Bristol Myers Squibb™

RESEARCH AND DEVELOPMENT

ZEPOSIA (OZANIMOD)
RISK MANAGEMENT PLAN

Version Number: 7.1

Data-lock Point for this RMP: 07-Apr-2023

Date of final sign off: 04-Mar-2024

Bristol-Myers Squibb
P.O. Box 4000
Princeton, NJ 08543-4000
USA

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ANNEXES

LIST OF ABBREVIATIONS

Term	Definition
5-ASA	5-aminosalicylic acid
ADA	Adalimumab
ADR	Adverse drug reaction
AE	Adverse event
AIHA	Autoimmune haemolytic anaemia
AKR	Aldo-keto reductase
ALT	Alanine aminotransferase
APVA	Additional pharmacovigilance activity(ies)
AST	Aspartate aminotransferase
AV	Atrioventricular
BCRP	Breast cancer resistance protein
BT	Total bilirubin
CBR	Carbonyl reductase
CI	Confidence interval
C_{max}	Maximum serum concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
CT	Computed tomography
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDD	Defined daily dose
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
EAIR	Exposure-adjusted incidence rate
EC	European Commission
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice

Term	Definition
GOL	Golimumab
GVP	Good Pharmacovigilance Practices
hERG	Human ether-a-go-go-related gene
HR	Heart rate
HSD	Hydroxysteroid dehydrogenase
IBD	Inflammatory bowel disease
IC_{50}	Ozanimod concentration needed to achieve 50% inhibition
IFN	Interferon
IFX	Infliximab
Ig	Immunoglobulin
IL	Interleukin
IM	Immunosuppressant
IR	Incidence rate
i.v.	Intravenous
JCV	John Cunningham Virus
LPLV	Last patient last visit
MAH	Marketing Authorisation Holder
MAO	Monoamine oxidase
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NCA	National Competent Authority
NMSC	Non-melanoma skin cancer
NOAEL	No observable adverse effect level
NOEL	No observed effect level
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OLE	Open-label extension
OR	Odds ratio
PASS	Postauthorisation Safety Study
PD	Pharmacodynamic
PK	Pharmacokinetic(s)

Term	Definition
PL	Package leaflet
PML	Progressive multifocal leukoencephalopathy
PRES	Posterior reversible encephalopathy syndrome
PSUR	Periodic Safety Update Report
PT	Preferred term
PUVA	Psoralen plus ultraviolet A
PY	Person-years
QD	Once daily
QPPV	Qualified Person for Pharmacovigilance
QTc	Concentration-corrected QT interval
QTcF	Corrected QT interval according to Fridericia's formula
RMP	Risk Management Plan
RR	Relative risk
RRMS	Relapsing remitting multiple sclerosis
S1P	Sphingosine-1-phosphate
S1Pn	Sphingosine-1-phosphate receptor n (where n is 1, 2, 3, 4 or 5)
SAE	Serious adverse event
SBP	Systolic blood pressure
SEER	Surveillance, Epidemiology and End Results
SIR	Standardised incidence rate
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TIA	Transient ischaemic attack
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UK	United Kingdom
ULN	Upper limit of normal
US(A)	United States (of America)
UV	Ultraviolet
VEDO	Vedolizumab
VTE	Venous thromboembolic event
VZV	Varicella zoster virus

EU RMP FOR ZEPOSIA

RMP version to be assessed as part of this application:

Version Number: 7.1

Data-lock Point for this RMP: 07-Apr-2023

Date of Final Sign-off: 04-Mar-2024

Rationale for submitting an updated RMP:

- Updated the status of Study RPC01-3001 from ongoing to completed throughout the RMP.
- Updated clinical trial exposure and safety data from Study RPC01-3001.
- Updated key message of the Patient/Caregiver's Guide in Annex 6 per PRAC AR for Zeposia (ozanimod) PSUR 6 (Procedure EMEA/H/C/PSUSA/00010852/202305)

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	NA	V3.0 / 14-Oct-2021
SII Non-clinical part of the safety specification	NA	V3.0 / 14-Oct-2021
SIII Clinical trial exposure	Updated with clinical trial exposure from Study RPC01-3001	V7.1/ pending
SIV Populations not studied in clinical trials	Update of Table 2.4.2-1 and Table 2.4.3-1	V7.1/ pending
SV Post-authorization experience	NA	V6.1 / 14-Aug-2023
SVI Additional EU requirements for the safety specification	NA	V2.0 / 02-Sep-2021
SVII Identified and potential risks	Updated with safety data from Study RPC01-3001	V7.1/ pending
SVIII Summary of the safety concerns	NA	V6.1 / 14-Aug-2023
Part III Pharmacovigilance Plan	Update to remove completed Study RPC01-3001 as APVA	V7.1/ pending
Part IV Plan for post-authorization efficacy studies	NA	V2.0 / 02-Sep-2021
Part V Risk Minimisation Measures	Update to remove Study RPC01-3001 as APVA Update to wording on routine risk minimisation measures for symptomatic bradycardia (Table 5.1-1)	V7.1/ pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part VI Summary of the Risk Management Plan	Update to align to updates made in the RMP.	V7.1/ pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Update to move Study RPC01-3001 from Ongoing to Complete	V7.1/ pending
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	Administrative update to eCTD sequence numbers	V7.1/ pending
ANNEX 4 Specific adverse drug reaction follow-up forms	NA .	V6.1 / 14-Aug-2023
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	NA	V2.0 / 02-Sep-2021
ANNEX 6 Details of proposed additional risk minimisation activities	Update to key message of the Patient/Caregiver's Guide	V7.1 / pending
ANNEX 7 Other supporting data	NA	V3.0 / 14-Oct-2021
ANNEX 8 Summary of changes to the risk management plan over time	Updated to reflect new EU RMP versions.	V7.1/ pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version number: 6.1

Approved with procedure: EMEA/H/C/004835/IB/0020

Date of approval (opinion date): 14-Aug-2023 (CHMP Opinion)

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler

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

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Ozanimod
Pharmacotherapeutic group(s) (ATC Code)	Selective immunosuppressants (L04AA38)
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Zeposia
Product Number	H0004835
Marketing authorization procedure	Centralised (EMEA/H/C/004835)
Brief description of the product	Ozanimod is a potent S1P receptor modulator, which binds with high affinity to SIP receptors 1 and 5. Ozanimod has minimal or no activity on S1P2, S1P3, and S1P4. In vitro, ozanimod and its major active metabolites demonstrated similar activity and selectivity for S1P1 and S1P5. The mechanism by which ozanimod exerts therapeutic effects in MS and UC is unknown but may involve reduction of lymphocyte migration into the CNS and intestine. The ozanimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leukocyte subpopulations, with greater decreases in cells involved in the adaptive immune response. Ozanimod has minimal impact on cells involved in innate immune response, which contribute to immunosurveillance. Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites including two major metabolites. In humans, approximately 94% of circulating total active substances exposure is represented by ozanimod (6%) and the two major metabolites CC112273 (73%) and CC1084037 (15%).
Hyperlink to the Product Information	Refer to PI
Indication(s) in the EEA	**Current:** <u>Multiple Sclerosis</u> Ozanimod is indicated for the treatment of adult patients with RRMS with active disease as defined by clinical or imaging features. <u>Ulcerative colitis</u> Ozanimod is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

Table 1-1: Product Details

Dosage in the EEA	**Current:** The recommended dose is 0.92 mg ozanimod QD. The initial dose escalation regimen of ozanimod from Day 1 to Day 7 is required. Following the 7-day dose escalation, the QD dose is 0.92 mg, starting on Day 8. *Special population* Hepatic impairment Patients with mild or moderate chronic hepatic impairment (Child-Pugh Class A or-B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day.
Pharmaceutical form (s) and strength(s)	**Current:** 0.23, 0.46, or 0.92 mg ozanimod hard capsules QD
Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Incidence, Prevalence, Mortality and Demographic Profile of the Patients with UC

Table 2.1.1-1: Epidemiologic Characteristics of Patients with UC

Ozanimod is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.	
Incidence	– The incidence of UC significantly increased in Europe and North America during the latter half of the 20th century and has showed stable or decreasing incidence since 1990. Since 1990, incidence has been rising in newly industrialised countries in Africa, Asia, and South America.[1] – Based on a systematic review of population-based observational studies published until December 2016[1] the incidence rate per 100,000 PY in Europe ranged from 0.97 (Romania, 2002 to 2003) to 57.9 (Faroe Islands, 2011), including 11.47 in Spain, 17.2 in the Netherlands, 1.9 in France, and 3.3 in Croatia. The incidence in Nova Scotia, Canada was 23.14. In Asia, it ranged from 0.15 (Philippines) to 6.02 (India). Incidence rate per 100,000 was 6.5 in Israel; 0.77 to 6.76 in Brazil; 17.4 in Australia and 3.29 in Algeria. – More recently published estimates in the UK;[2,3] reported an overall incidence per 100,000 PY of 23.2 (95% CI: 22.8-23.6),[3] and of 11.3 (crude), and age-adjusted incidences of 20.5 in patients of Indian descent, 8.2 among Europeans, and 11.2 in patients of Pakistani descent[2]. In a nationwide cohort of Danish patients with UC, the incidence was 18.6 (95% CI: 18.0-19.2) per 100,000 in 2010 to 2013; the incidence

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	increased throughout the study period (1980 to 2013).[4] In Northern France, a prospective population-based study (EPIMAD registry) evidenced a stable incidence of UC of at 4.4. per 100,000 PY from 1988 to 2014. In adolescents (10 to 16 years), however, the incidence of UC increased from 1.6 to 4.1 (+156%) over the period, more notably since 2003.[5,6] In Southern Europe, the incidence of UC was 25.3 in Catalonia (2016)[7] and 12.4 (95% CI: 7.6-19.1) per 100,000 PY in San Marino (2010 to 2014).[8]
Prevalence	– Prevalence continues to rise in many European countries, and in North America, Australia and New Zealand, and is expected to climb in newly industrialised countries.[1] – Ng et al[1] report UC prevalence rates per 100,000 ranging from 2.42 (Romania, 2003) to 505 (Norway [calculated prevalence using incidence rates of 1990 to 1994]) in Europe, including 412 in Germany (2010), 340 in Hungary (2013), 90.8 in the UK (1989). In Northern America, prevalence ranges from 139.8 in Quebec to 286.3 in Minnesota (2010). In Minnesota, the prevalence had increased by 34% since 2000.[9] – Further population-based studies estimated UC prevalence per 100,000 at 570 per 100,000 (2017) in the UK,[3] 225.6 in the Netherlands (2010),[10] 350 to 474 in Sweden (2010),[11,12] 354 in Catalonia (2016),[7] 311 in San Marino (2014).[8] – The forecast prevalence of UC in Canada for 2018 is 322 (95% CI: 318-326) per 100,000.[13]
Demographics of the population: age, gender, racial and/or ethnic origin	– Age at onset of disease has a bimodal distribution with an initial peak in the third decade and a smaller second peak between the ages of 50 and 80.[4,14] – Most studies report either an equal gender distribution or a slight predominance of incidence in males. – In general, Caucasians, and particularly people of Ashkenazi Jewish descent are more likely to have UC, whereas Asians are less likely to have UC in their countries of origin.[1] People of Indian descent living in the UK, however had higher UC incidence rates than White UK residents.[2]
Risk factors for the disease	– The pathogenesis of UC is multifactorial, involving genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors.[15,16] – A recent review[15] on UC mentions family history and Jewish ethnicity as risk factors for UC, as well as the association with specific loci. Genetics only explain 7.5% of the disease variance, however. Along with the rising incidence of UC worldwide, this suggests a greater importance of environmental factors in its development. According to this review: – Former cigarette smoking is one of the strongest risk factors associated with UC (OR 1.79, 95% CI: 1.37–2.34), while active smokers are less likely to develop UC compared with former and non-smokers (OR 0.58, 95% CI: 0.45-0.75) and have a milder disease course. – Appendectomy appears to confer a protective effect against UC, especially when done for acute appendicitis in young patients. – Patients newly diagnosed with UC are more likely than matched controls to have a history of gastroenteritis.

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A strong association between antibiotic use for any indication between 5 years and 3 months before UC onset, and new-onset UC (adjusted OR 2.94; 95% CI 2.23–3.88) was reported from a population-based study in Minnesota.[17] Dose-dependent relationships between antibiotic use and the risks of developing UC were observed. Only a small proportion of patients had been prescribed an antibiotic for a gastrointestinal infection (6% of IBDs versus 3% of controls).

Main treatment options

The following drugs are authorised in Europe for the treatment of UC:[18,19]

- Mesalazine (5-aminosalicylic acid [5-ASA]) and associated products: Olsalazine, Balsalazide, Sulfasalazine
- Corticosteroids: Prednisone, Prednisolone, Methylprednisolone, Budesonide, Beclomethasone
- IMs/Immunomodulators:
- Thiopurines:
  - Azathioprine
  - Mercaptopurine
  - Methotrexate (variable across countries)
- Biologicals:
  - TNF-α antibodies:
    - Infliximab
    - Adalimumab
    - Golimumab
  - Integrin antibodies
    - Vedolizumab
  - IL-12/IL-23 antagonist
    - Ustekinumab (approved in 2019)
- Janus kinase inhibitor:
  - Tofacitinib

In the EU5 (France, Germany, Italy, Spain and the UK), the patterns of treatment usage by line of therapy in 2017 were described among adult patients with moderate-to-severe UC who had prior exposure to either an IM or biologic.[20]

Table 2.1.1-1: Epidemiologic Characteristics of Patients with UC

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	First Line (N = 1060)	Second Line (N = 704)	Third Line (N = 376)	Fourth Line (N = 146)
No IM or biologic	499 (47.1%)	161 (22.9%)	61 (16.2%)	24 (16.4%)
IM without biologic	290 (27.4%)	292 (41.5%)	144 (38.3%)	39 (26.7%)
ADA	104 (9.8%)	73 (10.4%)	54 (14.4%)	30 (20.5%)
IFX	141 (13.3%)	134 (19.0%)	75 (19.9%)	28 (19.2%)
VEDO	9 (0.8%)	17 (2.4%)	25 (6.6%)	15 (10.3%)
GOL	14 (1.3%)	25 (3.6%)	15 (4.0%)	6 (4.2%)
Other biologic	3 (0.3%)	2 (0.3%)	2 (0.5%)	4 (2.7%)

- In the EU5, 47.1% used 5-ASAs and/or steroids in the first line while the remaining 52.9% used either an IM without a biologic (27.4%) or a biologic (25.6%; mostly either infliximab or adalimumab). The usage of an IM without a biologic was higher in both the second (41.5%) and third (38.3%) lines compared with the first line (27.4%). Similarly, the use of biologic therapy became increasingly common in subsequent lines.

Mortality and morbidity (natural history)

Natural History

- The natural history of the disease is periods of remission and flares. The majority of patients with UC have a mild-moderate course, generally most active at diagnosis and then in varying periods of remission or mild activity; about 14% to 17% of patients may experience an aggressive course.[21,22] The cumulative risk of relapse is approximately 70% at 10 years.
- In a given year, 48% of people with UC are in remission, 30% have mild disease activity, 20% have moderate disease activity, and 1% to 2% have severe disease.[23]
- Almost half of patients require UC-related hospitalisation at some point during disease course (23% at 5 years). Among those hospitalised once, the 5-year risk of re-hospitalisation is about 50%. The 5- and 10-year cumulative risk of colectomy is 4% to 10% and 6% to15%, respectively.[22,24,25,26] The frequency of colectomy has decreased in the past two decades.[26]

Mortality

- The all-cause mortality of UC is not greater than that in the general population.[27,28,29,30]
- An increased risk of death due to diseases of the digestive system of 1.98 to 14 times that in the non-UC population has been observed in some studies.[27,28,30]

Morbidity:

- Patients with IBD are at higher risk of complications in other organ systems, such as osteoporosis, venous thromboembolism, anaemia and CVD. Mental health morbidities are also important and common in IBD.

Venous Thromboembolism

- In population-based studies in Europe, incidence rates of VTE in patients with UC were reported from 1.10 (95% CI: 0.67-1.79) per 1000 PY in an inception cohort in Hungary to 2.44 per 1000 PY in Denmark in a study that included patients of all ages.[31,32] An older study in Manitoba found rates of were 3.00 per 1000 PY for DVT

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and 1.98 per 1000 PY for pulmonary embolism,[33,34] whereas recently the incidence rate in Taiwan was estimated at 0.94 per 1000 PY.[35]

- In a UC population from referral centres the incidence of all first VTEs was 5.4 per 1000 PY.[36]
- The RRs compared to the population without IBD was 1.5 for unprovoked events and nearly 2 for any VTE event in recent studies.[32,35] Extent of UC disease was associated with a higher risk of VTE.[31,35]

Anaemia

- The prevalence of anaemia in patients with UC treated in referral centres was estimated at 21% (95% CI: 15-27) in European countries[37] and the incidence was 12.9 (95% CI: 9.8-16.5) per 100 PY in a population-based cohort of patients with UC.[12] The two predominant types of anaemia in UC are iron-deficiency anaemia, and anaemia of chronic disease.

Cardiac ischaemia and cerebrovascular disease

In a recent meta-analysis of population-based inception cohort studies in IBD populations,[38] the pooled RRs for UC populations were as follows: cerebrovascular disease RR = 1.16 (95% CI: 1.06-1.28) (6 studies); coronary heart disease RR = 1.15 (95% CI:1.05-1.26) (5 studies); MI RR = 1.13 (95% CI: 1.02-1.26) (3 studies).

Important co-morbidities

The burden of extra-intestinal disease is high in patients with UC.[39] Up to one third of cases may have extraintestinal manifestations of the disease. In as many as 25% of patients, extraintestinal manifestations may predate the onset of gastrointestinal symptoms.[21] Among the most common extraintestinal manifestations are other chronic immune-mediated diseases such as erythema nodosum, ankylosing spondylitis and primary sclerosing cholangitis.

Immune-mediated diseases

Odds ratios (95% CI) greater than 2 for immune-mediated diseases in patients with UC compared to age- gender- and municipality-matched controls in a population-based study in Denmark.[40]

Immune-mediated disease	OR	(95% CI)
Primary sclerosing cholangitis	189.5	(47.0-763.4)
Pyoderma gangrenosum	27.3	(12.7-58.7)
Autoimmune hepatitis	8.6	(5.4-13.6)
Coeliac disease	4.5	(3.3-6.1)
Ankylosing spondylitis	3.9	(3.1-4.9)
Churg Strauss syndrome	3.9	(1.2-13.0)
Primary biliary cholangitis	4.2	(2.6-6.7)
Episcleritis	2.1	(1.2-3.9)
Iridocyclitis	2.4	(2.0-2.9)
Atrophic gastritis	2.4	(1.5-3.8)

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In addition, the following conditions had an OR between 2 and 1.5 with a 95% CI above unity: Psoriasis, Polyarteritis nodosa, Rheumatoid arthritis, Type 1 diabetes, Sarcoidosis, Asthma, Giant cell arteritis, Psoriatic arthritis, Grave's disease, Polymyalgia rheumatica.

AIHA

UC has been identified as one of the main conditions associated with warm antibody AIHA.[41] There are few studies on the frequency of AIHA in patients with UC, most of which are very likely to underestimate the condition. Uzzan et al[42] estimated the incidence of AIHA after IBD diagnosis at 4.1 per100,000 PY, and the prevalence among patients with UC at 150 per 100,000 using data from a large IBD prospective database in one referral centre.

Infections – serious and opportunistic - Herpes Zoster

In IBD patients the incidence rate of serious infections defined as those requiring a hospitalisation, ranged from 9.4 per 1000 PY in a population-based cohort of patients mostly naïve to thiopurines or anti-TNFα,[43] to 140 per 1000 PY and 60 per 1000 PY among anti-TNFα users and their propensity-score-matched non-user IBD controls, respectively.[44] The incidence rate of opportunistic infections in adult patients with IBD was 0.8 per 1000 PY.[43]

The epidemiological literature indicates that the age-specific incidence of herpes zoster is increasing in young adults.[45,46] In recent population-based studies, the incidence rate of herpes zoster in patients with UC are in the range of 7.22 to 9.0 per 1000 PY in Canada,[47,48] to 14.99 per 1000 PY in Korea.[49] An increase in risk compared to non-IBD controls of 30% to 40% may be inherent to the disease.[50,48]

A recent study reported increased risk of herpes zoster both before IBD diagnosis (hazard ratio: 1.42; 95% CI: 1.30–1.55) and also after diagnosis (hazard ratio: 1.52; 95% CI, 1.41-1.63).[48] Use of immunomodulating drugs is also an independent risk factor for herpes zoster in the UC population. Adjusted RRs are in the range of 1.43 to 1.96 for corticosteroids, from no increased risk to 3.1 for thiopurines, from 2.09 to 2.29 for anti-TNFα.[51,52,49,53] In the tofacitinib clinical development program for UC, the incidence rates per 1000 PY in patients exposed to tofacitinib 5 mg and 10 mg were 34.5 (17.8-60.2) and 42.5 (31.8-55.6).[54]

In Alberta, the risk of Clostridium difficile infection within 5 years of diagnosis of UC was 3.4%.[55]

Cancer

Colorectal cancer

Based on recently published studies, the risk of CRC in patients with UC ranges between no difference relative to the general population in three inception cohorts of patients in Italy, the Netherlands, and Canada followed for a relatively short time (medians 7 to 9 years)[56,57,58] to 94% increased risk in a French prevalent cohort of patients followed by gastroenterologists, which might be more diseased than the overall UC population.[59] In a large Scandinavian inception cohort of patients diagnosed in the past five decades the increase in risk was 66%.[60]

No studies were found on patients with moderately to severely active UC; however, extent and duration of disease, as well as persisting inflammation of the colon considerably increase the

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risk of CRC. The use of 5-ASA is protective, whereas thiopurines were shown to have a protective effect among patients with long-standing extensive colitis.[59,61]

Overall invasive cancers

The risk of overall invasive cancer in patients with UC may be up to 10% higher than in the general population,[62] although most recent studies do not find a statistically significant increased risk.[56,57,58] The risk of overall cancer increases with length of follow-up, as observed in the Netherlands where it was higher in the second decade after UC diagnosis.[57] Patients with childhood-onset UC have a two- to 2.6-fold higher risk of any cancer than the general population.[62,63]

Hematologic cancers

Patients with UC had a risk of hematologic cancers ranging from no increase to a 170% increase (highest SIR 2.7), and SIRs from 0.82 to 3.00 have been reported for Non-Hodgkin's lymphoma.[56,57,62,64] Thiopurines have been particularly implicated in IBD associated risk of lymphoma.[65]

NMSC

In a Danish population-based cohort study with 30-year follow-up (1978 to 2010), patients with UC had a significantly increased risk of developing NMSC after the first year of diagnosis (risk ratio, 1.8; 95% CI: 1.7–2.0).[62] In relatively short follow-up studies in the Netherlands and Italy, a slight excess in the risk of NMSC was reported which was not statistically significant.[56,57] In contrast, a very high risk of NMSC was found in an inception cohort of patients with UC in Quebec followed for a mean of 8 years (SIR 15.51 [10.05–20.97]).[58] According to the authors this may be an overestimate. An increase in risk of NMSC in patients with UC (1.47 (95% CI: 1.31-1.65)) was reported from a large administrative US database.[66] Among paediatric onset patients with UC there was an almost 4-fold risk of NMSC over the period 1964 to 2014 (SIR 3.9 [1.6-8.5]).[63]

Melanoma

In a systematic review of cohort studies reporting incident melanoma after IBD diagnosis, the risk of melanoma was increased among patients with UC (7 studies, 79,360 patients with UC: RR, 1.23; 95% CI: 1.01–1.50).[67] The pooled crude incidence rate was 22.7 per 100,000 PY (95% CI: 12.2-33.1) in patients with UC. Most of the studies were from the pre-biologic era.

Hepatic disorders

Hepatocellular and cholestatic abnormal liver biochemistry was found in 35% and 23% of patients with IBD, respectively, in a population-based inception cohort followed for 10 years from disease onset.[68] Similar results were found in a large referral centre: 28% of the patients with UC had abnormal hepatic biochemistries.[69] The degree of enzyme elevation was mild and was not associated with IBD activity. Abnormalities, however, appeared to have a negative impact in the long-term prognosis of IBD patients. Liver disease was present in 9.5% of patients with UC. Primary sclerosing cholangitis prevalence in UC ranges from 0.76% to 5.4%, cholelithiasis ranges between 1.1% in an inception cohort to 4.6% and 36.4% in referral centres, mean prevalence for non-alcoholic fatty liver disease was 23%.[70,69,71]

2.1.2 Incidence, Prevalence, Mortality and Demographic Profile of the Patients with RRMS

Table 2.1.2-1: Epidemiologic Characteristics of Patients with RRMS

Adult patients with active RRMS as defined by clinical or imaging features.	
Incidence	– The incidence of MS is known to vary between regions and countries; therefore, there is no uniform global incidence rate. The incidence rates of MS range from 0.07 per 100,000 in Guatemala to 13.4 per 100,000 in Canada. As many countries have unknown or unreported rates of MS, the true global burden of MS is likely to have been underestimated.[72] – In Europe, Bosnia and Herzegovina has the highest reported incidence of MS (12 per 100,000) followed by Latvia (11.6 per 100,000) and the Czech Republic (11 per 100,000). Countries with lower incidence rates of MS include Bulgaria (3.5 per 100,000), Italy, Spain, Switzerland and the UK (all 4 per 100,000).[72] – It is recognised that the diagnosis of MS has increased over the past few years, with several recent studies suggesting an increase in reported MS. A study in Poland reported that there is annual increment in incidence rates from 2010 to 2015 (the incidence rates were reported to be 2.92, 3.83, 4.00, 4.57, 5.70 and 6.20, respectively).[73] The cause of the increase in reported incidence rates is, however, unknown. A few potential explanations include better diagnosis and reporting systems, clear criteria for diagnosis and available treatment options.
Prevalence	– The prevalence of MS is increasing and is currently estimated to affect 2.3 million individuals worldwide. Following a similar pattern to the incidence, the prevalence of MS varies greatly across different regions and countries, ranging from 0.012 per 100,000 in Malawi to 291 per 100,000 in Canada.[72] – The highest prevalence of MS in Europe is generally reported to be in countries with high latitude including Denmark (227 per 100,000), Sweden (189 per 100,000), and the UK (164 per 100,000). The lowest prevalence of MS in Western Europe is reported to be in Portugal (56.2 per 100,000).[72]
Demographics of the population: age, gender, racial and/or ethnic origin	– The onset of MS typically occurs between the ages of 20 and 40 and predominantly affects women (two to three times more frequently than men).[74] – A cohort on 15,996 patients from 13 countries suggested that the average age of RRMS onset differs between countries of northern and southern latitude, with the age of onset being lower in female patients than male patients across various latitudes. The onset age for patients resident in countries of northern latitudes was 31.02 years for females and 33.66 years for males. For patients resident in southern latitudes, the age of onset was 33.69 years for females and 34.81 years for males. The onset age was the earliest in countries of north-central latitude, 29.66 years for female patients and 30.18 years for male patients. The average time between the onset and diagnosis of RRMS was between 4 to 5 years in all countries.[75] – There is no difference in female/male ratio in countries of different latitudes; the overall female/male ratio in northern latitudes was 2.66, 2.05 in the north-central latitude and 2.7 for patients in the southern latitude.[75] – MS is more common in people who live further away from the equator. In a worldwide European-descent cohort of 22,162 eligible patients from the MSBase registry, an earlier age at onset occurred in higher latitude regions and correlated inversely with variation in latitudinal UV radiation. These results suggest that environmental factors acting at the

Table 2.1.2-1: Epidemiologic Characteristics of Patients with RRMS

Adult patients with active RRMS as defined by clinical or imaging features.	
	population level could significantly influence disease severity characteristics in populations with genetic susceptibility.[76]
Risk factors for the disease	– The exact cause of MS remains unknown but is likely to be immune-mediated. There is strong evidence for an association between MS and genetic and environmental factors. The risk of developing MS is higher in relatives of a person with the disease than in the general population.[77,78,79] – Environmental factors that have been associated with MS include Epstein-Barr virus, low levels of vitamins, and smoking. These characteristics have all been documented to increase the risk of MS. Age and sex are also two important characteristics, with the onset of MS tending to occur in young adults and with women being at least twice as likely to suffer from the disease. Patients with existing autoimmune disease, type 1 diabetes, IBD or thyroid disease are also at higher risk of MS.[77,78,80,81]
Main treatment options	The following list is based on the European public assessment reports for human medicines published by the EMA.[82] This list does not include all products available on European markets through the decentralised procedure, which allows products to be available in certain countries only. Additionally, this is a listing of products without consideration for disease type, of line of treatment or disease activity. **Oral medications:** – Dimethyl fumarate: taken orally as a capsule, twice daily (also called BG12). – Fingolimod: taken orally as a capsule, QD. The first dose is taken under medical supervision to monitor HR and blood pressure. – Teriflunomide: taken orally as a tablet, QD. – Cladribine: taken orally as one or two tablets, QD, one treatment course a year for 2 years. Following completion of the two treatment courses, no further cladribine treatment is required in Years 3 and 4. **Injectable and infused medications:** – Beta IFN-1a: injected intramuscularly once a week or subcutaneously three times a week. – Peginterferon beta 1a: injected subcutaneously once every 2 weeks. – Beta IFN-1b: injected subcutaneously every other day. – Glatiramer acetate: injected subcutaneously daily. – Natalizumab: administered as an i.v. infusion via a drip once every 4 weeks. – Ocrelizumab: administered as two i.v. infusions 2 weeks apart with subsequent i.v. infusions taken every 6 months. Premedicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. – Alemtuzumab: administered as two treatment courses of i.v. infusions. Premedicated with corticosteroids for the first 3 days of treatment and oral prophylaxis for herpes infection starting on the first day of each treatment course. Mitoxantrone: administered as an i.v. infusion every 21 days.
Mortality and morbidity (natural history)	– Compared to the general population, MS has been associated with an increased mortality rate. A French observational study,[83] based on 27,603 patients with MS, calculated that the overall excessive mortality compared to the general population was around 1.48 (95% CI: 1.41-1.55) and increased considerably as the disease advances (2.20 [2.10-2.31]).

