)	1.465 (1.203, 1.784)	2.836 (2.331, 3.451)	48.2% over 12 months p < 0.0001	
RPC01-201B	… over 24 months	Adjusted mean (95% CI)	1.835 (1.523, 2.211)	3.183 (2.640, 3.838)	37.6% over 24 months p < 0.0001	
GdE lesions	# of GdE brain MRI lesions				% reduction Mostly treatment naïve pts	
RPC01-301	… at Month 12	Adjusted mean (95% CI)	0.160 (0.106, 0.242)	0.433 (0.295, 0.635)	63% at 12 month p < 0.0001	
RPC01-201B	… at Month 24	Adjusted mean (95% CI)	0.176 (0.116, 0.266)	0.373 (0.256, 0.543)	53% at 24 month p = 0.0006	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
CDP-3M (Pooled)	% of subjects with sustained EDSS worsening of ≥ 1.0 point confirmed at 3 months	% HR (95% CI)	7.6 HR=0.950 (0.679, 1.330)	7.8	Low rate of events in both arms. Limited study duration, particularly RPC01-301.	
CDP-6M (Pooled)[b] #	% of subjects with sustained EDSS worsening of ≥ 1.0 point confirmed at 6 months	% HR (95% CI)	5.8 HR=1.413 (0.922, 2.165)	4.0		
Whole-brain Volume Change	Mean (SD) change from baseline in normalized whole-brain volume on brain MRI scans				no dose-response in Study RPC01-201B and no clear dose-response in Study RPC01-301	
RPC01-301	… at Month 12	%	-0.41 (0.640)	-0.61 (0.686)	*nominal p<0.0001*	
RPC01-201B	… at Month 24	%	-0.71 (0878)	-0.94 (0.944)	*nominal p<0.0001*	
Cognitive Impairment	Change from baseline in number of correct responses on				For SMDT uncertainty about whether processing speed sufficiently covers overall cognitive function in MS	
RPC01-301	…SDMT at Month 12[a]	Mean (SD)	1.1 (8.58)	-0.4 (6.86)	*nominal p=0.0016*	
RPC01-201B	…PASAT at Month 24[a]	Mean (SD)	1.5 (6.90)	1.2 (6.70)	*nominal p=0.7263*	
Quality of Life	Change from baseline in MSQOL-54 Physical Health Composite Summary					
RPC01-301	… at Month 12	Mean (SD)	1.925 (11.870)	0.046 (12.578)	*nominal p=0.0364*	
RPC01-201B	… at Month 24	Mean (SD)	0.209 (12.321)	-1.526 (12.319)	*nominal p=0.0988*	
	Change from baseline in MSQOL-54 Mental Health Composite Summary					
RPC01-301	… at Month 12	Mean (SD)	0.260 (15.800)	-0.123 (15.240)	*nominal p=0.7104*	
RPC01-201B	… at Month 24	Mean (SD)	-1.517 (15.544)	-1.831 (16.422)	*nominal p=0.6997*	
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Elevations of liver enzymes	ALT ≥3x ULN and GGT >2.5x ULN Frequency during the study	%	ALT: 3.8% 0.5 mg 5.5% 1 mg GGT: 6.2% 0.5 mg 12.3% 1 mg	ALT: 3.1% GGT: 3.4%	Sustained increase peaking around 6M and usually decreasing within 1 M and remitting 4M after ozanimod cessation Lack of data for Child-Pugh class C pts. Lack of long-term data	Pool A1 Safety Population
Zoster infections	Overall rate of Zoster infections (incl. Herpes zoster and varicella zoster)	%	0.3% 0.5mg 0.6% 1 mg (Pool A1) 1.1% 1 mg (Pool B)	0.2%	Incidence increasing with long term treatment None of these was serious.	Pool A1 and Pool B
Grade 4 lymphopenia	Lymphocyte count reductions to <0.2 x 10^9/L	%	0.4% 0.5mg 3.3% 1 mg (Pool A1); 5.5% 1 mg (Pool B)	0%	After discontinuing ozanimod 0.92 mg, the median time to recovery of peripheral blood lymphocytes to the normal range was 30 days, with 90% of patients recovering to normal within 3 months	Pool A1 and Pool B
Macular oedema	Incidence during the study	%	0.2%	0%	Several confounding factors; no dose-response identified; all non-serious reactions	
Malignant tumours	Incidence during the study	%	0.6% 0.5mg 0.6% 1 mg	0.2%	No comparative long-term data, but human carcinogenicity usually has a long-time lag; the difference in incidence required attention	Pool A1