Table 2.1.2-1: Epidemiologic Characteristics of Patients with RRMS

Adult patients with active RRMS as defined by clinical or imaging features.	
	– A UK study based on 1822 MS cases estimated that the crude mortality rate for a patient with MS was 9.1 (95% CI: 7.6-10.8) per 1000 PY compared with 4.0 (95% CI: 3.6-4.3) per 1000 PY for that of the general population.[84] The authors also concluded that mortality rates were higher in patients with MS compared to their matched referents in each age group, and for both men and women.
Important co-morbidities	– There is strong evidence suggesting that MS is associated with a high prevalence of comorbidities. However, in a systematic review[85] of comorbidities in MS, considerable heterogeneity in comorbidities was identified between studies. The most frequently studied comorbidities were psychiatric, autoimmune, cancer, lung disease and epilepsy. Despite the inconsistencies between studies, the authors concluded that the five most prevalent comorbidities in MS were depression, anxiety, hypertension, hyperlipidaemia and chronic lung disease. Meta-analysis estimates for the prevalence of these comorbidities were depression 23.7 (95% CI: 17.4-30); anxiety 21.9 (95% CI: 8.76-35), hypertension 18.6 (95% CI: 13.9-23.2), hyperlipidaemia 10.9 (95% CI: 5.6-16.1) and chronic lung disease 10.0 (95% CI: 0-20.9).[85] – Amongst all comorbidities studied, the most frequently recorded acute comorbidity was infections (recorded in 80% of patients with MS). Depression was the most frequently recorded chronic comorbidity, occurring in 46% of patients. Other common comorbidities included COPD and asthma (19.7%) and hypertension (14.5%).[86] – Using the UK Clinical Practice Research Datalink, comorbidities and medication use at the time of and after the MS diagnosis date were compared between 6932 patients with MS and 68,526 patients without MS. Relative to patients without MS, patients with MS prior to diagnosis had an increased prevalence ($p < 0.05$) of depression, eye/ear infections, urinary tract infections, serious infections, autoimmune disorders, peripheral vascular disease, Raynaud's syndrome and macular oedema, and increased use of antidepressants, antipsychotics, antiepileptics, antihypertensives, proton pump inhibitors, antibiotics, as well as several symptomatic treatments. Over a median follow-up of 5 years post-diagnosis, patients with MS had increased rates of spasticity, neuropathy, epilepsy, osteoporosis, non-depressive psychiatric disorder, serious infection, venous thromboembolism, treated depression, peripheral vascular disease, suicidal behaviour, fracture, opportunistic infection, bowel dysfunction, major adverse cardiac event and herpes. Compared to the non-MS population, the overall cancer incidence rate was not increased. All-cause death was 2-fold higher in patients with MS.[87] **Cardiovascular Disease** – Conflicting information exists regarding the risk of CVD in MS ranging from no risk to high risk in various studies.[88] CVD is considered to be highly prevalent amongst patients with MS, relative to individuals without MS.[89] In this study, the rate ratio for MI was 1.85 (95% CI: 1.59-2.15), stroke was 1.71 (95% CI: 1.46-2.00), and heart failure was 1.97 (95% CI: 1.52-2.56). The increases in risk were particularly prominent for women. Similar results have been confirmed in a further study of 7667 patients with MS, in which an increased CVD risk (1.31 [95% CI: 1.22-1.41]) was reported.[90] – Using the UK Clinical Practice Research Database, rates of CVD in patients after MS diagnosis were compared with rates in a matched, non-MS patient population. In total, 5726 CVD- and CVD risk factor-free patients with MS were identified and compared with 57,331 patients without MS. Rates of TIA, angina or unspecified ischaemic heart disease, heart failure, bradycardia/heart block, other arrhythmias, or pericardial disease were similar;

Table 2.1.2-1: Epidemiologic Characteristics of Patients with RRMS

Adult patients with active RRMS as defined by clinical or imaging features.
however, patients with MS were at greater risk of peripheral vascular disease (incidence rate ratio, 2.35; 95% CI: 1.29-24.0) and venous thromboembolism (incidence rate ratio, 1.95; 95% CI: 1.48-2.51). Compared with patients without MS, rates of MI were increased in women (incidence rate ratio 2.55; 95% CI: 1.40–4.37.[91] **Infections** – Infections are associated with MS in several aspects. Infection is considered to be a potential trigger of MS as well as a risk for MS exacerbation.[92] In addition, several MS treatments also increase the rates of infections amongst patients with MS.[93] Large epidemiologic studies have found that infection is a common comorbidity amongst MS and patients with MS are two to four times more likely to be hospitalised for infection compared to the general population.[94,95] The most commonly types of infections are infections of the respiratory and urinary systems. Other common infections include skin infection and pneumonia.[94,95] **Suicide** Patients with MS are known to have an increased rate of depression and also a higher risk of suicide. A German study[96] investigated the risk factors for suicidal ideation in patients with MS. It was found that 22.1% of the 573 patients studied had suicidal ideation, of which depression was concluded to be a risk factor. Another recently conducted Swedish study[97] of 29,617 patients with MS found that the adjusted hazard ratio for attempted suicide amongst patients with MS, relative to the general population cohort, is 2.18 (95% CI: 1.97-2.43). Compared to the general population cohort, the hazard ratio for completed suicide is 1.87 (95% CI: 1.53-2.3).

2.2 Nonclinical Part of the Safety Specification

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 2.2-1.

Ozanimod has been characterised in nonclinical safety studies including repeated dose toxicity (rat and monkey), genotoxicity (bacterial reverse mutation and in vitro or in vivo mammalian cell systems), carcinogenicity (Tg.rasH2 mouse and conventional rat), reproductive and developmental toxicity, juvenile toxicity, phototoxicity, and immunotoxicology studies. Dose levels discussed in this section correspond to the ozanimod free base.

Characterisation of the nonclinical toxicology of ozanimod was complicated by the number of metabolites present in toxicology species and humans. No unique human metabolites have been identified. Three metabolites (CC112273, CC1084037, and RP101124) were identified as major human metabolites (> 10% of total drug-related exposure). Of these three major human metabolites, two (CC112273 and CC1084037) have similar activity and receptor selectivity compared to ozanimod, and the third (RP101124) is inactive. Most of the metabolites are structurally similar to ozanimod, with the changes limited to the hydroxyethyl amine side chain. Shortening of the hydroxyethyl amine side chain reduces the solubility but retains the S1P1/S1P5 potency and selectivity profiles.

In rodent species, ozanimod is the predominant component in circulation. The active circulating human metabolites (CC112273 and CC1084037) are also present in rodents and rabbits, but their exposures relative to ozanimod are lower due to their rapid elimination and therefore shorter half-life. In monkeys, levels of ozanimod and CC112273 are similar to each other, with high levels of CC1084037 also achieved. In humans, CC112273 is the predominant component in blood circulation, reaching approximately 73% of the drug-related exposure after 28 days of dosing.

The majority of the findings in the chronic toxicology, carcinogenicity, and reproductive toxicology studies are considered target-mediated effects of S1P agonist. As the two major active human metabolites have similar activity and receptor selectivity, the different proportionality and half-life observed in animals have no impact on the overall safety profile assessment. The rat and monkey had similar findings of decreased peripheral blood lymphocytes, decreased thymic corticomedullary ratios, and decreased size/cellularity of the splenic white pulp. These findings are expected based on the pharmacological effects of S1P agonist. More details on these studies are discussed below.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
Toxicity Studies • Repeated Dose Toxicity GLP-compliant toxicity studies were performed in rats for 28 days, 13 weeks, and 26 weeks (6 months) in duration. Reversibility was evaluated in the 28-day and 26-week studies. Doses were kept constant (0.2, 2, and 30 mg/kg/day) across the range of studies and spanned two orders of magnitude. The similar types of changes seen at higher doses compared to the lower doses were consistent with on-target pharmacology of highly selective compounds. Organ weight changes common to all of the studies included decreased spleen weights and increased lung weights. Decreases in absolute lymphocyte counts in the peripheral blood were present at the low dose of 0.2 mg/kg/day, consistent with S1P1 agonist pharmacology. As dose levels were increased to 2 mg/kg/day and 30 mg, absolute lymphocyte counts were decreased further, consistent with moderate to marked S1P1 agonist pharmacology. Histologic lesions consisted of minimal to moderate alveolar macrophage infiltrates, decreased corticomedullary ratio of the thymus, and depletion of lymphocytes in the spleen. All of these changes have been associated with agonist activity at S1P receptors. The lung changes were the determinant of adversity and established the NOAEL across these studies, which was 0.2 mg/kg/day. Findings at higher doses did not tend to increase in severity or become irreversible with longer duration of dosing. Evidence of immune suppression such as an increased incidence of opportunistic infections was not observed in these studies. GLP-compliant toxicity monkey studies included durations of 28 days, 13 weeks, and 39 weeks (9 months). Reversibility was evaluated in the 28-day and 39-week studies. In monkeys, absolute lymphocyte counts in the peripheral blood were minimally to mildly decreased beginning with the low doses (0.15 or 0.1 mg/kg day). With increasing doses (up to 30 mg/kg/day in the sub-chronic studies	In controlled clinical studies, the rates of cough and dyspnoea were low and consistent with those seen in the placebo (UC studies) or IFN active comparator (MS studies) populations. Mild changes in pulmonary function tests were observed which were not clinically significant and were not associated with AEs. No safety concern was identified. Clinically, dose-dependent reversible reductions in circulating lymphocytes were readily observed.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
and 15 mg/kg/day in the 39-week chronic study), the absolute lymphocyte counts were further decreased. Body weight, weight gain, and food consumption exhibited minimal to no changes across the studies. Organ weight changes included decreased spleen weights and increased lung weights. Histologic changes were similar to the rat and consisted of minimal to moderate alveolar macrophage infiltrates, decreased corticomedullary ratio of the thymus, and depletion of lymphocytes in the spleen. The lung changes were considered adverse and established the NOAEL in all of the studies (0.15 mg/kg/day in the sub-chronic studies and 0.1 mg/kg/day in the chronic study). Findings did not tend to increase in severity or become irreversible with longer duration of dosing. In summary, dosing of rats and monkeys with ozanimod resulted in adequate exposure to ozanimod, RP101124, CC112273, and CC1084037. Evidence of on-target pharmacology was present at the lowest doses in these studies and was easily monitored as mildly decreased peripheral blood lymphocyte numbers. Higher doses in these studies resulted in further suppression of peripheral blood lymphocytes. Although the lowest dose was identified as the NOAEL based upon pulmonary effects in each study, the lung changes did not increase in incidence or severity with longer duration of dosing and reversed following cessation of dosing. The results from these studies are adequate for the evaluation of the nonclinical safety of ozanimod and metabolites.	
• Reproductive and Developmental Toxicity Reproductive toxicology of ozanimod was assessed in the rat and rabbit. No findings of concern were identified in the fertility and early embryonic development study or the pre- and post-natal development study. However, in the embryo-foetal development studies in both the rat and rabbit, toxicity and teratogenic effects were present. These findings included generalised oedema (anasarca) in the rat, and malpositioned caudal vertebrae and great vessel abnormalities in the rabbit. These findings are consistent with the data available for the S1P knockout mouse, where germline knockout is embryonic lethal due to generalised haemorrhage (embryonic day 12.5 to 14.5). The vascular findings in rats and rabbits with ozanimod occurred at exposures that were at or near the clinical dose and were likely mediated by the S1P1 activity of both the parent ozanimod and the active metabolites. While exposure for the metabolites was lower in the rat and rabbit due to more rapid elimination (relative to humans), the dose-limiting vascular effects are consistent with expected pharmacology. Examination of ozanimod in rat juvenile toxicity studies identified the same effects as in adult rats (decreased peripheral blood lymphocytes, increased lung weights, and increased alveolar macrophages). Immunotoxicity assessment identified the expected pharmacological action of decreased lymphocyte count and also an inhibitory effect on primary and secondary T-dependent Ig G antibody responses.	There are limited data from the use of ozanimod in pregnant women. Female patients were required to use contraception in the clinical trial programme. Female patients were required to discontinue study medication in the event of pregnancy. Due to nonclinical findings, contraceptives should be used by women.
• Nephrotoxicity	

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
Although test article-related renal pathology was observed in the rat administered 30 mg/kg/day for 28 and 91 days and in the monkey administered 3 mg/kg/day for 91 days, longer term repeated administration of ozanimod for 26 weeks and 39 weeks at a maximum dose of 30 and 15 mg/kg/day in the rat and monkey, respectively, had no test article-related renal changes.	No clinically relevant effect on the kidney was observed in clinical trials.
• Hepatotoxicity Although test article-related higher mean absolute and relative liver weights were seen in the 3 and 30 mg/kg/day monkeys administered ozanimod for 91 days, longer term repeated administration of ozanimod for 39 weeks with 0.1, 1 and 15 mg/kg/day had no hepatic changes.	Although increases in ALT and GGT were observed in humans, no severe DILI was reported in clinical studies.
• Genotoxicity Assessment of genotoxicity for this programme was extensive due to the number of metabolites and included both non-GLP mutagenicity screening assays and definitive GLP-compliant assays. Bacterial reverse mutation assessment included ozanimod, all major metabolites, and selected minor metabolites. In vitro assays used arachlor-induced rat-S9 fractions for metabolic activation. Ozanimod and multiple metabolites were all negative for bacterial mutagenicity. Mammalian cell assays included an in vitro mouse lymphoma assay with ozanimod, an in vivo bone marrow micronucleus assay with ozanimod, a chromosomal aberration assay using human peripheral blood lymphocytes with CC112273, and a TK6 micronucleus assay with CC1084037. All of these mammalian cell assays were negative except for the TK6 micronucleus assessment for CC1084037, which was positive without S9 activation. To further assess the in vitro TK6 result, an additional combined in vivo rat bone marrow micronucleus and hepatic Comet Assay was conducted with CC1084037. The negative bone marrow micronucleus result and the negative hepatic Comet Assay results for CC1084037 provide sufficient assurance of the absence of genotoxic activity and no additional tests are warranted, according to the International Council for Harmonisation S2(R1). Overall, there are no genotoxicity concerns for the ozanimod programme.	Based on nonclinical data, no genotoxic or mutagenic effects in humans are expected. No increased risk of malignancies above background rates has been observed in clinical trials, although follow-up time is limited.
• Carcinogenicity Carcinogenicity risk was assessed through extensive genetic toxicology testing, in vivo carcinogenicity studies, assessment of proliferative lesions in the general toxicology studies, and surveillance in the clinical trials. There was no evidence in general toxicology studies, carcinogenicity studies, or clinical studies for increases across multiple tumour types due to potentially decreased immune-surveillance of tumours, which is a common concern with many immune suppressive agents. The only tumour type with increased incidence was hemangiosarcomas in mice. Based upon available mechanistic data, hemangiosarcomas in mice appear to be a species-specific endothelial cell effect with no evidence for increased incidence in rats or humans. While exposures in both rodent species to the metabolites CC112273 and CC1084037 was lower than	Longer follow-up and larger numbers of exposed patients are required to make any firm conclusions regarding risk of malignancy with ozanimod. Overall, the incidence of malignancy in -ozanimod treated patients was not increased beyond that expected for the target populations. No pattern was observed in type of malignancy.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
ozanimod due to more rapid elimination (relative to humans), adequate exposures to assess carcinogenicity were achieved, especially in the mouse 80 mg/kg/day dose (37-fold for CC112273 and 15-fold for CC1084037) to assess off-target carcinogenicity.	
• Immunotoxicity	
Immunotoxicity assessment identified the expected pharmacological action of decreased lymphocyte count and also an inhibitory effect on primary and secondary T-dependent IgG antibody responses.	A pharmacologic reduction in peripheral blood lymphocyte count was evident in clinical studies and may be relevant to an increased risk of serious or opportunistic infection if pronounced or prolonged. No increased risk of serious infection was observed in clinical studies. The efficacy and safety of vaccines during ozanimod treatment have not been studied. The SmPC provides guidance on vaccination.
General Safety Pharmacology	
• Cardiovascular	
The ozanimod concentration needed to achieve IC_{50} of the hERG channel current was 0.21 µM. The margin of inhibition of the hERG potassium current IC_{50} to the clinical exposure is 347-fold. The metabolite CC112273 had an IC_{50} of 0.6 µM. The margin of inhibition of the hERG potassium current IC_{50} to the clinical exposure of CC112273 is 31-fold. The IC_{50} for CC1084037 on the hERG potassium current was > 3.0 µM. The margin of inhibition of the hERG potassium current IC_{50} to the clinical exposure was greater than 800-fold.	Clinically, ozanimod is associated with transient, dose-related reductions in HR. After the initial dose of ozanimod 0.23 mg, the greatest mean reduction from baseline in HR occurred at Hour 5 on Day 1 (decrease of 1.2 bpm in MS clinical studies and 0.7 bpm in UC clinical studies), returning towards baseline at Hour 6.
Telemetered male monkeys administered up to 30 mg/kg ozanimod exhibited minor and transient prolongation of the PR interval (increased by about 10%) and diastolic blood pressure (DBP) (decreased by about 20%). Additionally, HR was decreased to a maximum of 29% at 4 hours after administration of 30 mg/kg. The NOEL for ozanimod in the cardiovascular evaluation conducted in conscious monkeys was 0.15 mg/kg. The C_{max} in monkeys achieved at 0.15 mg/kg was 11.3 times above the C_{max} achieved with the clinical administration of 0.92 mg ozanimod.	Two isolated cases of HR < 40 bpm were reported, neither of which was associated with an AE or required treatment (see Table 2.7.3.1-2). Initiation of ozanimod without dose escalation may result in greater reductions in HR. Ozanimod was not associated with clinically significant bradycardia or conduction effects (second or third-degree AV block). With chronic dosing, ozanimod was not associated with cardiac effects of concern. No signal for corrected QT interval prolongation has been observed in humans.
• Nervous system	
No statistically significant differences were observed in the functional observational battery evaluated in the rat administered ozanimod up to 30 mg/kg. In a rat self-administration study, no reinforcing effects were present, consistent with minimal to no misuse potential.	No clinical cognitive effects were observed in humans.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
• Respiratory Respiratory function, as evaluated with plethysmography, identified only minor increases in respiratory rate and decreases in tidal volume, leaving the minute volume unchanged at the highest dose tested of 30 mg/kg/day ozanimod for 7 days. Based on plethysmographic evaluation and lung weight data, the NOEL for ozanimod in rats is 0.2 mg/kg/day.	Clinically, pulmonary effects were nonserious and not dose-limiting. Respiratory AEs in the UC clinical studies and in the Phase 3 relapsing MS controlled studies were similar across treatment groups with few SAEs or AEs that led to discontinuation. Mild reductions in forced expiratory volume in 1 second and diffusing capacity occurred early in treatment with ozanimod 0.92 mg, but were not clinically meaningful and did not progress.
Mechanisms for Drug Interactions a. The metabolism of ozanimod is mediated by multiple biotransformation pathways including aldehyde dehydrogenase and alcohol dehydrogenase, CYP) isoforms 3A4, 1A1, and 2C8, MAO-B, CBRs, AKR 1C1 and 1C2, 3β-and 11β- HSD, and gut microflora, and hence no single enzyme system predominates the overall metabolism of ozanimod. b. MAO-B is responsible for the formation of CC112273 while CYP2C8 and oxido-reductases are involved in the metabolism of CC112273. CC1084037 is formed directly from CC112273 and the interconversion between these two active metabolites is mediated by CBR, AKR 1C1/1C2, and/or 3β- and 11β-HSD. c. Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6, and 3A and no induction effect on CYPs 1A2, 2B6, and 3A. d. Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on P-glycoprotein, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, and MATE2-K. CC112273 and CC1084037 inhibit BCRP with IC_{50} values of 25.2 nM and 22.8 nM, respectively. e. CC112273 and CC1084037 inhibited MAO-B with more than 1000-fold selectivity over MAO-A (IC_{50} > 10,000 nM) with IC_{50} values of 5.72 nM and 58 nM, respectively. Furthermore, ozanimod and CC112273 did not exacerbate an in vivo murine model of serotonin syndrome.	a. The risk of ozanimod being a victim of drug-drug interaction is low. There is no potential risk for Asian population based on multiple factors: 1) no clinically relevant PK differences between Asians (Japanese) and Caucasian; 2) alcohol dehydrogenase and aldehyde dehydrogenase are not major metabolic enzymes for ozanimod or the major active metabolites CC112273 and CC1084037 (Studies RPC01-1905 and RPC01-1911). b. Coadministration with MAO-B inhibitors may decrease exposure of CC112273 and consequently CC1084037. Coadministration with CYP2C8 inhibitors may increase CC112273 and CC1084037 exposure. Coadministration with CYP2C8 inducers may decrease CC112273 and CC1084037 exposure. No inhibitors or inducers of CBR, AKR or HSD have been identified and therefore the risks of drug interactions involving these enzymes are low. c. Ozanimod does not alter the metabolism of other concomitant drugs. Repeated dosing of ozanimod (7-day dose escalation followed by 0.92 mg QD for 5 days) had no effect on the single-dose PK of an oral contraceptive containing ethinylestradiol (35 µg) and

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings (from Nonclinical Studies)	Relevance to human usage
	norethindrone (1 mg), which are substrates of CYPs 3A, 2C19, and 2C9. While dosing of ozanimod was not long enough to attain steady state for CC112273 or CC1084037, in vitro data showed that CC112273 or CC1084037 does not inhibit or induce CYP enzymes and therefore it is not expected to have any effect on the PK of ethinylestradiol and norethindrone. d. At clinically relevant concentrations of CC112273 and CC1084037, inhibition of BCRP is not expected. e. The risk of interactions with adrenergic or serotonergic agents is low.
Other Toxicity-related Information or Data	
Ozanimod and the major metabolite CC112273 penetrate into the CNS in rats. No CNS toxicity has been observed in animals.	No CNS toxicity has been observed in humans.

2.3 Clinical Trial Exposure

According to the international standard for the naming and dosage strength designation of prescription drug products, three strengths of finished product (capsules) are proposed: ozanimod 0.23 mg (equivalent to 0.25 mg ozanimod HCl), 0.46 mg (equivalent to 0.5 mg ozanimod HCl) and 0.92 mg (equivalent to 1 mg ozanimod HCl). The clinical data presentations in this document refer to the finished product strengths (ie, 0.23 mg, 0.46 mg, and 0.92 mg ozanimod).

2.3.1 UC Studies

2.3.1.1 Study Information

Safety data supporting the UC indication are based on pooled safety analyses from 2 controlled studies and 1 open-label extension (OLE) study.

- RPC01-202: a multi-centre randomised double-blind, placebo-controlled Phase 2 study with a completed core period (Induction and Maintenance Periods) and a completed OLE period.
- RPC01-3101: a multi-centre randomised double-blind, placebo-controlled pivotal Phase 3 study with completed Induction and Maintenance Periods.
- RPC01-3102: a Phase 3 ongoing OLE study.

Pooled safety analysis included all patients who received at least 1 dose of study drug (ozanimod 0.92 mg and placebo). Note: for the dose ranging study RPC01-202, only patients treated at the therapeutic dose of 0.92 mg or placebo were included in the pooled analysis.

The safety pools supporting the UC indication included in this RMP are as follows:

- Pool F: Controlled UC Studies (RPC01-202 and RPC01-3101).
  - Induction Period analyses: RPC01-202 (placebo and ozanimod 0.92 mg) and RPC01-3101 (placebo and ozanimod 0.92 mg of Cohort 1).
  - Maintenance Period analyses: randomised, placebo-controlled RPC01-3101 Maintenance Period. Due to differences in study design, the Study RPC01-202 Maintenance Period was not pooled with RPC01-3101 for analysis.
- Pool G: Controlled and Uncontrolled UC Studies.
  - RPC01-202 (including Maintenance and OLE Period), RPC01-3101, RPC01-3102.

2.3.1.2 Patient Exposure

Exposure data for ozanimod in the UC studies are presented from Pool G, which included 1158 patients. A total of 227 patients who were treated with ozanimod 0.92 mg in the Study RPC01-3101 Induction Period and re-randomised to placebo in the Maintenance Period are included in the total count of the placebo group. Patients may be included in both placebo and ozanimod 0.92 mg treatment groups.

Exposure data are presented in Table 2.3.1.2-1 to Table 2.3.1.2-3.

Table 2.3.1.2-1: Duration of Exposure in Patients with UC

Duration of Exposure (at Least)	Placebo (N = 508)		Ozanimod 0.92 mg (N = 1158)	
	Persons, n (%)	Person-Years	Persons, n (%)	Person-Years
1 dose (total)	508 (100)	243.84	1158 (100)	1843.36
6 months	220 (43.3)	181.23	868 (75.0)	1772.30
1 year	36 (7.1)	37.27	715 (61.7)	1659.42
2 years	0	0	315 (27.2)	1083.29
3 years	0	0	155 (13.4)	696.88
4 years	0	0	84 (7.3)	451.59
5 years	0	0	58 (5.0)	337.00
6 years	0	0	19 (1.6)	118.34

Data lock point: 31-Mar-2020.
Denominators for percentages are N, the total number of patients in each treatment group.

Table 2.3.1.2-2: Exposure to Ozanimod by Age Group and Gender in Patients with UC

Age Group (Years)	Ozanimod 0.92 mg (N = 1158)					
	Persons, n (%)			Person-Years		
	Male	Female	Total	Male	Female	Total
≥ 18 to < 40	324 (57.4)	240 (42.6)	564 (48.7)	479.62	374.70	854.32
≥ 40 to < 65	334 (62.0)	205 (38.0)	539 (46.5)	567.18	355.23	922.40

Table 2.3.1.2-2: Exposure to Ozanimod by Age Group and Gender in Patients with UC

Age Group (Years)	Ozanimod 0.92 mg (N = 1158)					
	Persons, n (%)			Person-Years		
	Male	Female	Total	Male	Female	Total
≥ 65	30 (54.5)	25 (45.5)	55 (4.7)	40.27	26.37	66.64
Total	688 (59.4)	470 (40.6)	1158 (100)	1087.06	756.30	1843.36

Data lock point: 31-Mar-2020.
Denominators for each category of age or gender are the total numbers of patients in each associated category of age or gender.
Denominators for the total category of age or gender are the total numbers of patients in the associated treatment groups.

Table 2.3.1.2-3: Exposure to Ozanimod by Ethnic or Racial Origin in Patients with UC

Ethnic Origin	Ozanimod 0.92 mg (N = 1158)	
	Persons, n (%)	Person-Years
White	1036 (89.5)	1639.37
Asian	68 (5.9)	127.52
Black or African American	31 (2.7)	46.10
Other	22 (1.9)	29.74
Missing	1 (0.1)	0.63
Total	1158 (100)	1843.36

Data lock point: 31-Mar-2020.
Denominators for percentages are N, the total number of patients in each treatment group.

2.3.2 RRMS Studies

2.3.2.1 Study Information

Briefly, the safety pools supporting the RRMS indication included in this RMP are as follows:

- Pool A1: Active-controlled comparative Phase 3 studies in relapsing MS (two pivotal studies)
  - RPC01-201B: A pivotal Phase 3, 2-year, randomised, double-blind, double-dummy, active-controlled, parallel group study to evaluate the efficacy and safety of RPC1063 administered orally to relapsing MS patients.
  - RPC01-301: A pivotal Phase 3, multicentre, randomised, double-blind, double-dummy, active-controlled, parallel group study to evaluate the efficacy and safety of RPC1063 administered orally to relapsing MS patients.
- Pool B: All studies in relapsing MS (controlled and uncontrolled, five studies)
  - Both studies in Pool A1.

- RPC01-201A: A Phase 2, multicentre, randomised, double-blind, placebo-controlled, study with a blinded dose extension period to evaluate the efficacy and safety of RPC1063 administered orally to relapsing MS patients.
- RPC01-3001: A multisite, open-label extension trial of oral RPC1063 in relapsing MS in patients who completed Studies RPC01-201A, RPC01-301, RPC01-201B, or RPC01-1001. (Interim analysis; data cutoff date 30-Jun-2018).
- RPC01-1001: A Phase 1, multicentre, randomised, 12-week, open-label study to evaluate the multiple-dose PK and pharmacodynamics (PD) of RPC1063 in patients with relapsing MS.

- RPC01-3001 (OLE): Final analysis; DBL of 07-Apr-2023.

2.3.2.2 Patient Exposure

The Safety Population for Pool A1 included 2659 patients, of whom 882 patients received ≥ 1 dose of 0.92 mg ozanimod, 892 patients received ≥ 1 dose of 0.46 mg ozanimod, and 885 patients were exposed to ≥ 1 dose of IFN β-1a.

The Safety Population for Pool B included 2787 patients, of whom 2631 patients received ≥ 1 dose of 0.92 mg ozanimod and 1033 patients received ≥ 1 dose of 0.46 mg ozanimod. It should be noted that patients may be included in both the ozanimod 0.46 mg and 0.92 mg treatment groups but were counted only once in the total number of patients in Pool B.

The Safety Population for RPC01-3001 included 2494 patients, all of whom received ozanimod 0.92 mg in the OLE, including those treated with IFN β-1a and ozanimod 0.46 mg in the parent studies.

Exposure data for ozanimod in Pool A1, Pool B, and RPC01-3001 (OLE) are included in Table 2.3.2.2-1 to Table 2.3.2.2---5.

Table 2.3.2.2-1: Duration of Exposure to Ozanimod in Patients with Relapsing MS (Pool A1)

Duration of Exposure (at Least)	Persons, n (%)				Person-Years (Total Ozanimod)
	IFN β-1a 30 µg (N = 885)	Ozanimod 0.46 mg (N = 892)	Ozanimod 0.92 mg (N = 882)	Total Ozanimod (N = 1774)	
1 month	876 (99.0)	886 (99.3)	873 (99.0)	1759 (99.2)	2640.88
3 months	866 (97.9)	879 (98.5)	867 (98.3)	1746 (98.4)	2638.54
6 months	849 (95.9)	862 (96.6)	854 (96.8)	1716 (96.7)	2628.61
12 months	804 (90.8)	820 (91.9)	818 (92.7)	1638 (92.3)	2564.58
18 months	408 (46.1)	407 (45.6)	416 (47.2)	823 (46.4)	1620.62
24 months	310 (35.0)	291 (32.6)	299 (33.9)	590 (33.3)	1180.53
Total person-years	1304.76	1318.01	1323.33	2641.34	2641.34

Data lock point: 30-Jun-2018.

Table 2.3.2.2-2: Duration of Exposure to Ozanimod in Patients with Relapsing MS (Pool B)

Duration of Exposure (at Least)	Persons, n (%)			Person-Years (Total Ozanimod)
	Ozanimod 0.46 mg (N = 1033)	Ozanimod 0.92 mg (N = 2631)	Total Ozanimod (N = 2787)	
1 month	1024 (99.1)	2614 (99.4)	2765 (99.2)	7262.02
3 months	1004 (97.2)	2600 (98.8)	2744 (98.5)	7257.97
6 months	985 (95.4)	2565 (97.5)	2701 (96.9)	7243.01
12 months	938 (90.8)	2491 (94.7)	2619 (94.0)	7182.01
18 months	521 (50.4)	2141 (81.4)	2387 (85.6)	6883.62
24 months	395 (38.2)	1069 (40.6)	1809 (64.9)	5922.37
30 months	58 (5.6)	852 (32.4)	1690 (60.6)	5669.39
36 months	0	521 (19.8)	1018 (36.5)	3809.94
42 months	0	307 (11.7)	597 (21.4)	2437.05
48 months	0	154 (5.9)	295 (10.6)	1327.89
Total person-years	1602.26	5660.47	7262.73	7262.73

Data lock point: 30-Jun-2018.

Table 2.3.2.2-3: Duration of Exposure to Ozanimod in Patients with Relapsing MS - RPC01-3001 (OLE)

Duration of Exposure (at Least)	Persons, n (%) Total Ozanimod (N = 2494)	Person-Years (Total Ozanimod)
12 months	2393 (96.0)	12611.08
60 months	1989 (79.8)	11429.03
Total	2494 (100.0)	12664.74

Data lock point: 07-Apr-2023

Table 2.3.2.2-4: Exposure to Ozanimod by Age Group and Gender in Patients with Relapsing MS

Age Group (Years)	Persons, n (%) (Total Ozanimod)		Person-Years (Total Ozanimod)	
	Male	Female	Male	Female
Pool A1[a]				
18 to ≤ 40	439 (35.5)	797 (64.5)	647.41	1182.25
> 40 to ≤ 55	161 (29.9)	377 (70.1)	244.38	567.30
> 55	0	0	0	0

Table 2.3.2.2-4: Exposure to Ozanimod by Age Group and Gender in Patients with Relapsing MS

Age Group (Years)	Persons, n (%) (Total Ozanimod)		Person-Years (Total Ozanimod)	
	Male	Female	Male	Female
Total	600 (33.8)	1174 (66.2)	891.79	1749.55
Pool B[a]				
18 to ≤ 40	660 (35.0)	1228 (65.0)	1692.31	3138.46
> 40 to ≤ 55	259 (28.8)	640 (71.2)	713.75	1718.21
> 55	0	0	0	0
Total	919 (33.0)	1868 (67.0)	2406.06	4856.67
RPC01-3001 (OLE)[b]				
18 to ≤ 40	533 (21.4)	979 (39.3)	2766.29	4818.85
> 40 to ≤ 55	282 (11.3)	658 (26.4)	1437.36	3422.81
> 55	11 (0.4)	31 (1.2)	55.90	163.52
Total	826 (33.1)	1668 (66.9)	4259.56	8405.18

[a] Data lock point: 30-Jun-2018.

[b] Age reported at study entry. Data lock point: 07-Apr-2023

Table 2.3.2.2-5: Exposure to Ozanimod by Ethnic or Racial Origin in Patients with Relapsing MS

Ethnic Origin	Persons, n (%) (Total Ozanimod)	Person-Years (Total Ozanimod)
Pool A1		
White	1756 (99.0)	2615.86
Non-White[a]	18 (1.0)	25.48
Total	1774	2641.34
Pool B		
White	2758 (99.0)	7201.32
Non-White[a]	29 (1.0)	61.41
Total	2787	7262.73

[a] Black, Asian and Other ethnicity.
Data lock point: 30-Jun-2018.

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
UC studies (RPC01 3101, RPC01 3102 and RPC01 202) and Phase 3 MS studies (RPC01-201B and RPC01-301)			
Hypersensitivity to the active substance or to any of the excipients	Patients could be at risk of an undesirable reaction.	No	Hypersensitivity reactions, including rash and urticaria, have been reported uncommonly with ozanimod. Ozanimod is contraindicated in patients with hypersensitivity to the active substance or any of its excipients.
Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin measured during screening	• Patient safety based on nonclinical data. • These concomitant conditions could expose foetuses to a safety risk.	No	• Ozanimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Women of childbearing potential should use effective contraception during treatment, and for 3 months after treatment discontinuation, based on an elimination half-life of the major metabolite CC112273 of approximately 11 days. • Ozanimod/metabolites are excreted in milk of treated animals during lactation. Due to the potential for serious adverse reactions to ozanimod/metabolites in nursing infants, women receiving ozanimod should not breastfeed.
Recent (within the last 6 months) occurrence of MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnoea.	Contraindication for first-in-class S1P modulator, (fingolimod) in patients at high risk of bradycardia and cardiac conduction effects.	No	Ozanimod is contraindicated for initiation in patients who in the last 6 months had experienced MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation or NYHA Class III/IV heart failure. Ozanimod is also contraindicated for initiation in 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.
Clinically relevant hepatic, neurological,	These concomitant conditions could	No	• Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
pulmonary, ophthalmological, endocrine, renal, or other major systemic disease.	influence the interpretation of the study results and expose patients to a safety risk.		ozanimod. The PK of ozanimod was evaluated in patients with mild and moderate hepatic impairment and compared with patients with normal hepatic function. No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh class A or B). Use in patients with severe hepatic impairment (Child-Pugh class C) is contraindicated. • Risk factors for macular oedema include a history of uveitis or diabetes mellitus. • The PK of ozanimod was evaluated in patients with end stage renal disease and compared with patients with normal renal function. No dose adjustment is necessary for patients with renal impairment.
Prolonged QTcF, or at additional risk for QT prolongation (eg, hypokalaemia, hypomagnesemia, congenital long-QT syndrome).	Pharmacological effect of first-in-class S1P modulator, (fingolimod) and potential risk of QTcF prolongation.	Not considered to be missing information. These patients were excluded as the risk was not known with ozanimod at the initiation of the programme and required assessment.	• Study RPC01-102 revealed no effect on cardiac repolarisation with ozanimod doses escalated from 0.23 mg to 1.96 mg over 14 days. Ozanimod dosing duration in this study was not long enough for the major active metabolite CC112273 to reach the anticipated steady state due to its longer half-life. QTc analysis for ozanimod and CC112273 using data from another Phase 1 study (RPC01-1911) showed the upper boundary of the 95% CI for model-derived QTc (corrected for placebo and baseline) below 10 ms at maximum concentrations achieved with ozanimod ≥ 0.92 mg QD. • No effect on repolarisation was observed at the time of treatment initiation and during continuous dosing with ozanimod in pivotal UC or MS clinical studies. Therefore, a risk of further QT prolongation in patients with existing QT prolongation is unlikely.
Resting HR less than 55 bpm at screening (patients	Pharmacological effect of ozanimod and	No	• Screening (but not baseline) HR < 55 bpm at rest was an exclusion criterion.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
were allowed to be randomised who had a baseline HR less than 55).	possible additional effect on HR decrease.		• First dose, 6-hour monitoring for signs and symptoms of bradycardia is recommended in patients with resting HR < 55 bpm. • In the UC studies, 10 patients in the ozanimod 0.92 mg group had HR < 55 bpm at baseline. The minimum HRs recorded were not of clinical concern for these patients. • In the MS studies, there were 33/1774 patients randomised to ozanimod who had a baseline resting HR < 55 bpm on the first study day. No HR reductions of clinical concern were observed for these patients.
Diabetes mellitus Type 1, or uncontrolled Type 2 diabetes mellitus with haemoglobin A1c > 7% or > 9%, or diabetic patients with significant comorbid conditions such as retinopathy or nephropathy.	Patients with uncontrolled diabetes mellitus are at increased risk of cardiac disorders and macular oedema.	Not considered to be missing information. The SmPC notes that patients with diabetes are at increased risk of macular oedema.	The exclusion of patients with Type 1 or uncontrolled Type 2 diabetes mellitus and related significant complications was made to limit this as a confounding factor for evaluation of the effects of ozanimod as well as preventing a deterioration in diabetic patients should such risk be identified. The Phase 3 studies did not identify any specific risks. There is a theoretical increased risk of macular oedema in diabetic patients. The SmPC provides further guidance regarding macular oedema.
History of uveitis.	Patients with uveitis are at risk of macular oedema.	No	• In the ozanimod clinical studies, optical coherence tomography was used as a screening tool to identify patients for further ophthalmologic examination. If an abnormality was identified, or if visual signs or symptoms of macular oedema were observed, an ophthalmological examination was performed to confirm the diagnosis of macular oedema and/or to identify other ophthalmic abnormalities. • The MAH engaged an external review panel comprised of physician experts to evaluate each potential case of macular oedema in detail. • Although patients with history of uveitis were excluded, there were some patients with MS with unreported

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			uveitis as a history, confirmed by the external review panel. • The SmPC notes that patients with risk factors for macular oedema such as uveitis, diabetes mellitus or a history of retinal disease should undergo an ophthalmologic evaluation prior to treatment initiation with ozanimod. Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ozanimod should be discontinued. A decision on whether ozanimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient.
History or known presence of recurrent or chronic infection (eg, hepatitis A, B, or C, human immunodeficiency virus, syphilis, tuberculosis).	These concomitant conditions could influence the interpretation of the study results and expose patients to a potential safety risk. Consistent with the mechanism of action of S1P receptor modulators, a reduction in peripheral blood lymphocyte count is an expected PD outcome of therapy with ozanimod and therefore could potentially increase risk of infections associated with lymphopenia.	No	• Ozanimod is not associated with an increased risk of serious infections. Ozanimod increased the risk of herpes infections, upper respiratory tract infections and urinary tract infections. • The ozanimod SmPC recommends obtaining a recent (ie, within 6 months or after discontinuation of prior UC or MS therapy) complete blood cell count, including lymphocyte count, before initiation of ozanimod. The initiation of ozanimod administration in patients with an active infection should be delayed until the infection is resolved. Patients should be instructed to report promptly symptoms of infection to their physician. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. If a patient develops a serious infection, treatment interruption with ozanimod should be considered. The SmPC also provides guidance on vaccination.
History of cancer, including solid tumours and haematological	These concomitant conditions could influence the	Risk of malignancy with ozanimod is considered to be an Important Potential	• As history of malignancy is a strong predictor for recurrence or new malignancy, these patients were not included in the clinical programme.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved).	interpretation of the study results and expose patients to a safety risk.	Risk. Risk of colorectal cancer (UC indication) is also included as an Important Potential Risk.	• Despite the IR of malignancies reported with ozanimod being consistent with the background rate in both the UC and MS populations, and the general population of the same age range, the duration of observation is limited relative to the recognised latency periods for most malignancies, and as with other immunomodulators, there is a theoretical potential that the incidence of malignancies may increase with longer duration of treatment, however; IRs have not currently increased with longer exposure time. However, the types of malignancies observed in the development programme do not demonstrate any particular pattern and are not typical of those observed in an immunosuppressed population.
History of or currently active primary or secondary immunodeficiency, or concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies.	• These concomitant conditions could influence the interpretation of the study results and expose patients to a safety risk. Consistent with the mechanism of action of S1P receptor modulators, a reduction in peripheral blood lymphocyte count is an expected PD outcome of therapy with ozanimod and therefore in combination, the PD effect with	No	• Ozanimod is not associated with an increased risk of serious infections. In active-controlled MS clinical trials, ozanimod increased the risk of mostly nonserious upper respiratory tract infections, and urinary tract infections. In UC clinical studies, increases in upper respiratory tract infections and localised herpetic infections were observed with ozanimod. • The ozanimod SmPC recommends obtaining a recent (ie, within 6 months or after discontinuation of prior UC or MS therapy) complete blood cell count, including lymphocyte count, before initiation of ozanimod. The initiation of ozanimod administration in patients with any active infection should be delayed until the infection is resolved. If a patient develops a serious infection, treatment interruption with ozanimod should be considered. • In MS and UC clinical studies, patients who received ozanimod were not to receive concomitant antineoplastic, non-corticosteroid immunosuppressive (eg, azathioprine and 6-mercaptopurine in UC), or immune-modulating

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	underlying primary or secondary immunodeficiency could potentially expose the patient to an increased infection risk. • Concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies would be expected to increase the risk of immunosuppression.		therapies used for treatment of MS and UC. Concomitant use of ozanimod with any of these therapies would be expected to increase the risk of immunosuppression and should be avoided. In UC clinical studies, concomitant use of corticosteroids was allowed and did not appear to influence the safety or efficacy of ozanimod; however, long-term data on concomitant use of ozanimod and corticosteroids are still limited. When switching to ozanimod from immunosuppressive medicinal products, the half-life and mode of action must be considered to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation.
UC studies only (RPC01 3101, RPC01 3102 and RPC01 202)			
Severe extensive colitis	Severe extensive colitis is associated with a high risk of hospitalisation and colectomy. Inclusion of these patients could affect interpretation of the study results.	No	This is not the target population for ozanimod treatment.
Diagnosis of Crohn's disease or indeterminate colitis, or the presence or history of a fistula consistent with Crohn's disease or microscopic colitis,	Crohn's disease represents a different type of inflammatory bowel disease and may respond differently to ozanimod than UC. Crohn's disease is under	No	This is not the target population for ozanimod treatment.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
radiation colitis or ischaemic colitis	study with ozanimod in a separate clinical study program. Inclusion of these patients could affect the interpretation of the study results for UC.		
Positive stool examination for pathogens (ova and parasites, bacteria) or positive test for toxin-producing Clostridium difficile	Concomitant gastrointestinal infections could influence the interpretation of the study results and expose patients to a safety risk. Consistent with the mechanism of action of S1P receptor modulators, a reduction in peripheral blood lymphocyte count is an expected PD outcome of therapy with ozanimod and may negatively impact a patient with a gastrointestinal infection	No	Labelled warning information in the SmPC indicates that ozanimod use should be delayed in patients with active infections until the infection is resolved.
MS studies only (RPC01-201B and RPC01-301)			
Primary progressive disease	Primary progressive MS could influence the interpretation of the study data.	No	• Not considered to be missing information as this is not the target population. • The indication for ozanimod is for the treatment of adult patients with RRMS, although patients with progressive disease were allowed to enrol as long as they met the relapse (disease activity) criteria.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Suicide attempts in the past or current signs of major depression.	• These concomitant conditions could influence the interpretation of the study results. • Patients with MS are known to be at a higher risk of suicide (see Table 2.1.2-1)	No	• Baseline evaluation of suicidal ideation and suicidal ideation or behaviour was performed using Columbia Suicide Severity Rating Scale. In Phase 3 studies, the distribution of suicidal ideation and suicidal ideation or behaviour was similar across the groups at baseline, ranging from 0.5% to 0.7%. • A review of the incidence of psychiatric disorders in the relapsing MS Phase 2 and 3 studies did not identify an increased risk of depression with ozanimod. Furthermore, the review of changes in self-administered Columbia Suicide Severity Rating Scale did not identify a signal of concern for ozanimod.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure (Table 2.4.2-1).

Table 2.4.2-1: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are Rare or Very Rare	Patient numbers may not be sufficient to capture all rare (≥ 1/10,000 to < 1/1000) or very rare (< 1/10,000) adverse drug reactions (ADRs). The total UC population exposed to ozanimod in Studies RPC01-3101, RPC01-3102 and RPC01-202 was 1158 patients. The total MS population exposed to ozanimod in Studies RPC01-201A, RPC01-201B, RPC01-301, RPC01-3001 and RPC01-1001 was 2787 patients.	In UC studies, with 1158 patients exposed to ozanimod, at least one TEAE would be observed with a 95% probability of the true incidence being 0.26%. With 2787 patients exposed to ozanimod in MS studies, at least one TEAE would be observed with a 95% probability of the true incidence being 0.11%.

Table 2.4.2-1: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Due to Prolonged Exposure	Of 1158 patients treated with ozanimod 0.92 mg in UC clinical studies, 315 (27.2%), 84 (7.3%) and 19 (1.6%) have been treated for at least 2, 4 or 6 years, respectively. Further long-term data will be obtained from the ongoing RPC01-3102 open-label study. Of 2787 patients treated with ozanimod in relapsing MS clinical studies, 1809 (64.9%), 1018 (36.5%) and 295 (10.6%) have been treated for at least 2, 3 or 4 years, respectively. These numbers will increase as accrual to the long-term OLE study (RPC01-3001) continues. Of the 2494 patients treated with ozanimod in RPC01-3001 (OLE), 1989 (79.8%) have been treated for at least 60 months.	It is not anticipated that the safety profile will be different over time. Existing data from the controlled Phase 3 programme and OLE studies in UC and MS have not generally shown an increase in adverse reactions over time. Additional cases of nonserious herpes zoster were observed with longer-term exposure in MS studies. No new signals with respect to SAEs or AEs leading to study drug discontinuation were observed with long-term use in patients with UC or MS. OLE study is continuing in UC population, and this will continue to collect long-term safety data. A PASS is planned as an additional pharmacovigilance measure to better characterise the long-term safety profile in the MS population. A planned PASS in patients with UC will further characterise the long-term safety of ozanimod in a real-world setting.
Due to Cumulative Effects which have a Long Latency	Not applicable	No cumulative effects have been identified for ozanimod in UC or MS clinical studies.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

To ensure patient safety, specific populations of patients were excluded from the pivotal and supportive studies. Thus, experience in these populations is limited (Table 2.4.3-1).

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Ozanimod clinical studies required patients and partners to use highly effective methods of contraception to comply with a pearl index of less than 1%. Hormonal contraceptives were permitted and no drug interactions which might reduce their effectiveness were shown; repeated dosing of ozanimod (7-day dose escalation followed by 0.92 mg QD for 5 days) had no effect on the single-dose PK of an oral contraceptive containing ethinylestradiol (35 µg) and norethindrone (1 mg).

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	As of 22-Mar-2023, a total 78 events of potential exposure during pregnancy have been reported in patients treated with ozanimod across all indications, including 14 reported for female patients in ozanimod clinical trials for UC and 57 reported for female patients in ozanimod clinical trials for MS. The remaining 7 potential pregnancies in clinical trial participants occurred in 6 patients with Crohn's disease and 1 healthy volunteer. Embryofoetal toxicity is an Important Potential Risk for ozanimod; exposure and outcomes in pregnant women in the ozanimod clinical trial programme are discussed in Section 2.7.3.1 of Part II SVII. In summary, no teratogenicity was observed in the limited clinical experience of pregnancy.
Lactating women	There have been no reports of lactation exposure in females treated with ozanimod.
Paediatric population	The safety and efficacy of ozanimod in children and adolescents aged below 18 years have not yet been established. No data are available.
Elderly population	A total of 55 patients (4.7%) who received ozanimod in the UC studies were aged 65 years or over. Total ozanimod exposure in these patients was 66.64 PY. Of the 55 patients ≥ 65 years who were treated with ozanimod 0.92 mg, 28 of these patients (50.9%) were exposed for at least 12 months. Patients aged > 55 years were excluded from MS clinical studies upon study initiation. In RPC01-3001 (OLE) a total of 11 male and 31 female patients were aged 55 years or over (at study entry). Total ozanimod exposure in the male patients was 55.90 PY and 163.52 PY in the female patients. No ozanimod-treated patients with relapsing MS were aged over 65 years. Use in patients aged over 55 years is considered missing information for ozanimod and is discussed in Section 2.7.3.2 of Part II SVII. No dose adjustment is needed for patients over 55 years of age (SmPC Section 4.2). Population PK analysis showed that steady state exposure (AUC) of CC112273 in patients over 65 years of age were approximately 3 to 4% greater than patients 45 to 65 years of age and 27% greater than adult patients under 45 years of age. There is not considered a meaningful difference in the PK in elderly patients.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Study RPC01-1904 was a Phase 1, open-label study to characterise the PK and safety of a single 0.23 mg oral dose of ozanimod in 16 patients with mild (n = 8) or moderate (n = 8) hepatic impairment. There were no clinically meaningful differences in systemic exposures of ozanimod and CC112273 in patients with mild/moderate hepatic impairment compared with their matched healthy volunteers. In single dose and multiple dose studies in subjects with chronic liver disease, there was no meaningful impact of mild or moderate chronic hepatic impairment (Child-Pugh Class A or B) on the pharmacokinetics of ozanimod or the major metabolite CC112273 on Day 1, Day 5, or Day 8 of dosing. After dose escalation in the second trial, administration of 0.92 mg ozanimod resulted in increased CC112273 and CC1084037 mean unbound AUC0-last (measured up to 64 days

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	post-dose) in subjects with mild or moderate chronic hepatic impairment of 99.64% to 129.74% relative to healthy control subjects. The pharmacokinetics of ozanimod were not evaluated in patients with severe hepatic impairment. Patients with mild or moderate chronic hepatic impairment (Child-Pugh Class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day (SmPC Section 4.2). Use in patients with severe hepatic impairment is contraindicated (Child-Pugh Class C; SmPC Section 4.3).
Patients with renal impairment	One study in patients with renal impairment has been completed. Study RPC01-1906 was a Phase 1, open-label study to characterise the PK and safety of a single 0.23 mg oral dose of ozanimod in eight patients with end-stage renal disease and eight matched healthy volunteers with normal renal function. There were no clinically meaningful differences in systemic exposures of ozanimod and CC112273 in patients with end-stage renal disease compared with their matched healthy volunteers.
Patients with cardiovascular impairment	Patients with active cardiovascular conditions were excluded from the clinical trials programme. UC studies In UC studies, (Pool G), out of 1158 patients, 241 (20.8%) had a medical history that included CVD. In Pool G, at least one concomitant cardiovascular medication was used in 175 patients (15.1%) treated with ozanimod. MS studies For the MS studies, in Pool A1, at least one concomitant cardiovascular medication was used in 134 patients (15.2% of patients) treated with ozanimod 0.92 mg and 142 patients (15.9%) treated with ozanimod 0.46 mg. Of the 2659 patients in Pool A1, 154 (5.8%) had a cardiac disease history and 320 patients (12.0%) had a vascular disorder history.
Immunocompromised patients	Not applicable.
Patients with a disease severity different from inclusion criteria in clinical trials	There are no exposure data for patients with a disease severity different from inclusion criteria in clinical trials.
Population with relevant different ethnic origin	UC studies The majority of patients who received ozanimod in Pool G were of White ethnicity (1036 patients [89.5%]; 1639.37 PY of exposure). Of the non-White patients who received ozanimod in Pool G, ethnic origin was Asian in 68 patients (5.9%; 127.52 PY exposure) and Black or African American in 31 patients (2.7%; 46.10 PY exposure). Population PK analysis showed that CC112273 steady-state exposures in non-White patients with UC were increased by approximately 17% to 63% compared to White patients. The overall TEAE incidence in Pool G was similar between white and non-white patients who received placebo (40.4% versus 43.4%, respectively), but the overall TEAE incidence was lower among white patients than non-white patients who were treated with ozanimod 0.92 mg (68.0% versus 75.2%, respectively) and may be partially due to a slightly shorter

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	mean treatment exposure to ozanimod among white than non-white patients in Pool G (approximately 19 months versus 20 months, respectively). No patterns in SAE incidence related to race were apparent in Pool G. MS studies The extent of exposure for white patients in Pool A1 of the relapsing MS studies (total PY) for patients treated with ozanimod 0.92 mg was 1314.41; for ozanimod 0.46 mg, 1301.45; for total ozanimod, 2615.86. There were only 28 non-white patients in Pool A1 (18 treated with ozanimod and 10 treated with IFN β-1a), making comparisons to the white subgroup difficult. For non-white patients in Pool A1, a smaller proportion of each treatment group was exposed to ozanimod for ≥ 12 months (4 patients [66.7%] in the ozanimod 0.92 mg group and nine patients [75.0%] in the ozanimod 0.46 mg group) than for white patients (814 patients [92.9%] in the ozanimod 0.92 mg group and 811 patients [92.2%] in the ozanimod 0.46 mg group). In general, the extent of exposure ≥ 24 months in non-white patients was similar to that of white patients. Any differences in the extent of exposure for these patients should be viewed in the context of the small subgroup sample size. Healthy subjects Two Phase 1 Japanese PK bridging studies, RPC01-1905 and RPC01-1911, were conducted. In study RPC01-1905, 18 healthy Japanese subjects received single oral doses of 0.23, 0.46, or 0.92 mg (1:1:1) and eight healthy Japanese subjects received repeated doses of 0.23 mg QD on Days 1 to 4, 0.46 mg QD on Days 5 to 7, and 0.92 mg QD on Days 8 to 12. In Study RPC01-1911, 11 healthy Japanese subjects received ozanimod 0.46 mg QD for 28 days (including the initial 7-day dose escalation), 10 healthy Japanese subjects received ozanimod 0.92 mg QD for 28 days (including the initial 7-day dose escalation), and 12 healthy Japanese subjects received ozanimod 1.84 mg QD for 28 days (including the initial 7-day dose escalation plus another 3 days of 0.92 mg on Days 8 to 10). No clinically meaningful differences in the PK of ozanimod and CC112273 were observed between Japanese and Caucasian subjects after multiple-dose regimens of ozanimod up to 0.92 mg QD for 28 days.
Subpopulations carrying relevant genetic polymorphisms	Not studied.

2.5 Post-Authorization Experience

Ozanimod was approved in the EU for the MS indication on 20-May-2020 and for the UC indication on 18-Nov-2021.

Ozanimod was approved in the US for the MS indication on 25-Mar-2020 and for the UC indication on 27-May-2021.