[a] PASAT-3 was used in Study RPC01-201B and SDMT was used in Study RPC01-301.
[b] In a post hoc analysis of CDP-6M which included data from the OLE Study RPC01-3001, the HR (95% CI) was found to be 1.040 (0.730, 1.482).
Abbreviations: CI = confidence interval; SD = standard deviation; pts = patients; ARR = annualized relapse rate; GdE = Gadolinium-enhancing; CDP-3M = confirmed disability progression at 3 months; CD; SDMT = Symbol Digit Modalities Test P-6M = confirmed disability progression at 6 months; PASAT = Paced Auditory Serial Addition Test; MSQ-54 = Multiple Sclerosis Quality of Life-54; ALT = Alanine aminotransferase; GGT = Gamma-glutamyl transferase; ULN = Upper limit of normal

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Ozanimod 1 mg has shown a consistent, statistically significant and clinically relevant effect with regard to reducing the number of relapses (by 48.2% after 1 year of treatment in Study RPC01-301 and 36.7% after 2 years of treatment in Study RPC01-201B) compared to the established active comparator IFN β1-a in a study population with active RRMS. Effects of the pre-specified primary analysis for the 1 mg ozanimod dose were corroborated by sensitivity analyses of the primary endpoint as well as secondary endpoints evaluating focal inflammatory MRI activity. It was of particular interest, that from the presented subgroup analyses a consistent treatment effect of ozanimod on relapses was shown, regardless of absence/presence of high disease activity, number of relapses in the prior one and two years, respectively, absent/present GdE lesions, number of T2 lesions, EDSS score at baseline, or prior DMT use status at baseline. Therefore, there was no need to restrict the indication to a certain sub-population of active RRMS from an efficacy point of view.

Compared to IFN β1-a, ozanimod failed to demonstrate that its superior effects on inflammation was accompanied by slowing of disability progression. As derived from the pre-specified analysis, the HR of 0.950 correspond to a numerical 5% relative risk reduction in CDP-3M for ozanimod compared to IFN β-

1a. Regarding CDP-6M the HRs of 1.413 for 1 mg ozanimod correspond to a numerical relative risk increase for CDP-6M of 41.3%. These HRs are within sampling variability based on their 95% CIs of having no treatment effect. Additionally, provided sensitivity analyses showed no statistically significant difference in favour of IFN β1-a, while an unlikely scenario of approx. 4% higher CDP-6M rate after 2 years of ozanimod treatment compared to the active comparator IFN β1-a could formally not be excluded. The failure to show a beneficial effect on CDP-3M/6M rates compared to IFN β1-a may be attributed to the low CDP event rate in a population, mainly treatment naïve with low pre-existing disease activity, in combination with a too short study duration. It should be noted that the included patient population had a rather low disease activity with regard to number of relapses prior to inclusion in the study (mean number of 1.3 in the past year in both studies, mean number of 1.7 (Study RPC01-301) and 1.8 (in Study RPC01-201B), respectively in the past two years). While relapses are not the only factor implicated in future disability progression, relapses have been discussed in literature to indicate disease activity and to predict disability progression (Giovannoni et al. 2016). Based on experience with other SP1 receptor agonists, a lack or even detrimental effect on disability progression in the presence of a clear anti-inflammatory effects appears highly unlikely.

Long-term follow-up data will be provided by the Applicant, when all subjects included in OLE Study RPC01-3001 will have been exposed for a minimum of 5 years.

The safety database for ozanimod is considered comprehensive with more than 3,400 patients with either RRMS or IBD having been treated so far, including 2,765 subjects treated with ozanimod 1 mg for more than 1 years, 1,226 treated for more than 2 years, and 613 treated for more than 3 years. Patients have been followed for up to 75 months.

The currently available safety profile is qualitatively in line with that of other S1P receptor modulators. No unexpected safety issues were identified for ozanimod. Moreover, the most relevant safety findings with ozanimod in the MS clinical program occurred with a similar frequency as with other S1P receptor modulators, i.e. blood pressure changes, liver enzyme increases, macular oedema, decreases in PFTs, infections due to a dose-dependent reduction in ALC, and malignancies.