2.5.1 Method Used to Calculate Exposure

Sales data consists of all shipments of the Company's product to all applicable countries and includes commercial and free-of-charge units. Although these data represent the bulk of the Company's worldwide sales of ozanimod, they are only an estimation of the total quantity of product sold based on the total amount of product distributed in all countries worldwide. The sales data capture an estimated 80% to 85% of the true total worldwide sales data. Additionally, the sales data from vendors may vary from one reporting period to another because of changes in subscription agreements and changes to the number of data channels available within a given country (eg, direct-to-consumer sales, hospital sales, and home care sales). From the month-by-month estimates the proportion of sold/shipped units that occur during the interval are used to represent incident patients. The estimates of exposed time below should be interpreted with caution, taking into account the limitations of sales data.[98]

2.5.2 Exposure

Patient exposure can be estimated based on sales data. These data, which represent an estimate of the total quantity of ozanimod sold, indicate that an estimated 7,611,788 mg were sold from market approval through 30-Apr-2023. Using the WHO methodology, and with a DDD of 0.92 mg, this corresponds to 22,652 patient years of cumulative exposure. This estimate of patient exposure should be interpreted with caution, taking into account the limitations of sales data.[98]

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Ozanimod has not been studied in humans for its potential for abuse, misuse, tolerance, or dependence. Ozanimod and its major metabolite CC112273 failed to demonstrate any positive reinforcing effects in an animal self-administration study, consistent with minimal to no misuse potential. No concerns for abuse potential have been reported with other S1P modulators, and have not been reported with ozanimod, hence there is no anticipated risk of abuse or misuse of ozanimod. Ozanimod is subject to restricted medical prescription.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

The summary of safety concerns for the first approved RMP for ozanimod (Version 1.0) are presented in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	None
Important potential risks	Symptomatic bradycardia
	Severe liver injury
	Serious opportunistic infections including PML
	Macular oedema
	Malignancy

Table 2.7.1-1: Safety Concerns in the Initial RMP

	PRES
	Embryofoetal toxicity in exposed pregnant females
Missing information	Long-term cardiovascular effects
	Effects following withdrawal of drug
	Use in patients over 55 years

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks not considered important for inclusion in the list of safety concerns in the RMP are presented, with justification, in Table 2.7.1.1-1:

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	
Hypersensitivity (including rash and urticaria)	Analysis of events of rash in the UC studies (Pool F Induction Period) found a similar rate of rash events between ozanimod and placebo treatment groups (1.6% and 1.4% of patients, respectively). A slightly lower incidence of rash events was observed in ozanimod treated patients compared to placebo in the Maintenance Period (0.4% and 1.8%, respectively). Events were nonserious and mild to moderate in intensity. The incidence of these events was low. Reports of hypersensitivity, mostly nonserious, including rash and urticaria have uncommonly been reported in MS studies (< 1%). All except one severe event of urticaria and one severe event of dermatitis were mild to moderate and readily manageable.
Infections: nasopharyngitis, pharyngitis, respiratory tract infection viral, urinary tract infection, herpes zoster	In UC studies (Pool F Induction Period), the incidence of TEAEs in the SOC of infections and infestations was similar between treatment arms (9.9% and 10.7% in the ozanimod 0.92 mg and placebo groups, respectively. The overall incidence of infections in the Study RPC01-3101 Maintenance Period was higher in the ozanimod 0.92 mg treatment group than the placebo treatment group (23.0% versus 11.9%, respectively). Infections were mostly characterised by nonserious infections of the upper respiratory tract (nasopharyngitis, pharyngitis, viral respiratory tract infection). The incidence of infections leading to ozanimod discontinuation was low (0.6%), and there were no serious opportunistic infections in ozanimod-treated patients. In MS clinical studies, there was no increased risk of serious or opportunistic infections with ozanimod when compared to IFN β-1a. The incidence was low and similar across treatment groups. When serious infections occurred, the majority were typical bacterial infections and resolved without clinical sequelae following standard medical management. The initiation of ozanimod administration in patients with an active infection should be delayed until the infection is resolved. Patients who develop serious infections while taking ozanimod should consider interrupting treatment. In MS studies, Herpes zoster infections were infrequent with ozanimod and occurred at a similar frequency as IFN β1a. Upon completion of the OLE study (RPC01-3001), Herpes zoster infections occurred in 46 (1.8%) patients treated with ozanimod in this study. In UC studies, Herpes zoster infections occurred in 25 (2.2%) patients in the ozanimod 0.92 mg treatment group and 2 (0.4%) patients in the placebo treatment group. Thirteen (52.0%) of

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

	the 25 cases of herpes zoster infection occurred in patients aged > 50 years of age and at risk of herpes zoster. In both patient populations, Herpes zoster infections had a benign clinical course and did not usually prevent continued treatment with ozanimod. None was serious or disseminated. Since the patients enrolled in the UC and relapsing MS clinical programmes were required to demonstrate immunity to or be vaccinated against VZV, vaccination of patients without documented immunity to VZV is recommended at least 1 month prior to initiating treatment with ozanimod. No clinical data are available on the efficacy and safety of vaccinations in patients taking ozanimod. Live attenuated vaccines should be avoided during and for 3 months after treatment with ozanimod. If live attenuated immunisations are required, they must be administered at least 1 month prior to initiation of ozanimod. Because the elimination of ozanimod after discontinuation may take up to 3 months, continue monitoring for infections throughout this period. After discontinuing ozanimod 0.92 mg, the median time to recovery of peripheral blood lymphocytes to the normal range was approximately 30 days, with approximately 80% to 90% of patients recovering to normal within 3 months.
Hypertension	In the UC studies Induction Period (Pool F), patients treated with ozanimod 0.92 mg for up to 10 weeks had a mean SBP increase of approximately 3.7 mmHg versus 2.3 mmHg in patients who received placebo. At the end of the 52-week Maintenance Period (Study RPC01-3101), patients treated with ozanimod 0.92 mg had a mean SBP increase from baseline of approximately 5.1 mmHg versus 1.5 mmHg in patients who received placebo. There was no significant effect on DBP in patients with UC treated with ozanimod. Overall, mean increases in SBP and DBP in patients with UC treated with ozanimod were similar to those in patients with MS. In the UC Study RPC01-3101 Induction Period there was a higher incidence of hypertension- related TEAEs (hypertension and hypertensive crisis) reported in the ozanimod 0.92 mg group compared to the placebo (1.2% versus 0). The incidence in the Maintenance Period was similar in both treatment groups (2.2% and 2.2% for ozanimod and placebo, respectively). In UC clinical studies (Pool G) clinically significant, modest elevations in SBP (> 140 mm Hg) and DBP (> 90 mm Hg) were experienced by greater proportions of patients who were treated with ozanimod 0.92 mg than placebo (28.8% versus 17.0% and 27.1% versus 14.1%, respectively). The overall incidence of patients experiencing greater increases in SBP (> 160 mm Hg or > 180 mm Hg) or DBP (> 100 mm Hg or > 105 mm Hg) was low among patients treated with ozanimod 0.92 mg (< 5%) and placebo (< 3%) in Pool G. In the MS studies (Pool A1), patients treated with ozanimod had an average increase over IFN β-1a of approximately 1 to 2 mmHg in SBP, and no effect on DBP. The increase in SBP was first detected after approximately 3 months of treatment initiation and remained stable throughout treatment. Hypertension-related events (hypertension, essential hypertension, and blood pressure increased) were reported as a TEAE in 4.5% of patients treated with ozanimod 0.92 mg and in 2.4% of patients on IFN β-1a IM. There were no SAEs reported as being related to ozanimod and hypertension is readily clinically manageable. The EAIR of hypertension was 23.2 per 1000 person-years. Upon completion of the OLE study (RPC01-3001), the EAIR of hypertension was 18.9 per 1000 person-years.
Elevated ALT and GGT	In the UC studies (Pool F Induction Period), the mean elevation (change from baseline) in ALT, AST, GGT, alkaline phosphatase, and bilirubin was higher in the ozanimod 0.92 mg group than in the placebo group at both Week 5 and Week 10. During the Induction Period for UC study RPC01-3101, elevations of ALT above 5-fold the ULN occurred in 0.9% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo. Elevations of ALT of 3-fold the ULN or above occurred in 2.6% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo. In the

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

	Study RPC01-3101 Maintenance Period, 0.9% of patients treated with ozanimod 0.92 mg and no patients who received placebo had elevations 5-fold the ULN or greater. Elevations of 3-fold the ULN occurred in 2.3% of patients treated with ozanimod 0.92 mg and none who received placebo. Overall, in UC clinical studies, the discontinuation rate because of elevations in hepatic enzymes was 0.4% of patients with UC treated with ozanimod in both Induction and Maintenance Periods, and none in patients who received placebo in either period. No cases of severe DILI were reported with ozanimod in the active-controlled UC clinical trials. In active-controlled MS clinical trials, elevations of ALT to 5-fold the ULN or greater occurred in 1.6% of patients treated with ozanimod 0.92 mg and 1.3% of patients on IFN β-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ozanimod 0.92 mg and 3.1% of patients on IFN β-1a. When elevations in hepatic tests occurred, they were generally asymptomatic. The median time to elevation 3-fold the ULN was 6 months. The majority (79%) continued treatment with ozanimod with values returning to < 3-fold the ULN within approximately 2 to 4 weeks. In active controlled MS clinical trials, ozanimod was discontinued- for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate due to elevations in hepatic enzymes was 1.1% of patients on ozanimod 0.92 mg and 0.8% of patients on IFN β-1a. No cases of severe DILI were reported with ozanimod in the active controlled- MS clinical trials. In the MS studies (Pool A1), the EAIR for ALT increased was 33.9 per 1000 person-years. The EAIR for GGT increase was 25.1 per 1000 person-years. Upon completion of the OLE study (RPC01-3001), the EAIR for ALT increase was 10.3 per 1000 person-years. The EAIR for GGT increase was 16.7 per 1000 person-years. Recent (ie, within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with ozanimod. In the absence of clinical symptoms, liver transaminases and bilirubin levels should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted. If liver transaminases above 5 times the ULN are confirmed, treatment with ozanimod should be interrupted and only re-commenced once liver transaminase values have normalised. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked and ozanimod should be discontinued if significant liver injury is confirmed. Resumption of therapy will be dependent on whether another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction. Severe liver injury has been designated as an Important Potential Risk.
Orthostatic hypotension	Orthostatic hypotension was generally asymptomatic and therefore is not considered an important risk. In the UC studies (Pool G), orthostatic hypotension was reported as a TEAE for 0.2% patients treated with ozanimod and no patients who received placebo. In the MS studies (Pool A1), orthostatic hypotension was reported as a TEAE in 3.9% of patients treated with ozanimod 0.92 mg and in 4.3% of patients on IFN β-1a. Upon completion of the OLE study (RPC01-3001), orthostatic hypotension was reported in 3 (0.1%) patients treated with ozanimod in this study.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are no important identified risks for ozanimod. Important potential risks and missing information are discussed in Table 2.7.1.2-1.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important potential risks	
Symptomatic bradycardia	Bradycardia has been observed in both the UC and MS clinical trial populations, although there have been no cases of clinical consequence. There were no instances of loss of consciousness or syncope reported in association with bradycardia in the ozanimod clinical trials. In the marketed setting, patients with conditions that place them at risk of symptomatic bradycardia are contraindicated for initiation of ozanimod. Symptomatic bradycardia will be analysed in the postmarketing setting in real-world usage.
Severe liver injury	Severe drug-related liver injury has not been observed with ozanimod. All reports with ALT or AST ≥ 3 × ULN with total bilirubin > 2 × ULN have had alternative causes and therefore do not meet the criteria for Hy's law and do not constitute severe DILI. In view of the observation of elevations in aminotransferases with ozanimod treatment, the potential for severe liver injury will be characterised with greater product exposure in the postmarketing setting.
Serious opportunistic infections including PML	In controlled clinical trials with ozanimod, serious opportunistic infections (including PML) have not been observed.
Macular oedema	Patients in clinical studies were routinely monitored by optical coherence tomography to detect macular oedema. Macular oedema was observed during ozanimod treatment in patients with risk factors or other potential causes, eg, retinal vein thrombosis, diabetic retinopathy, macular degeneration, and prior retinal surgery. The macular oedema was generally reversible on drug discontinuation and there were no serious outcomes.
Malignancy	In UC studies the overall incidence of malignancies with ozanimod is generally comparable to rates reported in the literature observed in the UC and the general population in the same age ranges. In MS studies, invasive malignancies and NMSCs have been observed in patients receiving ozanimod. The rates observed are consistent with the background rates in the age-matched general and MS populations, have not increased in rate with increasing drug exposure, and the malignancies observed have not been typical of those seen in immunosuppressed populations. A broadening of exposure to a larger number of patients and for a longer duration in both the clinical trial and postmarketing setting will enable full characterisation of any potential risk of malignancy.
PRES	No cases of PRES were reported in UC studies. In MS controlled clinical trials with ozanimod, one case of PRES was reported in a patient with Guillain-Barré syndrome and is a recognised association with Guillain-Barré syndrome. PRES has been observed with other MS therapies. A potential for this risk merits further observation.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Embryofoetal toxicity in exposed pregnant females	Nonclinical studies identified embryofoetal mortality (rat), oedematous changes (rat), malpositioned testes (rat), delayed ossification, malpositioned caudal vertebrae and abnormalities of the great blood vessels (rabbit). The exposures in rats and rabbits to ozanimod and the major active metabolites were similar to or slightly above the clinical exposures. The use of ozanimod is contraindicated during pregnancy and women of childbearing potential not using effective contraception. Women of childbearing potential should use effective contraception during ozanimod treatment, and for at least 3 months after treatment discontinuation, based on an elimination half-life of the major metabolite CC112273 of approximately 11 days. There have been no safety concerns in the limited number of females who have become pregnant during clinical studies, although exposure has been limited to the first trimester of pregnancy.
Missing Information	
Long-term cardiovascular effects	Long-term follow-up in the UC and MS clinical development programmes is ongoing. Data will continue to be collected in the long-term extension studies in UC (RPC01-3102) and relapsing MS (Study RPC01-3001). Further, cardiovascular morbidity from long-term usage will be collected and analysed as part of postmarketing and ongoing trial pharmacovigilance activities.
Effects following withdrawal of drug	The major metabolite in humans, CC112273, has a long elimination half-life (approximately 11 days) and although the Phase 3 studies routinely observed patients for at least 28 days after drug discontinuation, this may not have been sufficient to observe effects following withdrawal of ozanimod and therefore this is classified as missing information. The protocols followed patients for AEs of special interest regardless of the duration following study drug discontinuation. Patients were followed for at least 30 to 90 days after their last dose in the UC studies. There were no observed withdrawal AEs. There were no AEs indicative of withdrawal effects observed after treatment discontinuation in UC clinical studies. In MS Pool B, a total of 123 patients receiving ozanimod 0.92 mg were followed for at least 28 days after their last dose of study drug. There were no observed withdrawal AEs or rebound MS disease in clinical trials of ozanimod after treatment discontinuation.
Use in patients over 55 years	In UC studies, patients up to the age of 75 were eligible for enrolment in clinical trials. Fifty-five patients aged ≥ 65 years were treated with ozanimod 0.92 mg including 28 patients (50.9%) exposed for at least 12 months. Multiple sclerosis is an illness predominantly in younger individuals and patients over 55 years old were not studied in clinical trials. Those currently enrolled in clinical trials will continue to be followed once they reach the age of 55 years. Any use in older patient populations will be included in postmarketing surveillance.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns or reclassification of safety concerns with the submission of the updated RMP.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The RMP search criteria have been defined for each study based on the MedDRA version as noted in Table 2.7.3-1. The important identified and potential risks of ozanimod are summarised in the following tables (Table 2.7.3.1-1 to Table 2.7.3.1-9) for the study cutoff dates listed in Section 2.3. Missing information for ozanimod is presented in Table 2.7.3.2-1.

Table 2.7.3-1: RMP Search Criteria

Study	MedDRA Version Used to Define RMP Search Criteria	MedDRA Version Used to Code AEs in Clinical Database	Data Lock Point
UC studies: RPC01-3101 (Pivotal Phase 3 UC Study)			
RPC01-3101 (Truenorth)	MedDRA Version 22.1	MedDRA Version 22.1	31-Mar-2020
UC studies: Pool F[a] (Controlled UC Studies)			
RPC01-202 (Touchstone)	MedDRA Version 15.1	MedDRA Version 15.1	10-Mar-2015
RPC01-3101	MedDRA Version 22.1	MedDRA Version 22.1	31-Mar-2020
UC studies: Pool G (Controlled and Uncontrolled UC Studies)			
RPC01-202	MedDRA Version 15.1	MedDRA Version 15.1	10-Mar-2015
RPC01-3101	MedDRA Version 22.1	MedDRA Version 22.1	31-Mar-2020
RPC01-3102	MedDRA Version 22.1	MedDRA Version 22.1	31-Mar-2020
RRMS studies: Pool A1 and Pool B			
RPC01-201B Phase 3 (Radiance)	MedDRA Version 18.1	MedDRA Version 18.1	12-May-2017
RPC01-301 Phase 3 (Sunbeam)	MedDRA Version 18.1	MedDRA Version 18.1	08-Feb-2017
RRMS studies: Pool B only (in addition to Pool A1 studies)			
RPC01-201A Phase 2	MedDRA Version 18.1	MedDRA Version 18.1	26-Sep-2016
RPC01-3001 Phase 3 OLE	MedDRA Version 18.1	MedDRA Version 18.1	30-Jun-2018
RPC01-1001 Phase 1	MedDRA Version 18.1	MedDRA Version 18.1	14-Apr-2017
RRMS Study: Not Pooled			
RPC01-3001 Phase 3 OLE	MedDRA Version 25.1	MedDRA Version 25.1	07-Apr-2023

[a] Pool F: Induction Period analyses: RPC01-202 (placebo and ozanimod 0.92 mg) and RPC01-3101 (placebo and ozanimod 0.92 mg of Cohort 1). Maintenance Period analyses: randomised, placebo-controlled RPC01-3101 Maintenance Period.

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Table 2.7.3.1-1: Important Identified Risk: Serious Opportunistic Infections Including PML

Important Identified Risk: Serious Opportunistic Infections Including PML	
Potential mechanisms	Although the modulation of S1P1 by ozanimod is the proposed mechanism causing the decrease in absolute lymphocyte count in patients, the lack of clinically significant consequences is likely due to the specificity of impact on lymphocyte subsets allowing continued immune surveillance. For example, while the majority of circulating T and B lymphocyte subsets decrease in level following ozanimod treatment, other immune cell populations including monocytes and natural killer cells and some CD8 effector memory cells remain unchanged.
Evidence source and strength of evidence	A case of PML has been observed with ozanimod treatment in the MS clinical trial, RPC01-3001 (OLE study).
Characterization of risk	<u>UC studies</u> No cases of serious opportunistic infection or PML were observed after ozanimod treatment in UC clinical studies. In the RPC01-3101 Maintenance Period, the incidence of TEAEs in the Infections and Infestations SOC was higher in the ozanimod 1 mg - ozanimod 1 mg treatment group than in the ozanimod 1 mg – placebo treatment group and was increased in ozanimod-treated patients compared to placebo to a similar degree (based largely on nonserious viral infections) regardless of concomitant corticosteroid use. Limited data are available on the longterm concomitant use with corticosteroids and its influence on infection. <u>MS studies</u> A case of serious opportunistic infection was observed with ozanimod in MS clinical trial, RPC01-3001, OLE study. A patient developed PML approximately 4 years and 3 months after initiating treatment with open label ozanimod. The patient's absolute lymphocyte count was between $0.4 \times 10^3/\mu L$ and $0.73 \times 10^3/\mu L$ during the study (reference range $1 \times 10^3/\mu L$ to $5 \times 10^3/\mu L$). The patient had symptoms including speech and balance problems that were interpreted as secondary to relapse of MS. Symptoms deteriorated and PML was identified by MRI and confirmed by a cerebrospinal fluid JCV DNA positive test. Ozanimod was subsequently discontinued and treatment with mirtazapine was initiated. The event outcome was reported as recovered/resolved with sequelae by the investigator.
Risk factors and risk groups	Patients with prolonged and profound lymphopaenia may be at increased risk of developing severe opportunistic infection, including PML, and also those who have received previous natalizumab treatment, although the risks appear to be very low.
Preventability	A recent (ie, within 6 months or after discontinuation of prior MS or UC therapy) complete blood cell count should be obtained, including lymphocyte count, before initiation of ozanimod (SmPC Section 4.4). Assessments of complete blood count are also recommended periodically during treatment. Absolute lymphocyte counts $< 0.2 \times 10^9/L$, if confirmed, should lead to interruption of ozanimod therapy until the level reaches $> 0.5 \times 10^9/L$ when reinitiation of ozanimod can be considered. The initiation of ozanimod administration in patients with any active infection should be delayed until the infection is resolved. When switching to ozanimod from immunosuppressive medicinal products, the half-life and mode of action must be considered to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation. Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, treatment with ozanimod should be suspended until PML has been excluded. If confirmed, treatment with ozanimod should be discontinued.

Table 2.7.3.1-1: Important Identified Risk: Serious Opportunistic Infections Including PML

Important Identified Risk: Serious Opportunistic Infections Including PML	
Impact on the risk-benefit balance of the product	Serious opportunistic infection is considered to be of public health concern and may have fatal outcomes in immunocompromised patients. However, this is anticipated to be a rare occurrence.
Public health impact	Serious opportunistic infection is considered to be of public health concern and may have fatal outcomes in immunocompromised patients. Progressive multifocal leukoencephalopathy is a rare opportunistic infection of the CNS caused by reactivation of a latent John Cunningham virus, with a prevalence of 0.2 cases per 100,000 persons in the general population.[99] The risk of PML is likely to be very low with treatment with S1P modulators in the absence of prior natalizumab treatment. With another S1P modulator, fingolimod, the risk of PML in the absence of prior natalizumab treatment was low, with an estimated risk of 0.069 per 1,000 patients (95% CI: 0.039–0.114), and an estimated IR of 3.12 per 100,000 PY (95% CI: 1.75-5.15).[100]
MedDRA Terms	See Annex 7 for a list of terms.

Table 2.7.3.1-2: Important Identified Risk: Macular Oedema

Important Identified Risk Macular Oedema	
Potential mechanisms	The event of macular oedema and its relationship to S1P receptor class agents is unclear. The nonselective S1P receptor modulator fingolimod has been shown to have secondary effects on vascular endothelial barrier function, thereby potentially compromising the blood-retina barrier.[101] Laboratory studies have demonstrated that the endothelial cell S1P receptor modulates intercellular junctions as well as the interplay between the cellular cytoskeleton and the extracellular matrix. Macular oedema with fingolimod is dose-dependent.
Evidence source and strength of evidence	An external review panel identified 3 cases of macular oedema with ozanimod 0.92 mg in the UC studies RPC01-202 and RPC01-3101 and 1 case of cystoid macular oedema with ozanimod 0.92 mg in the UC OLE study (Study RPC01-3102). All 4 cases of confirmed macular oedema were identified with optical coherence tomography 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. No trend in central foveal thickness changes was noted over time. All 4 cases of macular oedema resolved. In the MS studies, for Pool A1 there were three confirmed cases in the ozanimod 0.46 mg group, one confirmed case in the ozanimod 0.92 mg group and none in the IFN β-1a treatment group. In Pool B, there were three additional confirmed cases in the extension study RPC01-3001 (ozanimod 0.92 mg). Upon completion of the OLE study (RPC01-3001), two more confirmed cases of macular oedema were reported to a total of 5 cases. Following adjudication by a panel of ophthalmology experts including two neuro-ophthalmologists and a retinal specialist, 7 out of 9 cases were confounded by pre-existing risk factors including a history of macular oedema, uveitis, laser surgery, macular pucker, other ocular inflammation, or trauma. No clear time to onset pattern was identified. In 2 cases, drug was continued. In the remaining 7 cases, upon drug discontinuation, 6 cases showed full recovery and the case with trauma was stable. Post Marketing Experience

Table 2.7.3.1-2: Important Identified Risk: Macular Oedema

Important Identified Risk Macular Oedema

As of 01-Apr-2023, since marketing approval 13 cases of macular oedema were reported from sources other than Company-sponsored clinical trials. At least in 4 cases, time to event onset was within 90 days from the start of ozanimod. In half of these cases there was a presence of known risk factors, such as uveitis, diabetes mellitus and cataract surgery. While most reports had limited information, in 3 cases the diagnosis by an ophthalmologist was reported. In one case, the patient with a history of hyperglycemia presented with blurry vision and was diagnosed with bilateral macular oedema after 7 months on ozanimod for UC.

Characterization of risk

Frequency with 95% CI

UC studies

In Study RPC01-3101, there was one report of macular oedema in the ozanimod treatment group during the controlled Induction Period. Macular oedema was reported for 1 patient treated with ozanimod in the Study RPC01-3101 Maintenance Period.

In Pool G, macular oedema events (as adjudicated by the macular oedema review panel) were reported for 4 patients treated with ozanimod 0.92 mg and no patients who received placebo. None of these events was considered serious.

Macular oedema	**Pool G Number (%) of Patients**	
Total Number of Patients	**Ozanimod 0.92 mg (N = 1158)**	**Placebo (N = 508)**
Patients with ≥ 1 AE	4 (0.3)	0
Patients with ≥ 1 SAE	0	0

MS studies

Macular Oedema	**Pool A1 Number (%) of Patients**				**Pool B Number (%) of Patients**			**RPC01-3001 Number (%) of Patients**
Total Number of Patients	**IFN β-1a 30 µg (N = 885)**	**Ozanimod 0.46 mg (N = 892)**	**Ozanimod 0.92 mg (N = 882)**	**Total Ozanimod (N = 1774)**	**Ozanimod 0.46 mg (N = 1033)**	**Ozanimod 0.92 mg (N = 2631)**	**Total Ozanimod (N = 2787)**	**Total Ozanimod 0.92 mg (N = 2494)**
Patients with ≥ 1 AE	0	3 (0.3)	1 (0.1)	4 (0.2)	3 (0.3)	4 (0.2)	7 (0.3)	5 (0.2)
Patients with ≥ 1 SAE	0	0	0	0	0	0	0	0
IR per 100,000 PY (95% CI)	0.0 (0.0, 278.0)	223.7 (46.1, 653.9)	74.3 (1.9, 414.2)	148.9 (40.6, 381.3)	185.1 (38.2, 540.8)	70.3 (19.2, 180.0)	95.8 (38.5, 197.3)	39.5 (12.82 - 92.17)

In Pool A1, the proportion of patients experiencing at least one event of confirmed macular oedema was greater among ozanimod-treated patients (0.2%) compared to patients receiving control treatment (0%; the RR was not calculable). The proportion of ozanimod-treated

Table 2.7.3.1-2: Important Identified Risk: Macular Oedema

Important Identified Risk Macular Oedema	
	patients experiencing at least one event of macular oedema was similar in Pool B (0.3% of patients), and in the OLE study (RPC01-3001) alone (0.2% of patients). **Seriousness/Outcomes** UC studies There were no SAEs of macular oedema in Pool G. Macular oedema resolved for all of the non-serious macular oedema events. MS studies In Pools A1 and B, no SAEs of confirmed macular oedema were experienced by ozanimod-treated patients. Macular oedema resulted in discontinuation of ozanimod in four (0.2%) patients in Pool A and six (0.2%) patients in Pool B, as required in the clinical study protocols. Six cases were recovering/recovered and the case with ocular trauma was stable. In the OLE study (RPC01-3001) none of the confirmed cases of macular oedema were reported as SAEs. **Severity and Nature of Risk** UC studies There were no severe events of confirmed macular oedema in Pool G. Of the 4 patients with macular oedema events, 1 patient had an event of retinal vein thrombosis that led to dose interruption, 3 patients had events (PTs cystoid macular oedema and macular oedema) that led to study drug discontinuation. MS studies There were no severe events of confirmed macular oedema in Pools A1 or B. In the OLE study (RPC01-3001), one of the macular oedema events was reported as severe. The event outcome was reported as recovered/resolved after ozanimod discontinuation. Post Marketing Experience As of 01-Apr-2023, since marketing approval 13 cases of macular oedema were reported from sources other than Company-sponsored clinical trials. At least in 4 cases, time to event onset was within 90 days from the start of ozanimod. In half of these cases there was a presence of known risk factors, such as uveitis, diabetes mellitus and cataract surgery. While most reports had limited information, in 3 cases the diagnosis by an ophthalmologist was reported. In one case, the patient with a history of hyperglycemia presented with blurry vision and was diagnosed with bilateral macular oedema after 7 months on ozanimod for UC.
Risk factors and risk groups	Risk factors for developing macular oedema are cataract surgery, history of uveitis, diabetes mellitus, or retinal diseases.
Preventability	Patients with risk factors for macular oedema such as a history of uveitis, diabetes mellitus or a history of retinal disease should have an ophthalmologic evaluation prior to starting treatment with ozanimod and have follow-up evaluations while receiving therapy. Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with ozanimod should be discontinued. A decision on whether ozanimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient.
Impact on the risk-benefit balance of the product	There is no impact on the benefit risk of the product. Macular oedema is a rare occurrence and is easily manageable by drug discontinuation and symptomatic treatment as required.
Public health impact	Macular oedema may be suspected upon development of visual symptoms. It can be confirmed upon ophthalmological examination and confirmatory tests. Should macular oedema be confirmed, ozanimod should be discontinued and the macular oedema treated

Table 2.7.3.1-2: Important Identified Risk: Macular Oedema

Important Identified Risk Macular Oedema	
	according to standard medical practice. Full recovery is to be expected and long-term sequelae are expected to be rare.
MedDRA Terms	Adjudicated cases with PTs of Cystoid macular oedema, Macular cyst, Macular degeneration, Macular detachment, Macular hole, Macular ischaemia, Macular oedema, Macular opacity, Macular pseudohole, Macular rupture, Macular scar, Macular vasospasm, Maculopathy.