As opposed to non-selective S1P receptor modulators, ozanimod does not modulate $S1P_2$ and $S1P_3$ receptors. While it was agreed that the clinical effects of $S1P_2$ and $S1P_3$ chronic modulation on cardiovascular system deserved further investigation, preclinical studies suggest that modulation is associated with pro-inflammatory and pro-fibrotic responses. Nevertheless, cardiac effects in humans (Gergely *et al*., 2012) and reproduction toxicities observed with another selective S1P receptor modulator in animals underlined the predominant role of $S1P_1$ receptor modulation.

In view of the pharmacokinetic profile of ozanimod, the impact of $S1P_1$ receptor modulation on cardiac atrioventricular conduction therefore necessitated the development of an initial titration regimen. The applied dose escalation over 7 days led to mitigation of cardiac events caused by HR decreases. Titrated ozanimod compared favourably to non-titrated S1P receptor modulators in almost all first-dose cardiac monitoring outcomes evaluated by Matching Adjusted Indirect Comparison (MAIC). However, a more cautious approach was considered necessary in patients with underlying cardiac disease and in patients on concomitant medication affecting heart rhythm and/ or conduction, especially during treatment initiation. Based on a post-hoc analysis, both subsets of patients were reported to have had a higher incidence of cardiac and vascular adverse events in line with the cardiac safety profile of ozanimod (first-dose bradycardias and hypertension/ orthostatic hypotension during treatment). Therefore, appropriate risk mitigation measures proposed were an additional 6 hours post-dose observation on Day 1 of treatment in patients with certain pre-existing cardiac conditions and cardiologist advice for patients with relevant conditions/ medications (including antiarrhythmic drugs). Patients presenting with severe cardiac conditions (i.e. MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation or NYHA Class III/IV heart failure in the 6 months prior to treatment initiation; patients

with history or presence of second-degree AV block Type II or third-degree AV block or sick sinus syndrome unless the patient has a functioning pacemaker) are not to be treated with ozanimod (contraindication).

For comparisons presented in the MAIC report based on the 1-year and 2-years follow-up data, the overall safety profile of ozanimod was not suggested to be quantitatively different to S1P receptor modulators. The seemingly favourable outcome of some selected parameters (e.g. ALT values ≥ 3x ULN and ALC <0.2x 10^9/L) needs to be interpreted with caution considering several methodological limitations of such cross-study comparisons.

The frequency of malignancies was slightly higher for ozanimod compared to IFN β-1a in the controlled clinical trials, but no cluster of malignancies was observed as would be typically seen with immunosuppressants. Basal cell carcinoma and breast cancer dominated in the group of cutaneous and noncutaneous neoplasms (three events each). Of note, the overall incidence of malignancies was low and did not increase with long-term treatment. It was in the range of epidemiological (MS) data and in line with other S1P receptor modulators. Nevertheless, a causal relationship can neither be established nor ruled out based on available clinical data. Therefore, the proposed long-term studies are deemed essential to address the potential risk of malignancies.

Although, the risk for serious and opportunistic infections was not increased based on pooled incidences of events from controlled studies in Pool A1, the two controlled studies RPC01-301 and RPC01-201B differed in duration (12 and 24 months, respectively). The incidence of Herpes Zoster infections was reported at similar rates in all treatment groups of Study RPC01-301, but at a higher incidence in the ozanimod treatment groups as compared to IFN β-1a in Study RPC01-201B. The event rate further increased with considerably longer exposure in the OLE Study RPC01-3001. Longer treatment duration increased the risk for (serious) opportunistic infections, and this risk was retained for up to 3 months after treatment discontinuation, which can be explained by the long elimination half-life of the active metabolites. Therefore, monitoring for signs and symptoms of infection is recommended for this period. It remains uncertain if serious and opportunistic infections are more likely to occur if patients have previously been treated with immunosuppressants or are in need for concomitant immunosuppressant treatment due to other immune-mediated condition. A respective warning has been included in the SmPC, section 4.4. Similarly, it cannot not be ruled out that rare opportunistic infections like PML might occur. In this context, the case of a subject with unusual (partially recovered) worsening of the neurological status in the OLE Study RPC01-3001 was reported to EMA, for whom PML could formally not be excluded. Notwithstanding, there was a sustained improvement in the patient condition, which decreases the possibility of PML.