Table 2.7.3.1-3: Important Potential Risk: Symptomatic Bradycardia

Important Potential Risk Symptomatic Bradycardia	
Potential mechanisms	Although the negative chronotropic effects of ozanimod are likely to be related to S1P1 modulation, the low incidence of bradycardia and absence of clinically significant consequences observed in the clinical programme was likely to be due to the dose escalation regimen used for ozanimod. As observed in clinical studies, a dose escalation regimen over 7 days following treatment initiation is associated with a considerably lower bradycardic effect than observed with a higher single dose of ozanimod or other S1P receptor modulators in the absence of dose escalation. This may be due to a gradual internalisation of S1P1 on cardiac myocytes by ozanimod, lessening S1P1-mediated cardiac effects.
Evidence source and strength of evidence	Initiation of ozanimod may result in transient reductions in HR. A dose escalation schedule (0.23 mg ozanimod followed by 0.46 mg and 0.92 mg) attenuates the magnitude of HR reductions. Initiation of ozanimod without dose escalation may result in greater reductions in HR. Two isolated cases of HR < 40 bpm (1 MS, 1 UC) were reported, both of which were detected by continuous cardiac monitoring overnight, and neither of which was associated with an AE or required treatment. In UC clinical studies Induction Period, which implemented dose escalation (Pool F), there was a modest (0.7 bpm) maximum mean reduction from baseline in HR during the first 6 hours post-dose on Day 1. This reduction was not associated with clinically significant bradycardia or conduction effects (eg, second-degree type 2 or third-degree AV block). No symptomatic bradycardia occurred during controlled studies. During hourly cardiac monitoring, one patient in an open-label cohort with a predose HR of 56 bpm experienced headache, nausea and light-headedness after the first dose of ozanimod. The lowest reported HR was 43 bpm at Hour 2, which recovered to above baseline by Hour 5. No treatment or extended monitoring was required. Two isolated cases of HR < 40 bpm (1 MS, 1 UC) were reported. One patient in Study RPC01-202, experienced HR ≤ 40 bpm. The patient's HR during the first 6 hours after dosing on Day 1 (approximately 9 am to 3 pm) was ≥ 64 bpm, and the patient experienced the minimal HR of 38 bpm at 2 am. Over 24-hour Holter monitoring, maximum HR was 133 bpm and mean HR was 80 bpm. This event was not associated with an AE and did not require treatment. In active-controlled MS clinical trials, after the initial dose of ozanimod 0.23 mg, the greatest mean reduction from baseline in HR of 1.2 bpm occurred at Hour 5 on Day 1, returning towards baseline at Hour 6. With the use of a dose escalation regimen over the first 7 days of treatment initiation, there has only been one case of confirmed symptomatic bradycardia observed in active-controlled Phase 3 MS studies (Pool A1). This patient, with a pretreatment HR of 48 bpm experienced mild dizziness at Hour 6 on Day 1, in the presence of a HR of 47 bpm. The dizziness resolved after a single dose of atropine although HR remained at 44 bpm. It is likely that pre-existing dysautonomia contributed to the patient's bradycardia and blunted the HR response to atropine. The patient continued ozanimod treatment uneventfully. In Pool B, one further event of nonserious symptomatic bradycardia

Table 2.7.3.1-3: Important Potential Risk: Symptomatic Bradycardia

Important Potential Risk Symptomatic Bradycardia

was reported in one patient commencing 0.23 mg ozanimod. The patient experienced dizziness and sleepiness, with a lowest HR of 46 bpm at Hour 4. The event did not lead to dose modification or discontinuation. One patient in Study RPC01-201A, had a HR of 39 bpm at Hour 20 post-dose on Day 8, which returned to normal (60 bpm) at Hours 23 and 24 the same day. This occurrence was not associated with an AE and did not require treatment. In the RPC01-3001, OLE study, two additional events of nonserious symptomatic bradycardia were reported in two patients. Both events resolved without intervention and did not lead to dose modification or discontinuation.

Characterization of risk

UC studies

During the controlled Induction Period for Study RPC01-3101, bradycardia events were reported for 2 patients treated with ozanimod and no patients who received placebo. The IRs for bradycardia (including findings of asymptomatic HR < 45 bpm) per 1000 PY for the ozanimod (N = 429) and placebo (N = 216) groups were 56.48 (95% CI: 18.34-131.80) and 22.27 (95% CI: 0.56-124.07), respectively. The RR was 2.523 (95% CI: 0.072-30.998). There were no AEs of bradycardia reported in the Study RPC01-3101 Maintenance Period.

In Pool G bradycardia events occurred in 9 patients treated with ozanimod 0.92 mg (bradycardia AEs in 7 patients [0.6%] and HR < 45 bpm in 3 patients) and 1 patient who received placebo. There were no events of serious or severe bradycardia. Of the 9 patients with bradycardia events in UC studies, 3 patients had events that were considered by the MAH to represent symptomatic bradycardia during ozanimod treatment. Bradycardia events led to discontinuation of ozanimod for 2 patients with symptomatic bradycardia (PT bradycardia in both cases). Of these, one patient had a history of hypertension and was receiving concomitant perindopril and bisoprolol. The patient discontinued ozanimod on Day 22 after events of hypertension, bradycardia and asthenia, having previously had dose interruption for bradycardia and asthenia on Day 10. Bradycardia was ongoing following ozanimod discontinuation.

The second patient discontinued ozanimod after bradycardia with light-headedness and headaches in the evening associated with a lowest self-reported HR of 45 bpm. The patient had first-degree AV block and PR of 212 ms at baseline electrocardiogram (ECG). A cardiology consultation found no evidence of bradycardia. Symptoms resolved 4 days after discontinuation of ozanimod, with no corrective treatment. The patient had a history of arterial hypertension, but no concomitant antihypertensive medication use was recorded.

The remaining patient with symptomatic bradycardia experienced headache, nausea and light-headedness after the first dose of ozanimod. The lowest reported HR was 43 bpm at Hour 2, which recovered to above baseline by Hour 5. No treatment or extended monitoring was required and ozanimod dosing continued unchanged.

Bradycardia events of interest	**Pool G Number (%) of Patients**	
Total Number of Patients	**Ozanimod 0.92 mg (N=1158)**	**Placebo (N = 508)**
Patients with ≥ 1 AE	9 (0.8)	1 (0.2)
Bradycardia AEs	7 (0.6)	0
Heart rate < 45 bpm	3 (0.3)	1 (0.2)
Patients with ≥ 1 SAE	0	0

MS studies

In Pool A1, one event of nonserious symptomatic bradycardia (PTs: bradycardia; dizziness) occurred in one patient in the 0.46 mg ozanimod dose group upon receipt of an initial dose of 0.23 mg ozanimod (the RR was not calculable). The event, associated with nonserious

Table 2.7.3.1-3: Important Potential Risk: Symptomatic Bradycardia

Important Potential Risk Symptomatic Bradycardia	
	dizziness, was of moderate severity, resolved without sequelae and did not lead to dose modification or discontinuation. In Pool B, one further event of nonserious symptomatic bradycardia was reported in one patient commencing 0.23 mg ozanimod. The patient experienced dizziness and sleepiness, with a lowest HR of 46 bpm at Hour 4. The event did not lead to dose modification or discontinuation. In the RPC01-3001, OLE study, two additional events of nonserious symptomatic bradycardia were reported in two patients. The events did not lead to dose modification or discontinuation. Overall, there were no events of severe bradycardia. The IRs of symptomatic bradycardia per 100,000 PY (95% CI) in the total ozanimod groups for Pool A1 (N = 1774) and Pool B (N = 2787) were 37.2 (0.9, 207.5) and 27.4 (3.3, 98.8), respectively. The IR of symptomatic bradycardia per 100,000 PY (95% CI) in RPC01-3001 was 15.8 (1.91, 57.09).
Risk factors and risk groups	Symptomatic bradycardia is a rare occurrence and has not been of clinical consequence. The administration of ozanimod in patients on both a beta blocker and a calcium channel blocker has not been studied. Any reports of symptoms in patients receiving these drugs concurrently in clinical practice will be analysed.
Preventability	Bradycardia, including symptomatic bradycardia, has not been of concern upon initiation of ozanimod treatment following a dose escalation regimen starting with 0.23 mg. Section 4.4 of the SmPC states that initiation of ozanimod may result in transient reductions in HR and therefore the initial dose escalation regimen to reach the once daily dose (0.92 mg) on day 8 should be followed. Section 4.4 of the SmPC states that cardiologist advice should be obtained before initiation of ozanimod in certain patients (including those with a history of symptomatic bradycardia) to decide if ozanimod can safely be initiated and to determine the most appropriate monitoring strategy. Due to the risk of transient decreases in HR with the initiation of ozanimod, first-dose, 6-hour monitoring for signs and symptoms of symptomatic bradycardia is recommended in patients with resting HR < 55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (see section 4.3 of the SmPC).Section 4.2 of the SmPC provides advice regarding reinitiation of therapy following treatment interruption. The initiation pack covers not only dosing for the first 7 days, but also for resuming following treatment interruption. In addition, ozanimod is contraindicated for initiation in patients who in the last 6 months had experienced MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation or NYHA Class III/IV heart failure. Ozanimod is also contraindicated for initiation in patients with history or presence of seconddegree AV block Type II or thirddegree AV block or sick sinus syndrome unless the patient has a functioning pacemaker. Caution should be applied when ozanimod is initiated in patients receiving treatment with a beta-blocker or a calcium-channel blocker (eg, diltiazem and verapamil) because of the potential for additive effects on lowering HR. Betablockers and calcium-channel blockers treatment can be initiated in patients receiving stable doses of ozanimod. The administration of ozanimod in patients on both a beta blocker and a calcium channel blocker has not been studied.
Impact on the risk-benefit balance of the product	Symptomatic bradycardia may cause a patient to become dizzy or faint, which, if severe, could result in injury.
Public health impact	There is no public health impact. Symptomatic bradycardia is a rare occurrence and has not been demonstrated to be clinically important.
MedDRA Terms	UC studies

Table 2.7.3.1-3: Important Potential Risk: Symptomatic Bradycardia

Important Potential Risk Symptomatic Bradycardia	
	Adjudication of reports of the PTs: Sinus bradycardia, Bradycardia, Bradyarrhythmia, Heart rate irregular and Heart rate decreased to identify cases of symptomatic bradycardia. MS studies Adjudication of reports of the PTs Syncope, Bradycardia, Sinus bradycardia to identify cases of symptomatic bradycardia.

Table 2.7.3.1-4: Important Potential Risk: Severe Liver Injury

Important Potential Risk Severe Liver Injury	
Potential mechanisms	The mechanism of elevated hepatic enzymes in patients receiving ozanimod is not known and the effect appears to be reversible. Severe drug-related liver injury has not been observed.
Evidence source and strength of evidence	Severe DILI is considered to be of public health concern. Majority of the liver--related events in the ozanimod clinical studies (predominately ALT and GGT elevations) were mild to moderate in intensity and resolved while continuing treatment. Section 4.4 of the SmPC states that elevations of aminotransferases may occur in patients receiving ozanimod and advises that recent (ie, within last 6 months) transaminase and bilirubin levels should be available before treatment initiation. During the Induction Period for UC study RPC01-3101, elevations of ALT above 5-fold the ULN occurred in 0.9% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo. Elevations of ALT above 3-fold the ULN occurred in 2.6% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo. In the Study RPC01-3101 Maintenance Period, 0.9% of patients treated with ozanimod 0.92 mg and no patients who received placebo had elevations 5-fold the ULN or greater. Elevations of 3-fold the ULN occurred in 2.3% of patients treated with ozanimod 0.92 mg and none who received placebo. In the UC studies (Pool G), elevations in ALT > 3 × ULN were observed in 6.0% of patients treated with ozanimod 0.92 mg and 0.2% of patients who received placebo. Of the ozanimod-treated patients, the majority (approximately 96% on ozanimod 0.92 mg) continued treatment with ozanimod, with values returning to ≤ 3 × ULN within approximately 2 weeks. The majority of ALT elevations were isolated cases, as evidenced by the low incidence of consecutive elevations > 3 × ULN (2.0% of patients treated with ozanimod 0.92 mg in Pool G) or > 5 × ULN (0.3% in Pool G). Similarly, the incidence of total bilirubin elevations > 2 × ULN was 1.1% in Pool G. Two patients in Pool G, had TEAEs reported by the Investigator as DILI. Both patients had mild (≥ 2 × ULN) nonserious, but persistent ALT elevations (after starting ozanimod treatment in OLE Study RPC01-3102), with ALT returning to near normal values (< 1.5 × ULN) with continued ozanimod treatment. The TEAEs were not associated with any symptoms or other laboratory changes and did not require any treatment. One patient was discontinued from Study RPC01-3102 due to persistent ALT elevation; the second patient continued in the OLE study. Overall, in UC clinical studies, the discontinuation rate because of elevations in hepatic enzymes was 0.4% of patients with UC treated with ozanimod in both Induction and Maintenance Periods, and none in patients who received placebo in either period. In active-controlled MS clinical trials, elevations of ALT to 5-fold the ULN or greater occurred in 1.6% of patients treated with ozanimod 0.92 mg and 1.3% of patients on IFN β-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with

Table 2.7.3.1-4: Important Potential Risk: Severe Liver Injury

Important Potential Risk Severe Liver Injury	
	ozanimod 0.92 mg and 3.1% of patients on IFN β-1a. When elevations in hepatic tests occurred, they were generally asymptomatic. The median time to elevation 3-fold the ULN was 6 months. The majority (79%) continued treatment with ozanimod with values returning to < 3-fold the ULN within approximately 2 to 4 weeks. In active-controlled MS clinical trials, ozanimod was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate due to elevations in hepatic enzymes was 1.1% of patients on ozanimod 0.92 mg and 0.8% of patients on IFN β-1a. Although there have been instances (5/1774 [0.28%] patients in Pool A1) where observations of ALT or AST were ≥ 3-fold the ULN together with bilirubin > 2-fold the ULN in clinical trials, no cases of severe DILI (confirmed Hy's Law cases) were observed with ozanimod. In the RPC01-3001, OLE study elevations of ALT > 3-fold the ULN occurred in 3.7% of patients, and elevations > 5-fold the ULN in 0.8% of patients treated with ozanimod. About 25% of ALT elevations > 3-fold the ULN were within the first year, and about 50% of ALT elevations > 3-fold the ULN occurred after 24 months on the study. The incidence of ALT elevation > 3 fold the ULN on consecutive post-baseline assessment was 22 (0.9%), and ALT > 5 fold the ULN was 6 (0.2%). Eleven patients in the entire ozanimod clinical development program (Pool D) had concurrent elevations of ALT or AST ≥ 3 × ULN and bilirubin > 2 × ULN. Review of unblinded cases by an external panel of expert hepatologists concluded that there were no cases that met Hy's Law due to alternate explanations and the pattern of abnormalities.
Characterization of risk	<u>UC studies</u> No cases of severe DILI or confirmed Hy's Law cases were observed with ozanimod in the placebo-controlled UC clinical trials. <u>MS studies</u> No cases of severe DILI or confirmed Hy's Law cases were observed with ozanimod in the active-controlled MS clinical trials. In the RPC01-3001, OLE study, there were 4 subjects who had concurrent elevations of ALT/AST>3xULN and BT>2xULN. Review of these cases by external hepatology experts concluded that there were no cases that met Hy's Law criteria, due to alternate explanations and the pattern of abnormalities including resolution on drug.
Risk factors and risk groups	Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking ozanimod. However, it is not known whether these patients are at increased risk of severe liver injury.
Preventability	Elevations of aminotransferases may occur in patients receiving ozanimod. Recent (ie, within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with ozanimod. In the absence of clinical symptoms, liver transaminases and bilirubin levels should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted. If liver transaminases above 5 times the ULN are confirmed, treatment with ozanimod should be interrupted and only re-commenced once liver transaminase values have normalised. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked and ozanimod should be discontinued if significant liver injury is confirmed. Resumption of therapy will be dependent on whether another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction. Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking ozanimod. Ozanimod has not been studied in patients with severe pre-existing hepatic impairment (Child-Pugh class C) and should not be used in these

Table 2.7.3.1-4: Important Potential Risk: Severe Liver Injury

Important Potential Risk Severe Liver Injury	
	patients. Patients with mild or moderate chronic hepatic impairment (Child-Pugh Class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day.
Impact on the risk-benefit balance of the product	Severe DILI has the potential to be fatal, especially if not diagnosed and treated promptly. No cases have currently been observed with ozanimod.
Public health impact	Drug-induced liver injury is an infrequent but potentially severe event. The idiosyncratic nature and poor prognosis of DILI make this type of reaction a major safety issue during drug development, as well as the most common cause for the withdrawal of drugs from the pharmaceutical market. According to the US Acute Liver Failure Study Group, DILI accounts for more than 50% of acute liver failure, including hepatotoxicity caused by overdose of acetaminophen (39%) and idiosyncratic liver injury triggered by other drugs (13%).[102] Because of the significant patient morbidity and mortality associated with DILI, the US Food and Drug Administration has removed several drugs from the market, including bromfenac, ebrotidine, and troglitazone. DILI can affect both parenchymal and nonparenchymal cells of the liver, leading to a wide variety of pathological conditions, including acute and chronic hepatocellular hepatitis, fibrosis/cirrhosis, cholestasis, steatosis, as well as sinusoidal and hepatic artery/vein damage. The predominant forms of DILI include acute hepatitis, cholestasis, and a mixed pattern. Acute hepatitis is defined as a marked increase in aminotransferases coinciding with hepatocellular necrosis. Cholestasis is characterised by jaundice with a concurrent elevation in alkaline phosphatase, conjugated bilirubin, and GGT. Mixed pattern DILI includes clinical manifestations of both hepatocellular and cholestatic injury. The occurrence of DILI ranges from 1 in 10,000 to 1 in 100,000.[103]
MedDRA Terms	UC studies Combination of all SMQ Sub-SMQs under the Sub-SMQ Drug related hepatic disorders - comprehensive search. MS studies Standardised MedDRA Queries of Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions and Hepatitis, non-infectious. SMQ hepatic disorder, the sub-SMQ drug related hepatic disorders– severe events only and the PT acute hepatic failure. Cases with concurrent condition/procedure of hepatic transplant utilizing MedDRA PT liver transplant and/or hepatic/liver transplant mentioned as free text in case narratives.

Table 2.7.3.1-5: Important Potential Risk: Malignancy

Important Potential Risk Malignancy	
Potential mechanisms	S1P1 modulation results in decreased circulating lymphocytes due to their retention in lymphoid tissue. Only some subsets of immune cells (some T and B cell subsets) are impacted, however. Immune cells such as monocytes, effector memory RA T cells, and natural killer cells are still present in the periphery following S1P1 modulation, and immunosurveillance may contribute to the low level of malignancy noted.
Evidence source and	Malignancies are identified by medical review of all TEAEs (PTs) in the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps) for the UC population (see MedDRA

Table 2.7.3.1-5: Important Potential Risk: Malignancy

Important Potential Risk Malignancy	
strength of evidence	terms below). Events of colorectal carcinoma and high-grade dysplasia are also specifically monitored in the UC population. In total, 14 malignancies were observed in the UC studies: 6 NMSCs and 8 other malignancies. In UC studies (Pool G), malignancies were reported in 1.0% of patients in the ozanimod 0.92 mg treatment group and 0.4% in the placebo group. Both of the patients in the placebo group had received ozanimod during the Induction Period prior to being randomised to placebo maintenance. No malignancies were observed for patients exclusively exposed to placebo. Similar to MS, the overall incidence of malignancies with ozanimod is generally in line with rates reported in the literature in the UC population and the general population in the same age range. In the MS studies, for Pool A1 there were 4 treatment-emergent malignancies (excluding NMSCs) for ozanimod (0.46 and 0.92 mg doses) and 4 NMSCs versus 1 and 1 for IFN, respectively. In Pool B, there were 12 treatment- emergent malignancies (excluding NMSCs) for ozanimod (0.46 and 0.92 mg doses) and 9 NMSCs versus 1 and 1 for IFN, respectively. In the RPC01-3001, OLE study, there were 29 treatment-emergent malignancies (excluding NMSCs) and 12 NMSCs. Incidence rates of malignancies for ozanimod were within background rates in age matched MS and general populations (see Severity and Nature of Risk section below).
Characterization of risk	<u>UC studies</u> Malignancies were identified by medical review of all TEAEs (PTs) in the Neoplasms SOC. Malignancy was reported for 1 patient (0.2%) during the Induction Period for Study RPC01-3101. During the Study RPC01-3101 Maintenance Period, malignancies were reported for 2 patients (0.9%) in the ozanimod group and 2 patients (0.9%) in the placebo group. The 5 malignancies observed in Pool F and RPC01-3101 Maintenance Period, included 2 NMSC (1 squamous cell carcinoma [Induction Period] and 1 basal cell carcinoma) and 1 colon cancer, 1 breast cancer, and 1 rectal cancer (RPC01-3101 Maintenance Period). An additional 9 malignancies in Pool G included cutaneous basal cell carcinoma (4 patients), mucinous adenocarcinoma (mucinous adenocarcinoma of gastric, pancreatic, biliary or endometrial origin), breast cancer, lung cancer, prostate cancer and rectal cancer (1 patient each). The incidence of malignancies in the ozanimod treatment was 1.0%, corresponding to an IR of 6.3 per 1000 PY.

Table 2.7.3.1-5: Important Potential Risk: Malignancy

Important Potential Risk Malignancy

MS studies

	Pool A1 Number (%) of Patients				Pool B Number (%) of Patients			RPC01-3001 Number (%) of Patients
Total Number of Patients	**IFN β-1a 30 µg (N 885)**	**Ozanimod 0.46 mg (N = 892)**	**Ozanimod 0.92 mg (N = 882)**	**Total Ozanimod (N = 1774)**	**Ozanimod 0.46 mg (N = 1033)**	**Ozanimod 0.92 mg (N = 2631)**	**Total Ozanimod (N = 2787)**	**Total Ozanimod (N = 2494)**
Malignancies excluding NMSCs[a]								
Patients with ≥ 1 AE	1 (0.1)	1 (0.1)	3 (0.3)	4 (0.2)	1 (< 0.1)	11 (0.4)	12 (0.4)	29 (1.1)
Patients with ≥ 1 SAE	1 (0.1)	1 (0.1)	3 (0.3)	4 (0.2)	1 (< 0.1)	11 (0.4)	12 (0.4)	28 (1.1)
IR per 100,000 subject-years (95% CI)	75.4 (1.9, 420.0)	74.6 (1.9, 415.4)	223.2 (46.0, 652.2)	148.9 (40.6, 381.4)	61.7 (1.6, 343.6)	193.5 (96.6, 346.2)	164.2 (84.9, 286.9)	229.2 (153.5, 329.1)
Non-melanoma skin cancers								
Patients with ≥ 1 AE	1 (0.1)	2 (0.2)	2 (0.2)	4 (0.2)	2 (0.2)	7 (0.3)	9 (0.3)	12 (0.5)
Patients with ≥ 1 SAE	0	1 (0.1)	1 (0.1)	2 (0.1)	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	1(<0.1)
IR per 100,000 subject-years (95% CI)	75.4 (1.9, 420.1)	149.3 (18.1, 539.4)	148.7 (18.0, 537.3)	149.0 (40.6, 381.6)	123.5 (15.0, 446.1)	123.2 (49.5, 253.8)	123.3 (56.4, 234.1)	95 (49.1, 165.9)

[a] Note these data exclude 2 patients with pre-existing malignancies

In Pool A1, the proportion of patients experiencing at least one treatment-emergent event of a) malignancies excluding NMSCs and b) NMSCs was greater among ozanimod-treated patients (0.2% for both) compared to patients receiving control treatment (0.1% for both). In Pool B, the proportion of ozanimod-treated patients experiencing at least one treatment-emergent event of a) malignancies excluding NMSCs and b) NMSCs were 0.4% and 0.3%, respectively. In the RPC01-3001, OLE study, the proportion of ozanimod-treated patients experiencing at least one treatment-emergent event of a) malignancies excluding NMSCs and b) NMSCs were 1.1 % and 0.5% respectively.

Seriousness/Outcomes

UC studies

In Pool G, SAEs of malignancies were reported for 6 patients in the ozanimod group. Malignancies excluding NMSC were reported for 5 patients (adenocarcinoma, lung neoplasm

Table 2.7.3.1-5: Important Potential Risk: Malignancy

Important Potential Risk Malignancy

malignant, prostate cancer, rectal adenocarcinoma and rectal cancer Stage II in 1 patient each) and NMSC for 1 patient (basal cell carcinoma). Outcomes for malignancy AEs were resolved in 8 patients (0.7%), not recovered/resolved in 3 patients (0.3%) and fatal in 1 patient (<0.1%) (mucinous adenocarcinoma, Study RPC01-202).

MS studies

In Pools A1 and B, SAEs of treatment-emergent malignancies excluding NMSCs were experienced by 4 (0.2%) and 12 (0.4%) ozanimod treated patients. In Pool A1, the outcome of these events was recovering/resolving for 2 (0.1%) patients, recovered/resolved for 1 (< 0.1%) patient and not recovered/not resolved for 1 (< 0.1%) patient. In Pool B, the outcomes were recovering/resolving for 3 (0.1%) patients, recovered/resolved for 3 (0.1%) patients, recovered/resolved with sequelae for 2 (< 0.1%) patients and not recovered/not resolved for 4 (0.1%) patients.

Serious AEs of NMSC were experienced by 2 (0.1%) and 2 (< 0.1%) ozanimod treated patients in Pools A1 and B, respectively. In both Pool A1 and Pool B, the outcome was recovered/resolved for the 2 patients.

In Pool A1, non-cutaneous malignancies resulted in discontinuation of ozanimod in one (< 0.1%) patient. In Pool B, malignancies resulted in discontinuation of ozanimod in seven (0.3%) patients with non-cutaneous malignancies and in one (< 0.1%) patient with melanoma skin cancer.

In the RPC01-3001, OLE study, SAEs of treatment-emergent malignancies excluding NMSCs were experienced by 28 (1.1 %) patients. The outcomes of these events were recovered/resolved in 13 (0.5 %), not recovered/not resolved in 8 (0.3 %), recovering /resolving in 3 (0.1 %), fatal in 3 (0.1 %), and unknown in 1 (< 0.1 %) patients.

Serious AEs of NMSC was experienced by 1 (< 0.1 %) patient and the outcome of the event was recovered/resolved.

Severity and Nature of Risk

UC studies

In Pool G, severe AEs of malignancies were reported for 5 patients (all noncutaneous malignancies).

Of the patients who had malignancy AEs, 2 patients had AEs that led to dose interruption and 3 patients had AEs that led to treatment discontinuation.

There were 3 cases of CRC across the UC programme. Given the increased risk of CRC in patients with UC, these events were carefully reviewed by the MAH and rereviewed with the central reader, an external gastroenterologist consultant, and the external Data Monitoring Committee. In all cases, it was concluded while cancer could not be confirmed by biopsy prior to the event, there was prior evidence of colonic mass suggesting malignancy.

The IR per 100,000 PY (95% CI) for malignancies (excluding NMSC) in Pool G in the ozanimod group were similar to the rate of 570.7 (569.7 to 571.7) for the comparable age range (20 to 74 years) in the general US population in 2017 based on the Surveillance, Epidemiology and End Results (SEER) data (which exclude NMSC).

The IRs per 100,000 PY of cutaneous squamous cell carcinoma and basal cell carcinoma in the ozanimod groups in Pool G were 50 and 260, respectively, which are in the range of the expected IRs of NMSC. Incidence rates for NMSC vary considerably across countries. In Minnesota, the age and sex-adjusted (US 2010 population) incidence of NMSC per 100,000 PY was 483.7 over the period 2000 to 2010.[104] In Germany, the crude IRs of NMSC per 100,000 in 2012 were 278 and 241 in men and women, respectively, in the federal state of Schleswig-Holstein and 186 and 163 in men and women, respectively, in the federal state of Saarland.[105] An analysis of real-world data was conducted using MarketScan® (a USbased- commercial and

Table 2.7.3.1-5: Important Potential Risk: Malignancy

Important Potential Risk Malignancy

Medicare supplement claims database). Patients in MarketScan with an NMSC diagnosis in the year prior to index date were excluded from the analysis. The IRs per 100,000 PY were 761 in the general population and 1553 in the population with UC.

MS studies

In Pool A1, one patient had a severe event of breast cancer in the ozanimod 0.92 mg group. No further cases were reported in Pool A1. In Pool B, no patients had a severe event in the ozanimod 0.46 mg group, and 6 patients (0.2%) had severe events in the ozanimod 0.92 mg group. In the RPC01-3001, OLE study, 18 patients had severe events. The most common malignancy was basal cell carcinoma 11 (0.4 %) subjects, with an incidence rate of 87 (43.5, 155.7). There were 2 subjects with malignancies that died during the study. In addition, 2 subjects that died off the study had malignancy AEs that started during the study. One subject had the SAE of pancreatic carcinoma metastatic and another one had the SAE of glioblastoma multiforme IV WHO (severity Grade 5).

The IRs per 100,000 PY (95% CI) for malignancies (excluding NMSC) in Pool A1 in the ozanimod groups combined (148.9 [40.6, 381.4]) 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 SEER database analysis (which excludes NMSC).

The IR per 100,000 PY of NMSCs (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).[106,107]

For Pool B (all clinical studies), the IR per 100,000 PY (95% CI) for malignancies (excluding NMSC) was 164.2 (84.9, 286.9) per 100,000 PY. These IRs compare favourably with the rates observed in Pool A1 (223.5 and 148.9 per 100,000 PY, for the 0.92 mg and total ozanimod groups respectively), indicating that, with longer exposure, the incidence of malignancies in the RMS studies did not increase.

For the RPC01-3001, OLE study, the IR per 100,000 PY (95% CI) for malignancies (excluding NMSC) was 229.2 (153.5, 329.1) and 95.0 (49.1, 165.9) for NMSC malignancies.