As a result of the safety review, the following patients have been excluded from treatment in the SmPC (section 4.3) or a precautionary warning was added in section 4.2 or 4.4 of the SmPC:

- with a cardiac history or cardiac comorbidities or concomitant cardiac medication,
- with a hepatic medical history or severe hepatic impairment,
- with severe active infections, systemic opportunistic infections, and active chronic infections or those with prior or concomitant use of anti-neoplastic, immunosuppressive or immune-modulating therapies,
- with risk factors for Macular oedema, such as uveitis and diabetes,
- with known active malignancies,
- with a risk for severe pulmonary function impairment, such as COPD,
- who are elderly,
- who are pregnant.

Reported adverse events of special interest were translated into appropriate risk mitigation measures in the product information as well as in the RMP in line with other S1P receptor modulators.

Long-term safety of ozanimod will be further investigated in the ongoing OLE Study RPC01-3001. Additional data will be generated in the ORION study, a real-world safety – post authorisation, multinational, long-term non-interventional study, that is proposed to focus on the potential risks and missing information associated with ozanimod.

3.7.2. Balance of benefits and risks

Ozanimod has been shown to be more efficacious than IFN β1-a with regard to preventing relapses and inflammatory lesions in patients with active RRMS regardless of the level of inflammatory activity. Although a stronger anti-inflammatory effect could be expected to result in more pronounced slowing of disability progression and other S1P agonists have shown such effects (although partly in different settings), ozanimod failed to demonstrate superior efficacy vs. IFN β1-a regarding progression of disability as assessed through persistent worsening both at 3 and 6 months. This failure may be explained by a too short comparative observation period of 12 months in a study population with low pre-existing disease activity.

The safety profile of ozanimod in the RMS population did not present with any unexpected findings as compared to other S1P receptor modulators, namely fingolimod and the recently approved siponimod. Fingolimod was authorised more than 8 years ago in the EU and risk minimisation measures proved efficacious for the indication of highly active RRMS. Siponimod was recently granted approval for treatment of adult patients with SPMS with active disease. Siponimod, although indicated for treatment of a later stage of MS, presented with a qualitatively similar safety profile as compared to fingolimod and ozanimod.

The amount of clinical trial safety data of fingolimod and siponimod and post-marketing experience with fingolimod appears reassuring that the safety of ozanimod is likewise manageable with similar precautionary measures in place in the product information and post-authorisation safety measures. More specifically, ozanimod with the proposed titration scheme to the therapeutic dosage does not raise particular concerns on the cardiovascular system. Patients with severe cardiac pre-morbid conditions were excluded from clinical studies and are likewise to be excluded from treatment with ozanimod (contraindication in section 4.3). In other less severe instances of cardiovascular impairment, cardiologist advice should be obtained prior to initiation of treatment.

Notwithstanding, and similar to other S1P receptor modulators, there are other relevant safety concerns with chronic ozanimod use, i.e. pronounced lymphopenia that increases the risk for serious/ opportunistic infections, elevation of liver enzymes that may be problematic for patients with pre-existing hepatic conditions, and an increased risk of malignancies, including skin cancers. The latter safety issue especially emphasised the need for long-term follow-up given that carcinogenicity commonly takes longer than 2 years to express. The determination of the long-term safety risk is still outstanding and will be further addressed in the ongoing long-term OLE Study RPC01-3001 and in a real-world post marketing study.

During the procedure, the CHMP thoroughly discussed the safety profile of ozanimod as a key aspect to determine whether the benefit-risk balance can be considered positive for the broad indication of RRMS patients as requested by the Applicant or whether a restriction to highly active RRMS patients would be more appropriate. In order to bring crucial perspectives from physicians and patients to the discussions on this particular aspect, the CHMP agreed to convene a SAG-N meeting including MS experts and patients' representatives.

The SAG-N experts agreed that safety concerns are expected to be similar to the ones reported for other immunosuppressant therapies. As such, risks cannot be neglected but are considered manageable in clinical practice using similar measures to the ones implemented for other highly efficacy DMT including Fingolimod. Regarding the risks, the SAG-N experts highlighted the importance of teratogenicity, rebound after cessation of treatment and long-term malignancy. All these risks were currently proposed as important potential risks for ozanimod and as such will be subject of further investigations during the post-marketing phase, while comprehensive precautionary wording was implemented in the product information.

When considering benefit-risk assessment of a given medical product for a target population, efficacy, safety and quality of the medical product are thoroughly assessed by CHMP. Due to the rather short observation periods of pivotal studies, long-term effects are difficult to evaluate, and long-term studies are recommended.

Taking into consideration all post-marketing experience (including studies but also clinical practice) with DMT in patients with MS, there is an increasing evidence supporting an early and efficacious intervention in the early phase of MS for maintaining neurological function over a lifetime in patients with MS (Ziemssen et al, 2016). Indeed, the therapeutic management of MS has substantially evolved over the last years and current evidence supports treatment optimization including an early intervention with efficacious therapies. This position was specifically acknowledged by the SAG experts who confirmed that there is a trend towards an earlier use of highly effective DMT including Fingolimod in the early stages of RMS to attain a more favourable outcome in patients. In this regard, the evolution of the clinical management could favour a broad indication of Ozanimod (SAG-N minutes). A majority of SAG experts openly expressed their preference for using highly active DMT in a more liberal scenario, which is currently not feasible, mostly due to reimbursement restrictions based on labeling. Specific mention was done for Fingolimod for which it was noted that present reimbursement rules prevent early use in several member countries (SAG-N minutes). In the view of the SAG-N experts, a restriction of the target population to highly active RRMS based on the safety profile would not be justified. Overall, the SAG experts expressed the view that a broad indication for active RRMS could be considered for Ozanimod but only patients with active disease should be treated. Patient's representatives expressed the view that overall patients will likely be willing to assume these risks provided they are well-balanced with the expected efficacy, and they receive a straightforward information regarding long-term risks.

With the totality of clinical trial data for ozanimod, the changing treatment strategies with a trend towards an earlier use of highly effective DMT in clinical practice over the last years since approval of the first (oral) non-selective S1P receptor modulator, and the fact that the safety profile of ozanimod is at least not worse compared to that of fingolimod and manageable, which was further supported by SAG-N experts, the unrestricted indication is considered fully justified.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Zeposia is positive for the treatment of adult patients with RRMS with active disease, subject to the conditions listed in section 4 Recommendation.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Zeposia is favourable in the following indication:

Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease evidenced by relapses or imaging features.

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 the launch of Zeposia® in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State (MS) where Zeposia is marketed, all Healthcare Professionals who intend to prescribe Zeposia are provided with a Healthcare Professional Information Pack, containing the following:

- Information on where to find latest Summary of Product Characteristics (SmPC);
- Healthcare Professional checklist;
- Patient/Caregiver's guide;
- Pregnancy-specific patient reminder card.

Healthcare Professional Checklist
The Healthcare Professional checklist shall contain the following key messages:

- Dose escalation at treatment initiation
    - Start treatment with 0.23 mg once daily on Days 1-4, then increase the dose to 0.46 mg once daily on Days 5-7. Following the 7-day dose escalation, the maintenance dose is 0.92 mg once daily, starting on Day 8.

- Re-initiation of therapy following treatment interruption
    - The same dose escalation regimen described above is recommended when treatment is interrupted for:
        - 1 day or more during the first 14 days of treatment.
        - more than 7 consecutive days between Day 15 and Day 28 of treatment.
        - more than 14 consecutive days after Day 28 of treatment.
- If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.
- Monitoring requirements at treatment initiation:

    Before first dose
    - Perform baseline electrocardiogram (ECG) prior to the first dose of Zeposia;
    - Consider recent (within last 6 months) liver function test results for transaminase and bilirubin levels;
    - Consider recent (within 6 months or after discontinuation of prior MS therapy) complete blood cell count results, including lymphocyte count;
    - Arrange ophthalmological assessment before starting Zeposia treatment in patients with diabetes mellitus, uveitis, or a history of retinal disease.
    - A negative pregnancy test result in women of childbearing potential must be confirmed prior to starting Zeposia treatment.