Cases of lymphoma have been reported in ozanimod clinical program with numbers within expected range. Four cases of breast cancer (PTs of breast cancer and invasive breast carcinoma) have been reported in Pool B (3 reported in the active-controlled Phase 3 studies [Pool A1]) and 1reported in the RPC01-3001 OLE Study (Pool B [DLP 30-Jun-2018]). In the RPC01-3001 OLE study alone (DLP 07-Apr-2023), 7 cases of breast cancer (PTs of breast cancer [4], invasive lobular breast cancer [1], invasive breast cancer [1], and invasive ductal breast carcxinoma [1]) have been reported. Of these 7 cases, 1 case was previously reported in Pool B resulting in an overall total of 10 cases of breast cancer (3 from Phase 3 studies [Pool A1] and 7 from the RPC01-3001 OLE Study)

This is within the expected incidence over the treatment period of 4.86 events of breast cancer, calculated by applying the SEER IR for breast cancer in an age-matched (20- to 54-year-old) female population (92.4/100,000) to female patients' exposure to ozanimod in Pool B (5256.7 subject-years). Using these data, the IR for breast cancer in Pool B is estimated to be 76.1/100,000 (95% CI: 24.2, 183.5), corresponding to an SIR of 0.82-(data on file). By comparison, the SIR of breast cancer in the MS population has been estimated to range between 0.94 (95% CI: 0.77, 1.31) and 1.21 (95% CI: 1.05,1.39) across 4 different population-based studies.[108]

The MAH recently commissioned 3 epidemiological studies of comorbidities in MS, in Sweden, the UK and the US and compared these rates to a sample of the general population matched for age, gender, location and time of registration (data on file):

Table 2.7.3.1-5: Important Potential Risk: Malignancy

Important Potential Risk Malignancy	
	In Sweden using national registers, the IR of any cancer (including NMSC) was similar in 6602 persons with MS and a non-MS cohort of 61,828 persons with respective IRs of 585.0/100,000 and 577.2/100,000 PY. In the age bracket < 40 years, the IR of cancer was 135.7/100,000 PY in patients with MS (121.6/100,000 PY in the control person cohort); and in the age bracket 40-59 years the corresponding rates were 619.0/100,000 PY (MS) and 595.9/100,000 PY (non-MS).[109] In the UK using the Clinical Practice Research Datalink general practitioners register, cancer IRs (excluding NMSC) were similar in MS (N = 6932) and comparator populations (N = 68,526) with IRs around 110 to 139/100,000 PY for persons aged < 40 years, 513 to 512/100,000 PY for persons 40 to 59 years of age. In the US using the Department of Defense claims database, the IRs overall of cancer in MS was somewhat higher (594/100,000 PY; N = 8695) compared to the rate in the matched comparator population (504/100,000 PY; IR 1.18 [1.05, 1.32]; N = 86,934). In the age bracket < 40 years, the IR of cancer was 170/100,000 PY in patients with MS (131/100,000 PY in the control person cohort); and in the age bracket 40 to 59 years the corresponding rates were 786/100,000 PY (MS) and 558/100,000 PY (non-MS). The overall incidence of malignancies, whether cutaneous or non-cutaneous, observed for patients on ozanimod is generally comparable to rates reported in the literature for an age-matched population as well as those observed for patients with MS including those on disease modifying therapies. The malignancies reported do not demonstrate any particular pattern and are not typical of those observed in an immunosuppressed population.
Risk factors and risk groups	Risk factors for malignancies are not fully understood. Risk factors known to cause cancer include advancing age, and lifestyle (such as smoking, alcohol, certain infections, lack of physical activities, poor diet, obesity, excessive exposure to the sun or other radiation, exposure to chemicals or hormone replacement). Some genes such as BRCA are known to cause cancers (breast, ovarian and prostate). However, it is not known what proportion of cancer is caused by faulty genes. Patients who are profoundly immunosuppressed are also at increased risk of developing malignancy, typically lymphomas. Chronic inflammatory conditions may also increase the risk of cancer. Many cancers develop as a result of combination of genetics, environmental factors and lifestyle.[110]
Preventability	Any potential risk of malignancy/progression of malignancy can be minimised by contraindicating use of ozanimod in patients with active malignancies (see SmPC). Routine surveillance for malignancy, particularly in those with a personal or family history of malignancy is standard medical practice and would be expected to detect any conditions at an early or precancerous stage. Maintaining a healthy lifestyle such as stopping smoking, maintaining a healthy weight, reducing alcohol consumption, avoiding excessive exposure to sunlight and remaining active are considered to be preventative measures to reduce cancer risk.
Impact on the risk-benefit balance of the product	The rates of both NMSCs and other malignancies are low (< 1%) with ozanimod and are observed to be within the background rates in age matched individuals with MS not receiving ozanimod and also age matched individuals without MS. There is limited impact on the benefit-risk balance for ozanimod.
Public health impact	Cancer is one of the leading causes of morbidity and mortality worldwide. It was estimated that there will be 18.1 million new cancer cases (17.0 million excluding NMSC) and 9.6 million cancer death (9.5 million excluding NMSC) in 2018.[111] Cancer has significant impact on public health in every world region. The economic burden as a result of the treatment cost, loss of productivity and years of life lost due to premature death. For those who have survived cancer, there is also long-term impact on their quality of life.

Table 2.7.3.1-5: Important Potential Risk: Malignancy

Important Potential Risk Malignancy	
	Cancer is diverse in terms of its incidence and survival. Lung cancer is associated with highest incidence and mortality while breast cancer is the second most common cancer with lower mortality rate than stomach and liver cancers. Non-melanoma cancer, although not uncommon, has one of the lowest rates of mortality amongst all types of cancer. Non-melanoma skin cancers are common in the general population, are readily detectable and treatable, and therefore have limited public health impact. Invasive malignancies may have a greater impact as they are more difficult to treat and consequently may have fatal outcomes.
MedDRA Terms	UC studies Medical review of all reported AEs in the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps). MS studies Narrow scope of Sub-SMQ Malignant tumours, Narrow scope of Sub-SMQ Tumours of unspecified malignancy, and Broad scope of SMQ Malignant lymphomas.

Table 2.7.3.1-6: Important Potential Risk: Posterior Reversible Encephalopathy Syndrome

Important Potential Risk Posterior Reversible Encephalopathy Syndrome	
Potential mechanisms	Posterior reversible leukoencephalopathy syndrome is a recognised syndrome that was first described in 1996 in a retrospective study, which noted the most common clinical features as headache, abnormalities of visual perception, altered alertness, behavioural changes, altered conscious level/coma, and seizures.[112] There are two main hypotheses explaining the pathophysiology of PRES. Firstly, in a majority of patients the clinical presentation of PRES includes elevated arterial blood pressure, which may lead to hypertensive crisis and cerebral hyperperfusion. PRES may also result from endothelial dysfunction caused by circulating exogenous or endogenous toxins. This theory is supported by the frequent occurrence of PRES in patients with (pre)eclampsia, sepsis or during cytotoxic or immunosuppressive therapies.[113] The vulnerability of the posterior circulation may be explained by the paucity of autonomic innervation as compared to the anterior circulation; however, changes may also occur in other areas of the brain.[114] The resulting oedema is usually vasogenic and reversible but may become cytotoxic in some patients.[115] The findings on neuro-imaging in PRES include non-enhancing white matter abnormalities that appear as areas of low attenuation on CT scan and appear hypo-dense on T1-weighted imaging MRI and hyper-intense on T2-weighted imaging MRI. The lesions are mainly seen in the posterior regions of the cerebral hemispheres.[115,116] These abnormalities partially or completely resolve on follow-up scanning thereby suggesting subcortical oedema without infarction. Although MRI yields higher resolution and may show focal abnormalities beyond resolution of CT scanning, it is not mandatory for the diagnosis of PRES[112] but is generally considered to be the preferred investigation.[114] Other abnormalities diagnosed radiologically at presentation of PRES may include cerebral ischaemia, infarction, haemorrhage and herniation.[114] Differential diagnoses of PRES may include ictal/postictal

Table 2.7.3.1-6: Important Potential Risk: Posterior Reversible Encephalopathy Syndrome

Important Potential Risk Posterior Reversible Encephalopathy Syndrome	
	states, PML, infectious encephalitis, acute disseminated encephalomyelitis, Creutzfeldt-Jakob disease, cerebral venous sinus thrombosis, and ischaemic stroke.
Evidence source and strength of evidence	No cases of PRES were reported in UC clinical studies. In the OLE (RPC01-3001) study, no cases of PRES were reported. In controlled MS clinical trials with ozanimod, one case of PRES was reported in a patient with Guillain-Barré syndrome.
Characterization of risk	UC studies No cases of PRES were reported in UC clinical studies. MS studies In Pool A1, one serious case of PRES was reported in a patient with Guillain-Barré syndrome (known to be associated with PRES) who was treated with 0.92 mg ozanimod (the RR was not calculable). The case of PRES was severe in intensity and resulted in permanent discontinuation of ozanimod. The patient recovered with sequelae. No further cases were reported in Pool B or OLE study (RPC01-3001). The IR of PRES per 100,000 PY (95% CI) in the total ozanimod group for Pool A1 (N = 1774) was 37.2 (0.9, 207.5).
Risk factors and risk groups	Many patients with PRES have comorbidities, which may be severe conditions, such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension and may be predisposing factors. Radiologically, extensive bilateral white matter abnormalities suggestive of oedema in the posterior regions of cerebral hemispheres were seen in a variety of conditions,[117,114] including severe hypertension, uraemia, toxaemia of pregnancy, use of immunosuppressive drugs (ie, cyclosporine A) and cytotoxic agents, including alkylating agents, antimetabolites, mitotic inhibitors, antiangiogenic agents and anti-TNF-α agents, granulocyte colony-stimulating factor and erythropoietin. Infections and autoimmune disease have also been associated with PRES. Hypertension of renal origin has been reported to be a significant cause of PRES. Patients with renal dysfunction appear to be at higher risk of developing PRES despite only moderate acute elevation of their blood pressure.[118] In patients with PRES associated renal disease treated with antihypertensive medications, neurological deficits resolved within 2 weeks.[112] PRES can manifest with acute seizures without an obvious prodrome. These patients become seizure free after resolution of the imaging abnormalities and they do not require long-term antiepileptic therapy.[119,116] PRES in the setting of autonomic dysfunction may also be a complication of Guillain-Barré syndrome.[120,121]
Preventability	PRES is a syndrome characterised by sudden onset of severe headache, confusion, seizures and visual loss. Symptoms of PRES are usually reversible but may evolve into ischaemic stroke or cerebral haemorrhage. In controlled clinical trials with ozanimod, one case of PRES was reported in a patient with Guillain-Barré syndrome. If PRES is suspected, treatment with ozanimod should be discontinued.
Impact on the risk-benefit balance of the product	In controlled clinical trials with ozanimod, one serious case of PRES was reported and the relationship to ozanimod was uncertain. Thus, there is currently no impact on the risk-benefit balance.

Table 2.7.3.1-6: Important Potential Risk: Posterior Reversible Encephalopathy Syndrome

Important Potential Risk Posterior Reversible Encephalopathy Syndrome	
Public health impact	PRES is a neurological disorder of (sub)acute onset, which is characterised by various neurological symptoms including headache, impaired visual acuity, visual field defects, disorders of consciousness, confusion, seizures and focal neurological defects.[113] Recognition of the syndrome is critical as delay in the diagnosis or treatment can result in permanent neurological deficits while prompt early control of blood pressure or withdrawal of causative drugs can reverse the syndrome.[122] PRES is reversible once the cause is eliminated; however, permanent neurological impairment or death occurs in a minority of patients.[123] Mechanical ventilation is required in 35% to 40% of patients with PRES, for 3 to 7 days. Status epilepticus may require intensive care unit admission. No epidemiological data are available on the subgroup of patients with PRES requiring intensive care unit admission. Mean hospital length of stay was 20 days.[114]
MedDRA Terms	PTs: PRES, leukoencephalopathy.

Table 2.7.3.1-7: Important Potential Risk: Embryofoetal Toxicity in Exposed Pregnant Females

Important Potential Risk Embryofoetal Toxicity in Exposed Pregnant Females	
Potential mechanisms	Embryofoetal development was assessed both in the rat and in the rabbit with foetal findings. The findings included embryofoetal mortality (rat only), oedematous changes (rat only), malpositioned testes (rat only), delayed ossification, malpositioned caudal vertebrae and abnormalities of the great blood vessels (rabbit only).
Evidence source and strength of evidence	As of 22 March 2023, a total of 78 events of potential exposure during pregnancy have been reported in patients treated with ozanimod across all indications, including 14 reported for female patients in ozanimod clinical trials for UC and 57 reported for female patients in ozanimod clinical trials for MS. The remaining 7 potential pregnancies in clinical trial participants occurred in 6 patients with Crohn's disease and 1 healthy volunteer. In addition, there have been 29 pregnancies in partners of male patients receiving ozanimod (30 outcomes due to twins). Of these, there have been 21 live births (13 normal; 5 premature, including 1 set of twins; and 3 with congenital abnormalities, including Hirschsprung's disease, congenital hydrocele, and partial atrioventricular septal defect), 1 ongoing pregnancy, 1 spontaneous early loss and 7 lost to follow-up. In partners of ozanimod-treated male participants in the ozanimod clinical development program, no drug related AEs (as assessed by Investigator and Sponsor) were reported. Embryofoetal toxicity in exposed pregnant females is considered to be an Important Potential Risk due to findings in animal studies. Clinical trial patients were instructed to avoid pregnancy during the trials and for a period after discontinuing medication as specified in the protocol, and to immediately discontinue study medication if pregnancy were diagnosed. All exposures occurred during the first trimester of pregnancy.
Characterization of risk	There was no evidence of embryofoetal toxicity observed in the limited clinical experience of pregnancy.

Table 2.7.3.1-7: Important Potential Risk: Embryofoetal Toxicity in Exposed Pregnant Females

Important Potential Risk Embryofoetal Toxicity in Exposed Pregnant Females	
	Seriousness/Outcomes UC studies Of the 14 pregnancies reported for female patients in ozanimod clinical trials in UC, outcomes were 7 live births, 3 spontaneous early losses, and 4 elective terminations. The 7 live births resulted in 7 full-term healthy newborns. All ozanimod exposures were limited to the first trimester of pregnancy and all patients who had live births discontinued study medication upon diagnosis of pregnancy. MS studies Of the 57 pregnancies (58 outcomes due to twins) reported for female patients in ozanimod clinical trials in MS, outcomes were 33 live births (28 normal, 4 premature, and 1 with duplex kidney), 5 ongoing pregnancies, 8 spontaneous early losses (1 vanishing twin), 10 elective terminations, and 2 loss to followup. Duplex kidney is a common congenital anomaly and was not considered to be related to ozanimod (as assessed by Investigator and Sponsor). Other patient populations In addition to the UC and MS clinical programmes, there have been 6 potential pregnancies in patients with Crohn's disease and 1 pregnancy in a healthy volunteer. Of the 6 pregnancies in Crohn's disease studies, 2 resulted in a live birth without congenital abnormalities, 1 spontaneous early loss, 1 ongoing, and 2 loss to follow-up. The 1 pregnancy in a healthy volunteer resulted in elective termination. **Severity and Nature of Risk** As of 22 Mar 2023, there have been 42 live births and 6 ongoing pregnancies in clinical trial patients treated with ozanimod. The incidence of spontaneous abortion in clinical trial patients exposed to ozanimod (15%; 12 spontaneous loss of 78 pregnancies) is at the lower end of the expected incidence of early pregnancy loss in the general population (12% to 22%).[124,125] The rate of preterm births in the ozanimod study population (5.0% of pregnancies, 9.5% of live births) was similar to the global population estimate of 10.6% of live births, and the European estimate of 8.7% of live births.[126] The rate of preterm births in MS study population was 7.0% of pregnancies. No preterm births were observed in UC studies.
Risk factors and risk groups	No specific risk groups or risk factors have been identified.
Preventability	There are limited data from the use of ozanimod in pregnant women. Studies in animals have shown reproductive toxicity. Ozanimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Women of childbearing potential should use effective contraception during ozanimod treatment, and for at least 3 months after treatment discontinuation including dose interruptions, and for at least 3 months after stopping ozanimod.
Impact on the risk-benefit balance of the product	Clinical implications are potentially foetal loss or teratogenicity, likely to be of a skeletal nature or affecting large blood vessels, based on preclinical toxicity findings and known preclinical class effects. No findings of this nature have been observed in humans in the limited clinical experience of pregnancy with ozanimod treatment.
Public health impact	Major foetal abnormalities, if detected, will have a major impact on quality of life or could be fatal in utero.
MedDRA Terms	Clinical review of all pregnancies.

Table 2.7.3.1-8: Important Potential Risk: Thromboembolic Events

Important Potential Risk Thromboembolic Events	
Potential mechanisms	A potential mechanism of action for increased risk of TE events with S1P receptors is currently not established.
Evidence source and strength of evidence	In the ozanimod UC clinical development programme, the IR per 1000 PY for TE related events was 5.2 and 4.0 for ozanimod and placebo, respectively. The majority of the TE events occurred in older aged patients with documented risk factors. In MS controlled Phase 3 RRMS studies (Pool A1), the incidence of TE events were similar in ozanimod and IFN β-1a groups, with events reported in 2 patients in the ozanimod 1 mg treatment group, 3 patients in the ozanimod 0.5 mg group and 4 patients with IFN β-1a. The majority of the TE events occurred in patients with documented risk factors. In the RPC01-3001, OLE study, 13 additional serious TE events were reported.
Characterization of risk	UC Studies The frequency of TE events in the pooled controlled and uncontrolled studies is shown in the table below.

Summary of Thromboembolic-related Treatment-emergent Adverse Events – Pool G (Safety Population)

	Placebo (N = 508)		Ozanimod 1 mg (N = 1158)	
PT[a]	**n (%)[b]**	**IR[c]**	**n (%)[b]**	**IR[c]**
Thromboembolic Related Events	1 (0.2)	4.0	10 (0.9)	5.2
Ischaemic stroke	0	0	4 (0.3)	2.1
Retinal vein thrombosis	0	0	2 (0.2)	1.0
Coronary arterial stent insertion	0	0	1 (<0.1)	0.5
Deep vein thrombosis	0	0	1 (<0.1)	0.5
Pulmonary embolism	0	0	1 (<0.1)	0.5
Pulmonary microemboli	0	0	1 (<0.1)	0.5
Thrombophlebitis	1 (0.2)	4.0	1 (<0.1)	0.5

IR = incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PY = person-years.
[a] Coded using MedDRA, version 22.1.
[b] Patients are counted at most once per PT for multiple occurrences per treatment group.
[c] Incidence rate per 1000 PY was calculated as number of patients / SY X 1000 for specific PT subcategory.
Note: A total of 227 patients, who were treated with ozanimod 1 mg in RPC01-3101 Induction Period and were rerandomized to placebo in RPC01-3101 Maintenance Period, were included in the total count of the Placebo group.
Note: Patients may be included in both placebo and ozanimod 1 mg treatment groups.
Note: Pool G includes Studies RPC01-202, RPC01-3101, and RPC01-3102.
Source: ISS Table 27.3.G.

In Pool G, a total of 11 patients experienced 12 TE events, the majority (82%) of which had identified risk factors including hypertension, obesity, smoking history, prior DVT/ischemia, phlebitis, or cerebrovascular ischaemic attack and were predominantly >45 years of age.

The four events of ischaemic stroke occurred in patients exposed to ozanimod, the majority (75%) of which had documented risk factors; including tobacco use, hypertension (2 patients, 50%), and one patient (25%) had multiple risk factors including obesity, Type 2 diabetes, hypertension, tobacco use, and hyperlipidemia.

Table 2.7.3.1-8: Important Potential Risk: Thromboembolic Events

Important Potential Risk Thromboembolic Events

MS Studies

In MS controlled Phase 3 RRMS studies (Pool A1), the incidence of TE events were similar in ozanimod and IFN β-1a groups. The frequency of TE events in the pooled active controlled studies, as well as frequency of serious TE events in the RPC01-3001, OLE study, are shown in the table below.

Thromboembolic Events	**Pool A1 Number (%) of Patients**				**RPC01-3001 (OLE) Number (%) of Patients**
	IFN β-1a 30 µg (N = 885)	**Ozanimod 0.46 mg (N = 892)**	**Ozanimod 0.92 mg (N = 882)**	**Total Ozanimod (N = 1774)**	**Total Ozanimod (N = 2494)**
PT	n (%)	n (%)	n (%)	n (%)	n (%)
Thrombophlebitis	0	2 (0.2)	1 (0.1)	3 (0.2)	1 (<0.1)
Cerebral infarction	1 (0.1)	1 (0.1)	0	1 (<0.1)	0
Deep vein thrombosis	0	0	1 (0.1)	1 (<0.1)	0
Pulmonary embolism	0	0	1 (0.1)	1 (<0.1)	3 (0.1)
Post thrombotic syndrome	1 (0.1)	0	0	0	0
Acute myocardial infarction	1 (0.1)	0	0	0	0
Transient ischaemic attack	1 (0.1)	0	0	0	1 (<0.1)
Cerebrovascular accident	0	0	0	0	2 (<0.1)
Ischaemic stroke	0	0	0	0	2 (<0.1)
Cerebellar infarction	0	0	0	0	1 (<0.1)
Myocardial infarction	0	0	0	0	3 (0.1)

Note: Pool A1 events coded using MedDRA, version 18.1. RPC01-3001 events coded using MedDRA, version 25.1.

Source: RMS ISS Table 15.2 and Table 14.3.2.1 of the RPC01-3001 CSR.

A total of 5 patients with MS treated with ozanimod in MS controlled Phase 3 RRMS studies (Pool A1) experienced 6 TE events, the majority of which had identified risk factors including hypertension, thyroid disease, underlying prolonged hospitalization/ immobilization or varicose veins. One of the 5 patients had temporary interruption of study medication. The remaining events did not result in any change in treatment.

Seriousness/Outcome

Table 2.7.3.1-8: Important Potential Risk: Thromboembolic Events

Important Potential Risk Thromboembolic Events	
	In UC studies, (Pool G), 6 of the 12 TE events were SAEs including the 4 events of ischaemic stroke and the events of Pulmonary micro-emboli and Pulmonary embolism. All 6 SAEs were in the ozanimod treated group and all had an outcome of resolved. In MS Studies, (Pool A1), 2 of the 6 TE events on ozanimod treatment arm were SAEs (cerebral infarction and pulmonary embolism), both of which resolved. In RPC01-3001 (OLE), 2 events of TE (both pulmonary embolism) had a fatal outcome. **Severity and Nature of Risk** In UC studies, (Pool G), 6 of the 12 events were reported as severe (4 events of ischaemic stroke and events of pulmonary micro-emboli and pulmonary embolism). The severe events of ischaemic stroke led to discontinuation of ozanimod for 2 patients and ozanimod interruption for 1 patient. No action was taken for the fourth patient. The severe events of pulmonary micro-emboli and pulmonary embolism led to ozanimod interruption and drug withdrawal, respectively. The remaining events were non-serious, mild to moderate in severity and did not result in any change to study treatment, with exception of one mild event of retinal vein thrombosis for which treatment was interrupted. In MS studies (Pool A1), of the TE events reported in the ozanimod treatment group, the SAE of pulmonary embolism was severe in intensity and did not require any change to study drug. The same patient experienced a non-serious event of deep vein thrombosis, considered mild in intensity. The SAE of cerebral infarction occurred in a patient treated with ozanimod 0.5 mg, which was severe in intensity. Study drug was temporarily interrupted, and the patient subsequently withdrew consent from the study. The remaining events were non-serious, moderate in severity and did not require any change to study treatment. In RPC01-3001 OLE Study, the IR per 1000 PY of time were 0.24 for myocardial infarction, 0.24 for pulmonary embolism, and 0.16 for ischaemic stroke. These results are consistent with previously published estimates of the incidence of these outcomes based on the general MS patient population.
Risk factors and risk groups	Elderly age, prolonged hospitalisation/immobilisation, cancer, thyroid disease, oral contraceptive use, surgery, and pre-existing CVD including prior DVT/ischaemia, phlebitis or cerebrovascular ischaemic attack, and hypertension are risk factors for TE events. The risk of thromboembolism is also increased with inflammatory bowel disease. Lifestyle factors, including smoking, physical inactivity and increased weight are also associated with increased risk of TE events.
Preventability	Patients with cardiovascular risk factors, including MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation or NYHA Class III/IV heart failure are contraindicated for ozanimod treatment. Blood pressure should also be regularly monitored during treatment with ozanimod.
Impact on the risk-benefit balance of the product	The IR of TE events in patients treated with ozanimod 1 mg in the UC indication was similar to the IRs reported from the epidemiologic literature. In the MS indication, IR of TE was low and similar to rates reported in epidemiologic literature, and lower than the IFN arm which is not known to have a risk of TE events. Therefore, the overall impact on risk-benefit is considered low.
Public health impact	Thromboembolic events are often associated with significant morbidity and mortality.[127] In the general population, approximately 1 to 2 people per 1,000 are affected with a VTE per year, with a 10% to 30% mortality rate within 1 month. VTE is known to be associated with UC, with studies suggesting a two-fold risk in the IBD population.[128] This association is not seen in RRMS patients.

Table 2.7.3.1-8: Important Potential Risk: Thromboembolic Events

Important Potential Risk Thromboembolic Events	
MedDRA Terms	Relevant events from the narrow scope of Embolic and thrombotic events, arterial, and venous SMQs.

Table 2.7.3.1-9: Important Potential Risk: Risk of colorectal cancer (UC indication)

Important Potential Risk: Risk of colorectal cancer (UC indication)	
Potential mechanisms	Patients with UC are at increased risk of CRC and colonic neoplasia. It is unknown if ozanimod treatment could cause increased risk. S1P1 modulation results in decreased circulating lymphocytes due to their retention in lymphoid tissue; however, only some subsets of immune cells (some T and B cell subsets) are impacted. Immune cells such as monocytes, effector memory RA T cells, and natural killer cells are still present in the periphery following S1P1 modulation, and immunosurveillance may contribute to the low rate of malignancy noted.
Evidence source and strength of evidence	Colorectal cancer and events indicative of advanced colonic neoplasia (including colon adenomas and dysplasia) are identified by medical review of all TEAEs (PTs) in the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps) and the Gastrointestinal SOC, for the UC population (see MedDRA terms below). In Pool G, 3 cases of CRC were reported in the RPC01-3101 Maintenance Period, including 2 patients in the ozanimod 1 mg treatment group and in 1 patient re-randomised to the placebo treatment group during the Maintenance Period. Overall, in Pool G, colon adenoma was reported in 5 patients (including 4 patients on ozanimod treatment and 1 patient re-randomised to placebo in RPC01-3101 Maintenance Period). Colon dysplasia was reported in 1 patient on placebo.
Characterization of risk	In Pool G, CRC was reported in 3 patients, including 1 event of rectal adenocarcinoma noted at the RPC01-3101 End of Maintenance colonoscopy in a patient treated with ozanimod for 52 weeks, and 1 event of rectal cancer stage II, reported in a patient treated with ozanimod for 37 weeks in the OLE. This patient received placebo during the RPC01-3101 Induction and Maintenance Period. In the third case, adenocarcinoma of the colon was reported in a patient re-randomised to placebo in RPC01-3101 Maintenance Period; this patient had received ozanimod for 10 weeks during the Induction Period. The incidence of CRC in the ozanimod treatment groups is estimated at 0.2%. Overall, in Pool G, colorectal adenoma was reported in 5 patients (0.3%), including 4 patients in ozanimod treatment groups and 1patient on placebo for 42 weeks in the Maintenance Period (this patient had received ozanimod for 10 weeks during the Induction Period). Of the ozanimod treated patients, 1 had colon adenoma reported after 10 weeks (Day 71) in the Induction Period; the remaining 3 patients had received ozanimod treatment ranging from 49 to 71 weeks. One case of colon dysplasia was reported, in a patient treated with placebo, on Day 75 of the Induction Period. **Seriousness/Outcomes** All 3 cases of CRC were serious with outcomes reported as not recovered/not resolved. Two of the 5 cases of colon adenoma were serious. All 5 cases were reported as recovered.

Table 2.7.3.1-9: Important Potential Risk: Risk of colorectal cancer (UC indication)

Important Potential Risk: Risk of colorectal cancer (UC indication)	
	The case of colon dysplasia (placebo treatment) was reported as non-serious, severe in intensity, and not recovered. **Severity and Nature of Risk** All 3 cases of CRC were reported as severe in intensity, with 1 event (rectal cancer stage II) resulting in treatment discontinuation. No change in treatment was required for the event of rectal adenocarcinoma; the patient qualified for tumour resection and chemotherapy. Treatment was interrupted for the case of adenocarcinoma of the colon while the patient underwent a laparoscopic left hemi-colectomy. Maintenance treatment (placebo) was restarted, and the patient continued to enter the OLE, receiving 1 mg ozanimod. All 3 patients had risk factors described for development of CRC in UC patients including long disease duration and/or extensive disease and prior immunomodulator use. Baseline endoscopy also indicated that the malignancy may have already been present at baseline (from colonic and rectal masses in the area corresponding to the malignancy that were highly inflamed and difficult to visualise). The 2 serious events of colon adenoma were noted as moderate in intensity. One patient had multiple neoplasms of colon (hyperplastic polyp) noted after 58 weeks and underwent endoscopic polypectomy. No action was taken in relation to study drug. The other patient had a tubular adenoma of the sigmoid colon with intraepithelial neoplasm (low grade) noted at week 32 visit. Treatment was interrupted and restarted after 13 days, and the patient underwent endoscopic resection of the mucosa 1 month later. The remaining 3 events were all non-serious, mild in intensity and did not require any change study treatment.
Risk factors and risk groups	Patients with chronic inflammatory bowel conditions such as UC are at increased risk of CRC and advanced colonic neoplasia. Risk factors for CRC among UC patients include younger age at onset, extensive colitis, longer disease duration, concomitant primary sclerosing cholangitis,[129,130,131,132,62] family history of CRC, and persisting inflammation of the colon.[133] Patients with extensive colitis have a 3-fold increase in risk of CRC[61] and a 5-fold increase for those with long-standing extensive colitis.[59] Many cancers also develop as a result of a combination of genetics, environmental factors and lifestyle.[110] General risk factors known to cause cancer include advancing age and lifestyle (such as smoking, alcohol, certain infections, lack of physical activities, poor diet, obesity, excessive exposure to radiation, exposure to chemicals or hormone replacement).
Preventability	Routine surveillance and screening for CRC and neoplasia, particularly in patients with a personal or family history of malignancy would be expected to detect any conditions at an early or precancerous stage. Routine colorectal surveillance is recommended for adults aged 45 years or older who do not have signs or symptoms of CRC and who are at average risk for CRC (ie, no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease, or no personal diagnosis or family history of known genetic disorders that predispose them to a high lifetime risk of CRC [such as Lynch syndrome or familial adenomatous polyposis]).[134] Maintaining a healthy lifestyle such as stopping smoking, maintaining a healthy weight, reducing alcohol consumption and remaining active are considered to be preventative measures to reduce cancer risk.