    Until 6 hours after first dose for patients requiring first dose observation
    - In patients with certain pre-existing cardiac conditions (resting heart rate <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure)
        - Monitor for 6 hours after the first dose of Zeposia for signs and symptoms of symptomatic bradycardia, with hourly pulse and blood pressure measurement
        - Perform an ECG prior to and at the end of the 6-hour monitoring period.
    - Extended monitoring may be required in the following situations
        - heart rate less than 45 bpm
        - heart rate is the lowest value post-dose, suggesting that the maximum decrease in heart rate may not have occurred yet

- evidence of a new onset second-degree or higher AV block at the 6- hour post-dose ECG
- QTc interval ≥500 msec.

- When initiating Zeposia in patients with:
  - History of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnoea, history of recurrent syncope or symptomatic bradycardia;
  - Pre-existing significant QT interval prolongation (QTc greater than 500 msec.) or other risks for QT prolongation, and patients on medicinal products other than beta-blockers and calcium-channel blockers that may potentiate bradycardia;
  - Current class Ia (eg, quinidine, disopyramide) or class III (eg, amiodarone, sotalol) antiarrhythmic medicinal products;

  A cardiologist should be consulted before initiating Zeposia to determine if Zeposia can safely be initiated and to determine the most appropriate monitoring strategy.

- Caution should be taken when initiating Zeposia in patients taking medicines known to decrease heart rate.

- Zeposia is contraindicated in patients with:
  - Immunodeficient state predisposing to systemic opportunistic infections;
  - Severe active infections, active chronic infections such as hepatitis and tuberculosis;
  - Active malignancies;
  - Severe hepatic impairment (Child-Pugh class C);
  - Myocardial infarction (MI), unstable angina, stroke, transient ischaemic attack, decompensated heart failure requiring hospitalisation or New York Heart Association (NYHA) Class III/IV heart failure in the last 6 months;
  - History or presence of second-degree AV block Type II or third-degree AV block or sick sinus syndrome unless the patient has a functioning pacemaker;
  - During pregnancy and in women of childbearing potential not using effective contraception;
  - Hypersensitivity to the active substance or to any of the excipients.

- Zeposia reduces peripheral blood lymphocyte counts. Peripheral lymphocyte count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy) and monitored periodically during treatment with Zeposia Treatment should be interrupted if lymphocyte count is confirmed as $<0.2 \times 10^9$/l and the re-initiation of Zeposia can be considered if the level reaches $> 0.5 \times 10^9$/l.

- Zeposia has an immunosuppressive effect that predisposes patients to a risk of infection, including opportunistic infections, and may increase the risk of developing malignancies, including those of the skin. Patients should be carefully monitored, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered on a case-by-case basis.
  - Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Interruption of treatment during serious infections should be considered. Anti-neoplastic, immunomodulatory, or non-corticosteroid immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects.
  - Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended. Caution patients against exposure to sunlight without protection. Patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to 3 months after discontinuation of treatment with Zeposia.
  - Prompt diagnostic evaluation should be performed in patients with symptoms of infection while receiving, or within 3 months of stopping, treatment with Zeposia

- Prescribers should be vigilant for clinical symptoms including unexpected neurological or psychiatric symptoms or MRI findings suggestive of PML. If PML is suspected a complete physical and neurological examination (including the possibility of performing an MRI) should be performed and treatment with Zeposia should be withheld until PML has been excluded. If PML is confirmed, treatment with Zeposia should be discontinued.
- The use of live attenuated vaccines should be avoided during and for 3 months after discontinuation of treatment with Zeposia. Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of varicella or documentation of a full course of varicella vaccination. If negative, VZV vaccination is recommended at least 1 month prior to treatment initiation with Zeposia.

- Zeposia is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
  - A negative pregnancy test result must be confirmed prior to starting treatment in women of childbearing potential. It must be repeated at suitable intervals.
  - Women of childbearing potential should be informed before treatment initiation about the risks of Zeposia to the foetus, facilitated by the pregnancy-specific patient reminder card.
  - Women of childbearing potential must use effective contraception during Zeposia treatment and for at least 3 months after discontinuation of treatment with Zeposia.
  - Zeposia should be stopped 3 months before planning a pregnancy.
  - While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, Zeposia must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with Zeposia treatment and ultrasonography examinations should be performed.
  - Disease activity may possibly return when treatment with Zeposia is stopped due to pregnancy or planning a pregnancy.

- Liver function (transaminase and bilirubin levels) should be monitored at Months 1, 3, 6, 9 and 12 during Zeposia therapy and periodically thereafter.

- Blood pressure should be regularly monitored during treatment with Zeposia.

- Patient who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ozanimod should be discontinued. Patients with diabetes mellitus, uveitis or a history of retinal disease should undergo an ophthalmological evaluation prior to treatment initiation with ozanimod and have follow up evaluations while receiving therapy.

- Prescribers should provide patients/caregivers with the patient/caregiver guide and with the pregnancy-specific patient reminder card

Patient/Caregiver's Guide

The patient/caregiver's guide shall contain the following key messages:

- What Zeposia is and how it works;
- What multiple sclerosis is;
- Patients should read the package leaflet thoroughly before starting treatment and should keep it in case they need to refer to it again during treatment;
- Importance of reporting adverse reactions;
- Patients should have a baseline ECG prior to receiving the first dose of Zeposia.
- Zeposia should not be used if you have had a heart attack, angina, stroke or mini-stroke (transient ischaemic attack), or certain types of severe heart failure in the last 6 months or if you have certain types of irregular or abnormal heartbeats (arrhythmia) – your doctor will check your heart before starting treatment. Caution should be taken with concomitant use of medicines that slow your heart rate. Therefore, patients should tell any doctor they see that they are being treated with Zeposia.

- For patients with certain heart conditions heart rate should be monitored for 6 or more hours after the first dose of Zeposia, including hourly pulse and blood pressure checks. An ECG before and after the 6 hours should also be performed for these patients.
- Patients should report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea, or palpitations) after the first dose of Zeposia;
- Patients should inform their prescriber in case of treatment interruption, as the initial dose escalation regimen may need to be repeated, depending on duration of interruption and time since initiation of Zeposia treatment;
- 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;
- Patients are recommended to have varicella zoster (chickenpox) vaccination 1 month before starting Zeposia treatment, if the patient is not protected and wants to be protected against the virus;
- Signs and symptoms of infection, which should be immediately reported to the prescriber during and up to 3 months after discontinuation of treatment with Zeposia;
- Any symptoms of visual impairment should be reported immediately to the prescriber during and for up to 3 months after discontinuation of treatment with Zeposia;
- Zeposia must not be used during pregnancy or in women of childbearing potential who are not using effective contraception. Women of childbearing potential should:
    - Be informed about serious risks to the foetus;
    - Have a negative pregnancy test before starting Zeposia. It must be repeated at suitable intervals;
    - Be informed about the requirement of using effective contraception during and for at least 3 months after discontinuation of treatment with Zeposia;
    - Be informed that disease activity may possibly return when treatment with Zeposia is stopped due to pregnancy or planning a pregnancy;
    - Report immediately to the prescriber any (intended or unintended) pregnancy during and up to 3 months after discontinuation of treatment with Zeposia. Ultrasonography examinations should be offered if needed;
- A liver function test should be performed prior to treatment initiation; liver function monitoring should be performed at Months 1, 3, 6, 9 and 12 during Zeposia therapy, and should be performed periodically thereafter;
- Blood pressure should be regularly monitored during treatment with Zeposia;
- Zeposia may increase the risk of skin cancer. Patients should limit their exposure to sun light and UV (ultraviolet) light, by wearing protective clothing and applying regular sunscreen (with high sun protection factor).

Pregnancy-specific Patient Reminder Card

The pregnancy-specific patient reminder card (for women of childbearing potential) shall contain the following key messages:

- Zeposia 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 teratogenic risk of Zeposia and required actions to minimise this risk;
- Women of childbearing potential must use effective contraception while taking Zeposia and for 3 months after treatment discontinuation;
- A pregnancy test must be carried out and negative results verified by the prescriber before starting treatment. It must be repeated at suitable intervals;
- If a woman becomes pregnant while on treatment, ozanimod must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with Zeposia treatment and ultrasonography examinations should be performed;
- Zeposia should be stopped 3 months before planning a pregnancy;
- Disease activity may possibility return when treatment with Zeposia is stopped due to pregnancy or planning a pregnancy.

Conditions or restrictions with regard to the safe and effective use of the medical 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 ozanimod hydrochloride is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.