Table 2.7.3.1-9: Important Potential Risk: Risk of colorectal cancer (UC indication)

Important Potential Risk: Risk of colorectal cancer (UC indication)	
Impact on the risk-benefit balance of the product	The cumulative probability of CRC in patients with UC has been estimated as 2% at 10 years, 8% at 20 years, and 18% at 30 years.[135] In the HealthCore Integrated Research Database, the age and gender adjusted IR per 1000 PY for colon cancer is 2.07 among patients with moderate to severe IBD.[136] In UC studies, the rates of CRC with ozanimod were low and observed to be within the background rates in individuals with UC not receiving ozanimod. There is limited impact on the benefit-risk balance for ozanimod.
Public health impact	CRC is a leading cause of morbidity and mortality worldwide. CRC is reported as the fourth most common cancer (accounting for approximately 8% of all new cancer cases) and the fourth leading cause of cancer-related deaths worldwide.[137] The 5-year survival rate of CRC is 65%.[138] There is an economic burden for CRC as a result of the treatment cost, loss of productivity and years of life lost due to premature death. There is also a long-term impact on the quality of life of patients who have survived cancer.
MedDRA Terms	Medical review of all reported AEs that indicate possible colon or rectal carcinomas, adenomas or dysplasia in the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps) and the Gastrointestinal SOC for the UC population.

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Missing Information	**Evidence Source**
Population in need of further characterisation:	
Long-term Cardiovascular Effects Patients treated long-term with ozanimod, including those with existing or risk factors for cardiovascular morbidity. The population studied in the clinical programme excluded patients with active cardiovascular conditions. In the postmarketing population of treated patients, there may be more associated risk factors.	It is not anticipated that the safety profile will be different over time. Existing data from the controlled Phase 3 programme and OLE studies in UC or MS has not shown an increased risk of cardiovascular morbidity in the long-term. The frequency of long-term cardiovascular events occurring in patients in the RPC01-3001, OLE study is shown in the table below. One event (cardiac failure) had a fatal outcome.

	RPC01-3001 (OLE) **Number (%) of Patients** **(N = 2494)**
PT	
Angina unstable	1 (<0.1)
Cardiac failure	1 (<0.1)
Coronary artery stenosis	1 (<0.1)
Myocardial infarction	3 (0.1)

Coded using MedDRA, version 25.1.

Source: Table 14.3.2.1 of the RPC01-3001 CSR

Table 2.7.3.2-1: Missing Information

Missing Information	Evidence Source
	In RPC01-3001 OLE Study, the IR per 1000 PY of time were 0.24 for myocardial infarction and 0.08 for cardiac failure. These results are consistent with previously published estimates of the incidence of these outcomes based on the general MS patient population.
Effects Following Withdrawal of Drug There has been a low rate of discontinuation in Phase 3 studies with ozanimod. Consequently, and in consideration of the long half-life of the active metabolite CC112273, information on the potential for rebound effects in relation to MS disease state recrudescence, full recovery from lymphopenia and carry over effects to subsequent MS therapy initiation merits further study in the postmarketing setting. Effects following drug withdrawal will also continue to be monitored in patients with UC in the long-term extension study RPC01-3102 and the Study IM0471037 (UC PASS).	The major active metabolite in humans, CC112273, has a long elimination half-life of approximately 11 days and although the Phase 3 studies routinely observed patients for at least 28 days after drug discontinuation, this may not have been sufficient to observe effects following withdrawal of ozanimod. The analysis of data from the completed long-term OLE Study (RPC01-3001) did not show the evidence of the rebound effect following discontinuation of ozanimod. A total of 55 subjects had a confirmed relapse after ozanimod discontinuation. The median time to onset of relapse was 61 days. The majority of relapses, as assessed by Investigator, were moderate in severity, and resulted in complete recovery in most of the cases. No relapses resulted in a severe and persistent increase in disability. Four (0.2%) subjects, experienced AEs of lymphocyte count decreased that led to discontinuation. <u>UC studies</u> Of the patients for whom data were available in Pool G, 78 of 488 patients (16.0%) in the ozanimod 0.92 mg treatment group and 5 of 48 patients (10.4%) in the placebo treatment group had a TEAE with an onset after the last dose of study drug. The higher frequency of TEAEs in the ozanimod group can be attributed to differences in observation periods between groups, since most patients who completed or terminated placebo then entered an open-label study. No events indicative of withdrawal effects were observed in UC clinical studies. <u>MS studies</u> The protocols allowed for patients to be followed for AEs of special interest regardless of the duration following study drug discontinuation. Thus, in Pool A1, a total of 123 patients were followed for at least 28 days after their last dose of study drug. In the OLE study (RPC01-3001), 1973 subjects were followed for up to 90 days after their last dose of ozanimod. A total of 157 (8%) subjects had a least one TEAE reported, with the most common event being COVID-19 (0.8%), nasopharyngitis (0.5%), upper respiratory tract infection (0.4%) and respiratory tract infection viral (0.2%). No events were reported that are not consistent with the known safety profile of ozanimod. There was no signal observed in clinical trials of ozanimod following treatment discontinuation of adverse effects or rebound MS disease. The totality of the data analysed across all data cut-off dates throughout the ozanimod development programs demonstrated no pattern of AEs following drug discontinuation that would suggest withdrawal or rebound effects. There were no exacerbations or new occurrences of depression or increased suicidality, or worsening anxiety or sleepiness after discontinuation of ozanimod treatment.
Use in Patients Over 55 Years	The UC studies included patients aged up to 75 years. There were no signals of increased risk or increased severity of S1P effects (eg, blood

Table 2.7.3.2-1: Missing Information

Missing Information	Evidence Source
Patients over 55 years old, including those who reach this age during ongoing trials and those exposed during marketed use.	pressure, liver enzymes) in the elderly. The rate of these effects in elderly patients was similar to that in patients aged < 65 years. There was no signal of a higher frequency or severity of effects compared to the placebo group in elderly patients than seen in their younger counterparts. Fifty-five patients aged ≥ 65 years were treated with ozanimod 0.92 mg, and 28 of these patients (50.9%) were exposed for at least 12 months. Due to the small sample size of the subgroup ≥ 65 years in the UC studies, no conclusions can be drawn regarding the difference in the overall incidence of TEAEs between patients < 65 years and ≥ 65 years in Pool G. Patients over 55 years old were not included in the MS controlled Phase 3 RRMS studies. In the RPC01-3001, OLE study, 250 patients were over the age of 55 years old at the time of reported AE onset. Overall, the frequency of any TEAE, including serious TEAEs, was similar in patients over 55 years (any TEAE 71.2%, serious TEAE 16%) and in the overall RPC01-3001 population (any TEAE 89%, serious TEAE 15.3%). Population PK analysis showed that CC112273 steady-state exposure in patients over 65 years of age with UC were approximately 3% to 4% greater than patients 45 to 65 years of age and 27% greater than adult patients under 45 years of age. This is not considered a meaningful difference in the PK in elderly patients.

2.8 Summary of the Safety Concerns

Safety concerns are summarized in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	Serious opportunistic infections including PML
	Macular oedema
Important potential risks	Symptomatic bradycardia
	Severe liver injury
	Malignancy
	PRES
	Embryofoetal toxicity in exposed pregnant females
	Thromboembolic events
	Risk of colorectal cancer (UC indication)
Missing information	Long-term cardiovascular effects
	Effects following withdrawal of drug
	Use in patients over 55 years

3 PART III: PHARMACOVIGILANCE PLAN

Routine Pharmacovigilance activities, as described in the Pharmacovigilance System Master File and Drug Safety's Standard Operating Procedures are in accordance with "Good Pharmacovigilance Practices in the European Union." The Routine Pharmacovigilance System is detailed in the current version of the Pharmacovigilance System Master File.

In addition to expedited reporting, the MAH vigilantly undertakes follow-up on all AEs, including serious AEs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the AEs.

Emerging potential safety signals can be detected by periodic and if appropriate, cumulative evaluation of the AEs. The results will be compiled in the PSUR, in accordance with Guidelines on GVP in the EU/EEA.

In addition, data regarding identified and potential risks will be presented in the PSUR. The data presentation will include all case reports collected during the period covered by the PSUR together with cumulative data.

Using the data obtained from this plan, the benefit/risk profile of ozanimod will be re-evaluated on a periodic basis via the PSUR. If necessary, the related sections of the RMP will be updated accordingly.

3.1 Routine Pharmacovigilance Activities

Proposed ADR follow-up forms for pregnancy and PML are included in Annex 4. In addition, potential PML cases will be reviewed by external experts. The results will be provided periodically with the PSURs. Reports of NMSC, cases of thromboembolic events and cases of rebound effects (by indication) will be presented in each PSUR.

3.2 Additional Pharmacovigilance Activities

The MAH plans to conduct an observational cohort PASS in patients with UC (Study IM0471037) to evaluate the long-term real-world safety of ozanimod following treatment with ozanimod in this population (Table 3.2-1, see Annex 3 for the hyperlink to the UC PASS protocol).

Long-term safety of ozanimod in patients with UC will be assessed in Study RPC01-3102 (Table 3.2-1, see Annex 3 for the hyperlink to the RPC01-3102 protocol).

A multi-national MS PASS is ongoing, to utilise data from several existing relevant databases and registries in the EU and the US (Study IM047-009, ORION; Ozanimod Real-World Safety - A Post-Authorisation Multi-National Long-Term Non-Interventional Study) to assess the long-term safety profile of ozanimod in MS (Table 3.2-1; see Annex 3 for the hyperlink to the ORION study protocol).

Table 3.2-1: Post-Authorization Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
Study IM0471037 (UC PASS)	To evaluate the long-term real-world safety of ozanimod, and specifically to further characterise the safety concerns following treatment with ozanimod in patients with UC.	Observational cohort study of patients with UC treated for the first time with ozanimod or alternative treatments.	Patients treated in the postmarketing real-world setting in accordance with the SmPC.	Protocol submission Study start Interim study reports Final study report Status updates	May-2022 TBD TBD TBD Status updates will be provided with PSURs
Study RPC01-3102: a multicentre, open label extension trial of oral RPC1063 in patients with moderately to severely active UC.	To characterise the long-term safety of ozanimod in patients with moderately to severely active UC.	This study is an ongoing OLE of the following studies: RPC01-202 or RPC01-3101.[a]	Male or female patients with moderately to severely active UC who completed one of the following parent studies: RPC01-202 or RPC01-3101	LPLV Final study report expected Status updates	Mar-2025 Aug-2025 Status updates will be provided with PSURs
Study IM047-009: ORION; Ozanimod Real-World Safety - A Post-Authorisation Multi-National Long-Term Non-Interventional Study	To evaluate the long-term safety profile of ozanimod in the real-world setting.	A multi-national observational PASS of patients with MS treated with ZEPOSIA® or alternative treatments.	Patients treated in the postmarketing real-world setting in accordance with the SmPC.	Study to start Protocol submission Interim study reports Final study report Status updates	Study to start after the EC Decision. Dec-2020 Interim study reports at 3 years (Q42024) and 5 years (Q4-2026) Q4-2033 Status updates will be provided with PSURs

[a] Only those patients who have previously participated in a trial of RPC1063 (eg, RPC01-3101 or completed at least 1 year of the open-label period of RPC01-202) and meet eligibility criteria will be eligible for entry in this trial.

3.3 Summary Table of Additional Pharmacovigilance Activities

Ongoing and planned studies/activities in the postauthorisation pharmacovigilance development plan are summarised in Table 3.3-1.

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
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				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
UC Indication				
Study IM0471037 (UC PASS)/ Planned	To evaluate the long-term safety of ozanimod in patients with UC in the real-world setting.	Serious opportunistic infections including PML, macular oedema, symptomatic bradycardia, severe liver injury, malignancy, PRES, thromboembolic events, risk of colorectal cancer (UC indication), long-term cardiovascular effects, effects following withdrawal of drug, use in patients over 55 years old.	Protocol submission Study start Interim study reports Final study report Status updates	May-2022 TBD TBD TBD Status updates will be provided with PSURs
Study RPC01-3102 / Ongoing	To characterise the long-term safety of ozanimod in patients with moderately to severely active UC.	Macular oedema, severe liver injury, malignancy, PRES, embryofoetal toxicity in exposed pregnant females, thromboembolic events, risk of colorectal cancer (UC indication), long-term cardiovascular effects, effects following withdrawal of drug, use in patients over 55 years old.	LPLV Final study report expected Status updates	Mar-2025 Aug-2025 With PSURs
MS Indication				
Study IM047-009: (ORION) / Ongoing	To evaluate the long-term safety profile of ozanimod in the real-world setting.	Serious opportunistic infections including PML, macular oedema, symptomatic bradycardia, severe liver injury, malignancy, PRES, thromboembolic	Study to start Protocol submission	Study to start after the EC Decision. Dec-2020

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
		events, long-term cardiovascular effects, use in patients over 55 years old.	Interim study reports	Interim study reports at 3 years (Q42024) and 5 years (Q4-2026)
			Final study report	Q4-2033
			Status updates	Status updates will be provided with PSURs

4 PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorisation efficacy studies for ozanimod.

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

5.1 Routine Risk Minimisation Measures

Routine risk minimisation measures are summarised in Table 5.1-1.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Serious opportunistic infections including PML	**Routine risk communication:** SmPC Sections 4.3, 4.4, and 4.8. PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Ozanimod is contraindicated in patients with severe active infections, active chronic infections such as hepatitis and tuberculosis (SmPC Section 4.3). Recommendation to discontinue ozanimod if PML is confirmed is included in SmPC Section 4.4. 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 risk of infection, clinical symptoms or MRI findings that physicians should be vigilant for signs suggestive of PML, and treatment instructions in cases suggestive of PML are provided in SmPC Section 4.4. Patients are advised not to take ozanimod if they have severe infection and to consult their doctor if they develop infections (PL Section 2). Patients are advised to consult their doctor or pharmacist before taking ozanimod if they notice symptoms that may be due to PML, in PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Ozanimod is subject to restricted medical prescription.
Macular oedema	**Routine risk communication:** SmPC Sections 4.4 and 4.8. PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Recommendation to discontinue ozanimod if macular oedema is confirmed is included in SmPC Section 4.4. Recommendations for treatment of patients with risk factors for macular oedema are described in SmPC Section 4.4.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Patients are advised to consult their doctor or pharmacist before taking ozanimod if they have ever had problems with their vision or other symptoms of build-up of fluid in the macula in PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Ozanimod is subject to restricted medical prescription.
Important Potential Risks	
Symptomatic bradycardia	**Routine risk communication:** SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1. PL Sections 2, 3 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Ozanimod is contraindicated in patients who in the last 6 months experienced MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation or NYHA Class III/IV heart failure, patients with history or presence of seconddegree AV block Type II or thirddegree AV block or sick sinus syndrome unless the patient has a functioning pacemaker (SmPC Section 4.3). 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. Application of a dose escalation regimen to attenuate the magnitude of HR reduction is included in SmPC Sections 4.4 and 5.1 and PL Section 3. Patients are advised not to take ozanimod if they have some types of arrythmia in PL Section 2. Warning regarding use in patients with low HR, or receiving treatment that reduces HR, is included in PL Section 2. Recommendation that cardiologist advice should be obtained before initiation of ozanimod in certain patients (including those with a history of symptomatic bradycardia) to decide if ozanimod can safely be initiated and to determine the most appropriate monitoring strategy (SmPC Section 4.4). Due to the risk of transient decreases in HR with the initiation of ozanimod, first-dose, 6-hour monitoring for signs and symptoms of symptomatic bradycardia is recommended in patients with resting HR < 55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (see section 4.3 of the SmPC). **Other routine risk minimisation measures beyond the Product Information:** An initiation pack covering dosing for the first 7 days will be used to facilitate compliance with the recommended dose initiation schedule: Days 1 to 4: ozanimod 0.23 mg, Days 5 to 7: ozanimod 0.46 mg, prior to maintenance from Day 8 at 0.92 mg. The initiation pack covers not only dosing for the first 7 days, but also for resuming treatment following treatment interruption.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Legal status: Ozanimod is subject to restricted medical prescription.
Severe liver injury	**Routine risk communication:** SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2. PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Ozanimod is contraindicated in patients with severe hepatic impairment (Child-Pugh class C; SmPC Section 4.3). Patients with mild or moderate chronic hepatic impairment (Child-Pugh Class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day (SmPC Sections 4.2 and 5.2). Recommendations for liver function monitoring, including measurement of transaminase and bilirubin levels before treatment initiation, are included in SmPC Section 4.4. Statement that ozanimod should be discontinued if significant liver injury is confirmed included in SmPC Section 4.4. Patients are advised not to take ozanimod if they have severe liver problems in PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Ozanimod is subject to restricted medical prescription.
Malignancy	**Routine risk communication:** SmPC Sections 4.3 and 4.4. PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Ozanimod is contraindicated in patients with active malignancies (SmPC Section 4.3). Advice regarding monitoring of patients with concurrent conditions or known factors, such as previous antineoplastic non-corticosteroid 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). Patients are advised not to take ozanimod if they have cancer in PL Section 2. Patients are advised to limit sun light exposure and UV light, by wearing protective clothing and applying regular sunscreen (with high sun protection factor) (PL Section 2). **Other routine risk minimisation measures beyond the Product Information:** None proposed.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Legal status: Ozanimod is subject to restricted medical prescription.
PRES	**Routine risk communication:** SmPC Section 4.4. PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation to discontinue ozanimod if PRES is suspected is included in SmPC Section 4.4. Patients are advised to talk to their doctor if they develop possible symptoms of PRES in PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Ozanimod is subject to restricted medical prescription.
Embryofoetal toxicity in exposed pregnant females	**Routine risk communication:** SmPC Sections 4.3, 4.4, 4.6 and 5.3. PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** 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 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). Recommendation to discontinue ozanimod if a woman becomes pregnant during treatment is included in 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. Patients should inform their doctors if they become pregnant and receive specialised pre-natal monitoring (PL Section 2). **Legal status:** Ozanimod is subject to restricted medical prescription.
Thromboembolic events	**Routine risk communication:** SmPC Sections 4.3, 4.4, and 4.8. PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Use of ozanimod is contraindicated in patients who in the previous 6 months had a

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	MI, unstable angina pectoris, stroke/TIA, decompensated heart failure (requiring inpatient treatment), or NYHA Class III/IV heart failure (SmPC Section 4.3). Blood pressure should be regularly monitored during treatment with ozanimod (SmPC Section 4.4). **Legal status:** Ozanimod is subject to restricted medical prescription.
Risk of colorectal cancer (UC indication)	**Routine risk communication:** SmPC Sections 4.3 and 4.4. PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Ozanimod is contraindicated in patients with active malignancies (SmPC Section 4.3). Advice regarding monitoring of patients with concurrent conditions or known factors, such as previous antineoplastic non-corticosteroid immunosuppressive therapy, is included in SmPC Section 4.4. Patients are advised not to take ozanimod if they have cancer in PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Ozanimod is subject to restricted medical prescription.
Missing Information	
Long-term cardiovascular effects	**Routine risk communication:** None proposed. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Ozanimod is subject to restricted medical prescription.
Effects following withdrawal of drug	**Routine risk communication:** SmPC Section 4.4. PL Sections 2 and 3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** 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 after ozanimod discontinuation is included in SmPC Section 4.4. Patients are advised to talk to their doctor if they have worsening disease after withdrawal of ozanimod in PL Sections 2 and 3. **Other routine risk minimisation measures beyond the Product Information:** None proposed.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Legal status: Ozanimod is subject to restricted medical prescription.
Use in patients over 55 years	**Routine risk communication:** SmPC Sections 4.2 and 5.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Ozanimod is subject to restricted medical prescription.

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are provided in Table 5.2-1 (Healthcare Professional Checklist, Patient/Caregiver's Guide, and Pregnancy-specific Patient Reminder Card) and summarised in Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

Healthcare Professional Checklist	**Objectives:** Ozanimod healthcare professional checklist to be provided to prescribing healthcare professionals for the Important Identified Risks of serious opportunistic infections including PML, and of macular oedema and Important Potential Risks of symptomatic bradycardia, severe liver injury, malignancy, and embryofoetal toxicity in exposed pregnant females. **Rationale for the additional risk minimisation activity:** Healthcare professionals to understand the occurrence of the risks specified above and the appropriate management of these risks. **Target audience and planned distribution path:** The target audience is healthcare professionals who intend to prescribe ozanimod. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Expedited reporting (E+R) as per EU guidance, GVP PSUR as per EU guidance, GVP (E+R) [E = Evaluation; R = Reporting] Methods of Assessment – Cases received pertaining to these risks to be reviewed on an ongoing basis and summarised at the time of the PSUR. – Assessment through PASSes. – Modifications and corrective action will be taken accordingly. Criteria for Success:

Table 5.2-1: Additional Risk Minimisation Measures

	Outcome Indicator: Frequency and severity of AEs pertaining to these risks, including outcomes. No increase in frequency of severe/serious events pertaining to above mentioned risks. Planned Dates for Assessment: Next PSUR update with next data lock point covered.
Patient/Caregiver's Guide	**Objectives:** Patient/caregiver's guide to be provided to patients or caregivers for the Important Identified Risks of serious opportunistic infections including PML, and of macular oedema, and Important Potential Risks of symptomatic bradycardia, severe liver injury, malignancy, and embryofoetal toxicity in exposed pregnant females. **Rationale for the additional risk minimisation activity:** Patients and caregivers to understand the occurrence of the risks specified above and the appropriate management of these risks. **Target audience and planned distribution path:** The target population is patients who are prescribed ozanimod or caregivers. The planned distribution path is via the Healthcare Professional as agreed upon by the NCA. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Expedited reporting (E+R) as per EU guidance, GVP PSUR as per EU guidance, GVP (E+R) [E = Evaluation; R = Reporting] Methods of Assessment – Cases received pertaining to these risks to be reviewed on an ongoing basis and summarised at the time of the PSUR. – Assessment through PASSes. Modifications and corrective action will be taken accordingly. Criteria for Success: Outcome Indicator: Frequency and severity of AEs pertaining to these risks, including outcomes. No increase in frequency of severe/serious events pertaining to above mentioned risks. Planned Dates for Assessment Next PSUR update with next data lock point covered.
Pregnancy specific Patient Reminder Card	**Objectives:** Provision of information to patients for the risk of embryofoetal toxicity in exposed pregnant females. **Rationale for the additional risk minimisation activity:** Patients to understand the occurrence of embryofoetal toxicity in exposed pregnant females and the appropriate management of this risk. **Target audience and planned distribution path:** The target population is patients who are prescribed ozanimod and the planned distribution path is the provision of a pregnancy-specific patient reminder card as agreed upon by the NCA. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Expedited reporting (E+R) as per EU guidance, GVP PSUR as per EU guidance, GVP (E+R) [E = Evaluation; R = Reporting] Methods of Assessment

Table 5.2-1:	Additional Risk Minimisation Measures
	– Pregnancy reports to be reviewed on an ongoing basis. Pregnancies to be summarised at the time of the PSUR. – Assessment through PASSes. Modifications and corrective action will be taken accordingly. Criteria for Success: Outcome Indicator: Frequency and severity of adverse pregnancy outcomes. No increase in frequency of adverse pregnancy outcomes. Planned Dates for Assessment: Next PSUR update with next data lock point covered.

5.3 Summary of Risk Minimisation Measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
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 to discontinue ozanimod if PML is confirmed is included in SmPC Section 4.4. 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 risk of infection, clinical symptoms or MRI findings that physicians should be vigilant for signs 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ADR follow-up form for PML (see Annex 4). External expert review of potential PML cases.

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: – Healthcare Professional checklist – Patient/caregiver's guide	**Additional pharmacovigilance activities:** Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients)
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 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:** Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients)
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:** Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients)

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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 (Child Pugh Class C) (SmPC Section 4.3, PL Section 2). Patients with mild or moderate chronic hepatic impairment (Child Pugh Class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day in SmPC Sections 4.2 and 5.2. 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. **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:** Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients)
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 antineoplastic non-corticosteroid 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). **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Reports of NMSC will be discussed in the PSUR **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients)

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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:** Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients)
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 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ADR follow-up form for pregnancy (see Annex 4). **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients)

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Thrombo-embolic events	**Routine risk minimisation measures:** Use of ozanimod is contraindicated in patients who in the previous 6 months had a MI, unstable angina pectoris, stroke/TIA, decompensated heart failure (requiring inpatient treatment), or NYHA Class III/IV heart failure (SmPC Section 4.3). Blood pressure should be regularly monitored during treatment with ozanimod (SmPC Section 4.4). PL Section 2 **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Thromboembolic events will be presented in each PSUR **Additional pharmacovigilance activities:** Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients)
Risk of colorectal cancer (UC indication)	**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 antineoplastic non-corticosteroid immunosuppressive therapy, 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:** Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS)
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:** Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients)
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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Cases of rebound effects will be presented in each PSUR (by indication) **Additional pharmacovigilance activities:**

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	and treatment is included in SmPC Section 4.4 and PL Sections 2 and 3. Advice to monitor patients for infections after ozanimod discontinuation is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS)
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:** Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients).

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Zeposia

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

Zeposia's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zeposia should be used.

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

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

I. The medicine and what it is used for

Zeposia is authorised for the treatment of adult patients with relapsing remitting multiple sclerosis (MS) with active disease, and for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent (see SmPC for the full indication). It contains ozanimod as the active substance and it is given by oral route of administration.

Further information about the evaluation of Zeposia's benefits can be found in Zeposia's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/zeposia

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

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

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

II.A List of important risks and missing information

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

List of important risks and missing information

Important identified risks	Serious infection in patients with weakened immune systems (serious opportunistic infections including progressive multifocal leukoencephalopathy [PML])
	Swelling of a part of the retina (macular oedema)
Important potential risks	Symptomatic slow heart rate (HR; symptomatic bradycardia)
	Severe liver injury
	Cancer (malignancy)
	Syndrome characterised by headache, confusion, seizures and visual loss (posterior reversible encephalopathy syndrome [PRES])
	Toxicity to unborn child in women who have received treatment with ozanimod (embryofoetal toxicity in exposed pregnant females)
	Blood clots (thromboembolic events)
	Risk of colorectal cancer (UC indication)
Missing information	Heart problems that develop following long-term treatment with ozanimod (long-term cardiovascular effects)
	Effects following withdrawal of drug
	Use in patients over 55 years

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk

Serious Infections in Patients with Weakened Immune Systems (Serious Opportunistic Infections Including PML)	
Evidence for linking the risk to the medicine	A case of PML (a rare infection of the brain) has been observed with ozanimod treatment in the MS clinical trial RPC01-3001 open-label extension (OLE) study.
Risk factors and risk groups	Patients with prolonged and profound lymphopaenia (reduced white blood cells) may be at increased risk of developing severe opportunistic infection, including PML, and also those who have received previous natalizumab treatment, although the risks appear to be very low.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, and 4.8. Package Leaflet (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). Recommendation to discontinue ozanimod if PML is confirmed is included in SmPC Section 4.4. 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 risk of infection, clinical symptoms or magnetic resonance imaging findings that physicians should be vigilant for signs 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. Patients are advised not to take ozanimod if they have severe infection and to consult their doctor if they develop infections (PL Section 2). Patients are advised to consult their doctor or pharmacist before taking ozanimod if they notice symptoms that may be due to PML, in PL Section 2. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.
Additional pharmacovigilance activities	Study IM0471037 (UC PASS) Study IM047-009 (ORION study MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.
Swelling of a part of the retina (macular oedema)	
Evidence for linking the risk to the medicine	An external review panel identified 3 cases of macular oedema with ozanimod 0.92 mg in the UC studies RPC01-202 and RPC01-3101 and 1 case of cystoid macular oedema with ozanimod 0.92 mg in the UC OLE study (Study RPC01-3102). All 4 cases of confirmed macular oedema were identified with optical coherence tomography 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. No trend in central foveal thickness changes was noted over time. All 4 cases of macular oedema resolved. In the MS studies, for Pool A1 there were three confirmed cases in the ozanimod 0.46 mg group, one confirmed case in the ozanimod 0.92 mg group

Important identified risk

	and none in the IFN β-1a treatment group. In Pool B, there were three additional confirmed cases in the extension study RPC01-3001 (ozanimod 0.92 mg). Upon completion of the OLE study (RPC01-3001), two more confirmed cases of macular oedema were reported to a total of 5 cases. Following adjudication by a panel of ophthalmology experts including two neuro-ophthalmologists and a retinal specialist, 7 out of 9 cases were confounded by pre-existing risk factors including a history of macular oedema, uveitis, laser surgery, macular pucker, other ocular inflammation, or trauma. No clear time to onset pattern was identified. In 2 cases, drug was continued. In the remaining 7 cases, upon drug discontinuation, 6 cases showed full recovery and the case with trauma was stable. <u>Post Marketing Experience</u> As of 01-Apr-2023, since marketing approval 13 cases of macular oedema were reported from sources other than Company-sponsored clinical trials. At least in 4 cases, time to event onset was within 90 days from the start of ozanimod. In half of these cases there was a presence of known risk factors, such as uveitis, diabetes mellitus and cataract surgery. While most reports had limited information, in 3 cases the diagnosis by an ophthalmologist was reported. In one case, the patient with a history of hyperglycemia presented with blurry vision and was diagnosed with bilateral macular oedema after 7 months on ozanimod for UC.
Risk factors and risk groups	Patients with risk factors for macular oedema such as a history of uveitis or diabetes mellitus.
Risk minimisation measures	**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 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
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients). Study IM0471037 (UC PASS). Study IM047-009 (ORION study MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risks

Symptomatic Slow Heart Rate (Symptomatic Bradycardia)	
Evidence for linking the risk to the medicine	Initiation of ozanimod may result in transient reductions in HR. A dose escalation schedule (0.23 mg ozanimod followed by 0.46 mg and 0.92 mg) attenuates the magnitude of HR reductions. Initiation of ozanimod without dose escalation may result in greater reductions in HR. Two isolated cases of HR < 40 bpm (1 MS, 1 UC) were reported, both of which were detected by continuous cardiac monitoring overnight, and neither of which was associated with an adverse event (AE) or required treatment. In UC clinical studies Induction Period, which implemented dose escalation (Pool F), there was a modest (0.7 bpm) maximum mean reduction from baseline in HR during the first 6 hours post-dose on Day 1. This reduction was not associated with clinically significant bradycardia or conduction effects (eg, second-degree type 2 or third-degree atrioventricular block). No symptomatic bradycardia occurred during controlled studies. During hourly cardiac monitoring, one patient in an open-label cohort with a pre-dose HR of 56 bpm experienced headache, nausea and light-headedness after the first dose of ozanimod. The lowest reported HR was 43 bpm at Hour 2, which recovered to above baseline by Hour 5. No treatment or extended monitoring was required. As discussed above, two isolated cases of HR < 40 bpm (1 MS, 1 UC) were reported. One patient in Study RPC01-202, experienced HR ≤ 40 bpm. The patient's HR during the first 6 hours after dosing on Day 1 (approximately 9 am to 3 pm) was ≥ 64 bpm, and the patient experienced the minimal HR of 38 bpm at 2 am. Over 24-hour Holter monitoring, maximum HR was 133 bpm and mean HR was 80 bpm. This event was not associated with an AE and did not require treatment. In active-controlled MS clinical trials, after the initial dose of ozanimod 0.23 mg, the greatest mean reduction from baseline in HR of 1.2 bpm occurred at Hour 5 on Day 1, returning towards baseline at Hour 6. With the use of a dose escalation regimen over the first 7 days of treatment initiation, there has only been one case of confirmed symptomatic bradycardia observed in active-controlled Phase 3 MS studies (Pool A1). This patient, with a pre-treatment HR of 48 bpm experienced mild dizziness at Hour 6 on Day 1, in the presence of a HR of 47 bpm. The dizziness resolved after a single dose of atropine although HR remained at 44 bpm. It is likely that pre-existing dysautonomia contributed to the patient's bradycardia and blunted the HR response to atropine. The patient continued ozanimod treatment uneventfully. In Pool B, one further event of nonserious symptomatic bradycardia was reported in one patient commencing 0.23 mg ozanimod. The patient experienced dizziness and sleepiness, with a lowest HR of 46 bpm at Hour 4. The event did not lead to dose modification or discontinuation. One patient in Study RPC01-201A, had a HR of 39 bpm at Hour 20 post-dose on Day 8, which returned to normal (60 bpm) at Hours 23 and 24 the same day. This occurrence was not associated with an AE and did not require treatment. In the RPC01-3001, OLE study, two additional events of nonserious symptomatic bradycardia were reported in two patients. Both events resolved without intervention and did not lead to dose modification or discontinuation.
Risk factors and risk groups	Symptomatic bradycardia is a rare occurrence and has not been of clinical consequence. The administration of ozanimod in patients on both a beta blocker and a calcium channel blocker has not been studied. Any reports of symptoms in

Important potential risks

	patients receiving these drugs concurrently in clinical practice will be analysed.
Risk minimisation measures	**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.
Additional pharmacovigilance activities	Study IM0471037 (UC PASS). Study IM047-009 (ORION study MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.
Severe Liver Injury	
Evidence for linking the risk to the medicine	Severe drug-induced liver injury (DILI) is considered to be of public health concern. Majority of the liver-related events in the ozanimod clinical studies (predominately alanine aminotransferase [ALT] and gamma glutamyltransferase elevations) were mild to moderate in intensity and resolved while continuing treatment. Section 4.4 of the SmPC states that elevations of aminotransferases may occur in patients receiving ozanimod and advises that recent (ie, within last 6 months) transaminase and bilirubin levels should be available before treatment initiation. During the Induction Period for UC study RPC01-3101, elevations of ALT above 5-fold the upper limit of normal (ULN) occurred in 0.9% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo. Elevations of ALT above 3-fold the ULN occurred in 2.6% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo. In the Study RPC01-3101 Maintenance Period, 0.9% of patients treated with ozanimod 0.92 mg and no patients who received placebo had elevations 5-fold the ULN or greater. Elevations of 3-fold the ULN occurred in 2.3% of patients treated with ozanimod 0.92 mg and none who received placebo. In the UC studies (Pool G), elevations in ALT > 3 × ULN were observed in 6.0% of patients treated with ozanimod 0.92 mg and 0.2% of patients who received placebo. Of the ozanimod-treated patients, the majority (approximately 96% on ozanimod 0.92 mg) continued treatment with ozanimod, with values returning to ≤ 3 × ULN within approximately 2 to

Important potential risks

	4 weeks. The majority of ALT elevations were isolated cases, as evidenced by the low incidence of consecutive elevations > 3 × ULN (2.0% of patients treated with ozanimod 0.92 mg in Pool G) or > 5 × ULN (0.3% in Pool G). Similarly, the incidence of total bilirubin elevations > 2 × ULN was 1.1% in Pool G. Two patients in Pool G, had treatment-emergent adverse events (TEAEs) reported by the Investigator as DILI. Both patients had mild (≥ 2 × ULN) nonserious, but persistent ALT elevations (after starting ozanimod treatment in OLE Study RPC01-3102), with ALT returning to near normal values (< 1.5 × ULN) with continued ozanimod treatment. The TEAEs were not associated with any symptoms or other laboratory changes and did not require any treatment. One patient was discontinued from Study RPC01-3102 due to persistent ALT elevation; the second patient continued in the OLE study. Overall, in UC clinical studies, the discontinuation rate due to elevations in hepatic enzymes was 0.4% of patients with UC treated with ozanimod in both Induction and Maintenance Periods, and none in patients who received placebo in either period. In active-controlled MS clinical trials, elevations of ALT to 5-fold the ULN or greater occurred in 1.6% of patients treated with ozanimod 0.92 mg and 1.3% of patients on interferon (IFN) β-1a. Elevations of 3-fold the ULN or greater occurred in 5.5% of patients treated with ozanimod 0.92 mg and 3.1% of patients on IFN β-1a. When elevations in hepatic tests occurred, they were generally asymptomatic. The median time to elevation 3-fold the ULN was 6 months. The majority (79%) continued treatment with ozanimod with values returning to < 3-fold the ULN within approximately 2 to 4 weeks. In active-controlled MS clinical trials, ozanimod was discontinued for a confirmed elevation greater than 5-fold the ULN. Overall, the discontinuation rate due to elevations in hepatic enzymes was 1.1% of patients on ozanimod 0.92 mg and 0.8% of patients on IFN β-1a. Although there have been instances (5/1774 [0.28%] patients in Pool A1) where observations of ALT or aspartate aminotransferase (AST) were ≥ 3-fold the ULN together with bilirubin > 2-fold the ULN in clinical trials, no cases of severe DILI (confirmed Hy's Law cases) were observed with ozanimod. In the RPC01-3001, OLE study elevations of ALT > 3-fold the ULN occurred in 3.7% of patients, and elevations > 5-fold the ULN in 0.8% of patients treated with ozanimod. About 25% of ALT elevations > 3-fold the ULN were within the first year, and about 50% of ALT elevations > 3-fold the ULN occurred after 24 months on the study. The incidence of ALT elevation > 3 fold the ULN on consecutive post-baseline assessment was 22 (0.9%), and ALT > 5 fold the ULN was 6 (0.2%). Eleven patients in the entire ozanimod clinical development program (Pool D) had concurrent elevations of ALT or AST ≥ 3 × ULN and bilirubin > 2 × ULN. Review of unblinded cases by an external panel of expert hepatologists concluded that there were no cases that met Hy's Law due to alternate explanations and the pattern of abnormalities.
Risk factors and risk groups	Patients with pre-existing liver disease may be at increased risk of developing elevated hepatic enzymes when taking ozanimod. However, it is not known whether these patients are at increased risk of severe liver injury.

Important potential risks

Risk minimisation measures	**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). Patients with mild or moderate chronic hepatic impairment (Child-Pugh Class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day in SmPC Sections 4.2 and 5.2. 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. **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients). Study IM0471037 (UC PASS). Study IM047-009 (ORION study MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.
Important Potential Risk: Cancer (Malignancy)	
Evidence for linking the risk to the medicine	Malignancies are identified by medical review of all TEAEs (preferred terms [PTs]) in the System Organ Class (SOC) Neoplasms benign, malignant and unspecified (incl. cysts and polyps) for the UC population. Events of colorectal carcinoma and high-grade dysplasia are also specifically monitored in the UC population. In total, 14 malignancies were observed in the UC studies: 6 NMSCs and 8 other malignancies. In UC studies (Pool G), malignancies were reported in 1.0% of patients in the ozanimod 0.92 mg treatment group and 0.4% in the placebo group. Both of the patients in the placebo group had received ozanimod during the Induction Period prior to being randomised to placebo maintenance. No malignancies were observed for patients exclusively exposed to placebo. Similar to MS, the overall incidence of malignancies with ozanimod is generally in line with rates reported in the literature in the UC population and the general population in the same age range. In the MS studies, for Pool A1 there were 4 treatment-emergent malignancies (excluding NMSCs) for ozanimod (0.46 and 0.92 mg doses) and 4 NMSCs versus 1 and 1 for IFN, respectively. In Pool B, there were 12 treatment-emergent malignancies (excluding NMSCs) for ozanimod (0.46 and 0.92 mg doses) and 9 NMSCs versus 1 and 1 for IFN, respectively. In the RPC01-3001, OLE study, there were 29 treatment-emergent malignancies (excluding NMSCs) and 12 NMSCs. Incidence rates of malignancies for ozanimod were within background rates in age matched MS and general populations.
Risk factors and risk groups	Risk factors for malignancies are not fully understood. Risk factors known to cause cancer include advancing age, and lifestyle (such as smoking,

Important potential risks

	alcohol, certain infections, lack of physical activities, poor diet, obesity, excessive exposure to the sun or other radiation, exposure to chemicals or hormone replacement). Some genes such as BRCA are known to cause cancers (breast, ovarian and prostate). However, it is not known what proportion of cancer is caused by faulty genes. Patients who are profoundly immunosuppressed are also at increased risk of developing malignancy, typically lymphomas. Chronic inflammatory conditions may also increase the risk of cancer. Many cancers develop as a result of combination of genetics, environmental factors and lifestyle.
Risk minimisation measures	**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 antineoplastic non-corticosteroid 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). **Additional risk minimisation measures:** – Healthcare Professional checklist – Patient/caregiver's guide.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients). Study IM0471037 (UC PASS). Study IM047-009 (ORION study MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.
Syndrome Characterised by Headache, Confusion, Seizures and Visual Loss (Posterior Reversible Encephalopathy Syndrome)	
Evidence for linking the risk to the medicine	No cases of PRES were reported in UC clinical studies. In the OLE (RPC01-3001) study, no cases of PRES were reported. In controlled MS clinical trials with ozanimod, one case of PRES was reported in a patient with Guillain-Barré syndrome.
Risk factors and risk groups	Many patients with PRES have comorbidities, which may be severe conditions, such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension and may be predisposing factors. Radiologically, extensive bilateral white matter abnormalities suggestive of oedema in the posterior regions of cerebral hemispheres were seen in a variety of conditions, including severe hypertension, uraemia, toxaemia of pregnancy, use of immunosuppressive drugs (ie, cyclosporine A) and cytotoxic agents, including alkylating agents, antimetabolites, mitotic inhibitors, antiangiogenic agents and antitumour necrosis factor alpha agents, granulocyte colony-stimulating factor and erythropoietin. Infections and autoimmune disease have also been associated with PRES. Hypertension of renal origin has been reported to be a significant cause of PRES. Patients with renal dysfunction appear to be at higher risk of

Important potential risks

	developing PRES despite only moderate acute elevation of their blood pressure. In patients with PRES associated renal disease treated with antihypertensive medications, neurological deficits resolved within 2 weeks. PRES can manifest with acute seizures without an obvious prodrome. These patients become seizure free after resolution of the imaging abnormalities and they do not require long-term antiepileptic therapy. PRES in the setting of autonomic dysfunction may also be a complication of Guillain-Barré syndrome.
Risk minimisation measures	**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.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients). Study IM0471037 (UC PASS). Study IM047-009 (ORION study MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.
Toxicity to Unborn Child in Women who have Received Treatment with Ozanimod (Embryofoetal Toxicity in Exposed Pregnant Females)	
Evidence for linking the risk to the medicine	As of 22 March 2023, a total of 78 events of potential exposure during pregnancy have been reported in patients treated with ozanimod across all indications, including 14 reported for female patients in ozanimod clinical trials for UC and 57 reported for female patients in ozanimod clinical trials for MS. The remaining 7 potential pregnancies in clinical trial participants occurred in 6 patients with Crohn's disease and 1 healthy volunteer. In addition, there have been 29 pregnancies in partners of male patients receiving ozanimod (30 outcomes due to twins). Of these, there have been 21 live births (13 normal; 5 premature, including 1 set of twins; and 3 with congenital abnormalities, including Hirschsprung's disease, congenital hydrocele, and partial atrioventricular septal defect), 1 ongoing pregnancy, 1 spontaneous early loss and 7 lost to follow-up. In partners of ozanimod-treated male participants in the ozanimod clinical development program, no drug related AEs (as assessed by Investigator and Sponsor) were reported. Embryofoetal toxicity in exposed pregnant females is considered to be an Important Potential Risk due to findings in animal studies. Clinical trial patients were instructed to avoid pregnancy during the trials and for a period after discontinuing medication as specified in the protocol, and to immediately discontinue study medication if pregnancy were diagnosed. All exposures occurred during the first trimester of pregnancy.
Risk factors and risk groups	No specific risk groups or risk factors have been identified.

Important potential risks

Risk minimisation measures	**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 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	Study RPC01-3102 (UC patients)

Blood Clots (Thromboembolic Events)	
Evidence for linking the risk to the medicine	In the ozanimod UC clinical development programme, the incidence rate (IR) per 1000 person-years for thromboembolic (TE) related events was 5.2 and 4.0 for ozanimod and placebo, respectively. The majority of the TE events occurred in older aged patients with documented risk factors. In MS controlled Phase 3 relapsing remitting MS studies (Pool A1), the incidence of TE events were similar in ozanimod and IFN β-1a groups, with events reported in 2 patients in the ozanimod 1 mg treatment group, 3 patients in the ozanimod 0.5 mg group and 4 patients with IFN β-1a. The majority of the TE events occurred in patients with documented risk factors. In the RPC01-3001, OLE study, 13 additional serious TE events were reported.
Risk factors and risk groups	Elderly age, prolonged hospitalisation/immobilisation, cancer, thyroid disease, oral contraceptive use, surgery, and pre-existing cardiovascular disease including prior DVT/ischaemia, phlebitis or cerebrovascular ischaemic attack, and hypertension are risk factors for TE events. The risk of thromboembolism is also increased with inflammatory bowel disease. Lifestyle factors, including smoking, physical inactivity and increased weight are also associated with increased risk of TE events.
Risk minimisation measures	**Routine risk minimisation measures:** Use of ozanimod is contraindicated in patients who in the previous 6 months had a myocardial infarction, unstable angina pectoris, stroke/transient ischaemic attack, decompensated heart failure (requiring

Important potential risks

	inpatient treatment), or New York Heart Association Class III/IV heart failure (SmPC Section 4.3). Blood pressure should be regularly monitored during treatment with ozanimod (SmPC Section 4.4). **Additional risk minimisation measures** None proposed.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients). Study IM0471037 (UC PASS). Study IM047-009 (ORION study, MS patients). See Section II.C of this summary for an overview of the postauthorisation development plan.
Risk of colorectal cancer (UC indication)	
Evidence for linking the risk to the medicine	Colorectal cancer and events indicative of advanced colonic neoplasia (including colon adenomas and dysplasia) are identified by medical review of all TEAEs (PTs) in the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps) and the Gastrointestinal SOC, for the UC population. In Pool G, 3 cases of colorectal cancer (CRC) were reported in the RPC01-3101 Maintenance Period, including 2 patients in the ozanimod 1 mg treatment group and in 1 patient re-randomised to the placebo treatment group during the Maintenance Period. Overall, in Pool G, colon adenoma was reported in 5 patients (including 4 patients on ozanimod treatment and 1 patient re-randomised to placebo in the RPC01-3101 Maintenance Period). Colon dysplasia was reported in 1 patient on placebo.
Risk factors and risk groups	Patients with chronic inflammatory bowel conditions such as UC are at increased risk of CRC and advanced colonic neoplasia. Risk factors for CRC among UC patients include younger age at onset, extensive colitis, longer disease duration, concomitant primary sclerosing cholangitis, family history of CRC, and persisting inflammation of the colon. Patients with extensive colitis have a 3-fold increase in risk of CRC and a 5-fold increase for those with long-standing extensive colitis. Many cancers also develop as a result of a combination of genetics, environmental factors and lifestyle. General risk factors known to cause cancer include advancing age and lifestyle (such as smoking, alcohol, certain infections, lack of physical activities, poor diet, obesity, excessive exposure to other radiation, exposure to chemicals or hormone replacement).
Risk minimisation measures	**Routine risk communication:** 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 antineoplastic non-corticosteroid immunosuppressive therapy, is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.

Important potential risks

Additional pharmacovigilance activities	Study RPC01-3102 (UC patients). Study IM0471037 (UC PASS). See Section II.C of this summary for an overview of the postauthorisation development plan.

Missing information

Heart Problems that Develop Following Long-term Treatment with Ozanimod (Long-term Cardiovascular Effects)	
Risk minimisation measures	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients) Study IM0471037 (UC PASS). Study IM047-009 (ORION study, MS patients) See Section II.C of this summary for an overview of the postauthorisation development plan.
Effects Following Withdrawal of Drug	
Risk minimisation measures	**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 after ozanimod discontinuation is included in SmPC Section 4.4. **Additional risk minimisation measures:** None proposed.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients). Study IM0471037 (UC PASS). See Section II.C of this summary for an overview of the postauthorisation development plan.
Use in Patients Over 55 Years	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2. **Additional risk minimisation measures:** None proposed.
Additional pharmacovigilance activities	Study RPC01-3102 (UC patients). Study IM0471037 (UC PASS). Study IM047-009 (ORION study, MS patients).

Missing information

	See Section II.C of this summary for an overview of the postauthorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ozanimod.

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

Postauthorisation Safety Study in UC (Study IM0471037)

Purpose of the study: To evaluate the long-term real-world safety of ozanimod, and specifically to further characterise the safety concerns following treatment with ozanimod in UC.

Long-term Follow-up of Study RPC01-3102 in UC

Purpose of the study: To characterise the long-term safety of ozanimod in patients with moderately to severely active UC.

ORION Study - Ozanimod Real-World Safety - A Post-Authorisation Multi-National Long-Term Non-Interventional Study (Study IM047-009)

Purpose of the study: The primary objective of this MS PASS is to evaluate the long-term safety profile of ozanimod in the real-world setting.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of Contents

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Pregnancy Surveillance Form Part I (Antepartum Information)

PATIENT IDENTIFIER: *(FOR STUDIES, MUST INCLUDE PROTOCOL, SITE & SUBJECT NUMBERS)*	CASE # (BMS ONLY)	LOCAL COUNTRY NUMBER: (BMS ONLY)

BMS RECEIPT DATE (BMS USE ONLY)	Click here to enter a date.	WWPS RECEIPT DATE (BMS USE ONLY)	Click here to enter a date.

REPORT TYPE:	☐ SPONTANEOUS OR ☐ STUDY	COUNTRY*	
	☐ INITIAL REPORT OR ☐ FOLLOW-UP REPORT	*If UK, was Country of Incidence, Specify if Northern Ireland below? Yes ☐ No ☐	

EVENT: PREGNANCY

EXPOSURE TYPE: ☐ MATERNAL DRUG EXPOSURE OR ☐ PATERNAL DRUG EXPOSURE

FOR PATERNAL DRUG EXPOSURE ONLY: WAS PREGNANT PARTNER INFORMED CONSENT FORM SIGNED? ☐ NO ☐ YES

IF NO, DID THE MALE SUBJECT PROVIDE ALL OF THE PREGNANCY SURVEILLANCE INFORMATION BELOW? ☐ NO ☐ YES

REPORT TYPE: ☐ PROSPECTIVE REPORT OR ☐ RETROSPECTIVE REPORT

WERE THERE ANY ADDITIONAL MATERNAL/PATERNAL ADVERSE EVENTS? ☐ NO ☐ YES

IF YES, REPORT THE ADVERSE EVENTS APPROPRIATELY (FOR STUDIES, REFER TO STUDY-SPECIFIC INSTRUCTIONS)

MATERNAL INFORMATION DATE OF BIRTH:	AGE AT CONCEPTION:	HEIGHT:	WEIGHT:	RACE:
Click here to enter a date.		☐ inches ☐ cm	☐ lb ☐ kg	☐ WHITE ☐ BLACK ☐ ASIAN ☐ AMERICAN INDIAN OR ALASKAN NATIVE ☐ NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER ☐ Aboriginal ☐ Torres Strait Islander ☐ OTHER RACE:

NUMBER OF PREGNANCIES INCLUDING THIS ONE	NUMBER OF BIRTHS	NUMBER OF LIVING CHILDREN

ONSET DATE LAST MENSTRUAL PERIOD (LMP):	Click here to enter a date.	APPROXIMATE DATE OF CONCEPTION:	Click here to enter a date.	DATE PREGNANCY WAS CONFIRMED:	Click here to enter a date.
		ESTIMATED DATE OF DELIVERY:	Click here to enter a date.	TEST METHOD:	☐ SERUM ☐ URINE

ESTIMATED GESTATIONAL AGE WHEN PREGNANCY DIAGNOSED:	WEEKS	DETERMINED BY:	☐ FETAL ULTRASOUND ☐ DATE FROM LMP

CONTRACEPTION AT TIME OF CONCEPTION: ☐ NO ☐ YES ☐ UNKNOWN (IF YES, SPECIFY)

RELEVANT MATERNAL MEDICAL HISTORY/RISK FACTORS	DATE OF ONSET	IF APPLICABLE SPECIFY PERTINENT DETAILS
	Click here to enter a date.	
	Click here to enter a date.	
	Click here to enter a date.	
	Click here to enter a date.	

PATERNAL INFORMATION: AGE YEARS DATE OF BIRTH: Click here to enter a date.

RELEVANT PATERNAL MEDICAL HISTORY/RISK FACTORS	DATE OF ONSET	IF APPLICABLE SPECIFY PERTINENT DETAILS
	Click here to enter a date.	
	Click here to enter a date.	
	Click here to enter a date.	
	Click here to enter a date.	

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Pregnancy Surveillance Form Part I (Antepartum Information)

PATIENT IDENTIFIER: *(FOR STUDIES, MUST INCLUDE PROTOCOL, SITE & SUBJECT NUMBERS)*	CASE # (BMS ONLY)	LOCAL COUNTRY NUMBER: (BMS ONLY)

MEDICATION NAME AND INDICATION	PREGNANCY RELATED TO MEDICATION?*	DOSE AND UNITS	FREQ	ROUTE **	PERIOD(S) OF DRUG EXPOSURE ***	ONCOLOGY DRUGS ONLY	START AND STOP DATES
1. INDICATION ☐ MATERNAL OR ☐ PATERNAL ☐ NON-STUDY OR ☐ STUDY	☐ NOT RELATED ☐ RELATED					CYCLE #: CUMULATIVE DOSE WITH UNITS	Click here to enter a date. Click here to enter a date. OR ☐ ONGOING
2. INDICATION ☐ MATERNAL OR ☐ PATERNAL ☐ NON-STUDY OR ☐ STUDY	☐ NOT RELATED ☐ RELATED					CYCLE #: CUMULATIVE DOSE WITH UNITS	Click here to enter a date. Click here to enter a date. OR ☐ ONGOING
3. INDICATION ☐ MATERNAL OR ☐ PATERNAL ☐ NON-STUDY OR ☐ STUDY	☐ NOT RELATED ☐ RELATED					CYCLE #: CUMULATIVE DOSE WITH UNITS	Click here to enter a date. Click here to enter a date. OR ☐ ONGOING
4. INDICATION ☐ MATERNAL OR ☐ PATERNAL ☐ NON-STUDY OR ☐ STUDY	☐ NOT RELATED ☐ RELATED					CYCLE #: CUMULATIVE DOSE WITH UNITS	Click here to enter a date. Click here to enter a date. OR ☐ ONGOING
5. INDICATION ☐ MATERNAL OR ☐ PATERNAL ☐ NON-STUDY OR ☐ STUDY	☐ NOT RELATED ☐ RELATED					CYCLE #: CUMULATIVE DOSE WITH UNITS	Click here to enter a date. Click here to enter a date. OR ☐ ONGOING
6. INDICATION ☐ MATERNAL OR ☐ PATERNAL ☐ NON-STUDY OR ☐ STUDY	☐ NOT RELATED ☐ RELATED					CYCLE #: CUMULATIVE DOSE WITH UNITS	Click here to enter a date. Click here to enter a date. OR ☐ ONGOING
7. INDICATION ☐ MATERNAL OR ☐ PATERNAL ☐ NON-STUDY OR ☐ STUDY	☐ NOT RELATED ☐ RELATED					CYCLE #: CUMULATIVE DOSE WITH UNITS	Click here to enter a date. Click here to enter a date. OR ☐ ONGOING

* MANDATORY FOR ALL STUDIES

**ROUTE:

1 = ORAL 2 = INTRAVENOUS 3 = SUBCUTANEOUS 4 = OTHER

***PERIOD(S) OF DRUG EXPOSURE: (INCLUDE ALL THAT APPLY)

0 = PRIOR TO CONCEPTION 1 = 1ST TRIMESTER 2 = 2ND TRIMESTER

3 = 3RD TRIMESTER 4 = LABOR & DELIVERY 5 = UNKNOWN

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Pregnancy Surveillance Form Part I (Antepartum Information)

PATIENT IDENTIFIER: *(FOR STUDIES, MUST INCLUDE PROTOCOL, SITE & SUBJECT NUMBERS)*	CASE # (BMS ONLY)	LOCAL COUNTRY NUMBER: (BMS ONLY)

PRENATAL DIAGNOSTIC TESTING	BASE-LINE	DATE	TEST RESULTS UNITS	NORMAL RANGE	
				LOW	HIGH
	☐	Click here to enter a date.			
	☐	Click here to enter a date.			
	☐	Click here to enter a date.			
	☐	Click here to enter a date.			
	☐	Click here to enter a date.			
	☐	Click here to enter a date.			
	☐	Click here to enter a date.			

DESCRIBE RESULTS IN DETAIL, IF APPLICABLE:

REPORTER INFORMATION: ☐ BMS STUDY INVESTIGATOR ☐ NON-BMS STUDY SPONSOR ☐ OTHER*

*QUALIFICATION: (COMPLETE ONLY IF "OTHER" IS CHECKED)

☐ PHYSICIAN ☐ PHARMACIST ☐ NURSE/NURSE PRACTITIONER ☐ OTHER HEALTH PROFESSIONAL

☐ CONSUMER ☐ ATTORNEY ☐ OTHER NON-HEALTH PROFESSIONAL

PERSON COMPLETING THE FORM (IF DIFFERENT FROM INVESTIGATOR/SPONSOR) :

PRINTED NAME

SIGNATURE

DATE: Click here to enter a date.

INSTITUTION/ORGANIZATION:

STREET ADDRESS:

CITY:

STATE/PROVINCE:

POST CODE: COUNTRY: PHONE NUMBER:

Email address

INVESTIGATOR/SPONSOR/OTHER:

LAST NAME

FIRST NAME MIDDLE INITIAL

SIGNATURE: DATE: Click here to enter a date.

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Pregnancy Surveillance Form Part II (Pregnancy Outcome)

PATIENT IDENTIFIER: *(FOR STUDIES, MUST INCLUDE PROTOCOL, SITE & SUBJECT NUMBERS)*	CASE # (BMS ONLY)	LOCAL COUNTRY NUMBER: (BMS ONLY)

PREGNANCY OUTCOME:

MODE OF DELIVERY:

LABOR/DELIVERY COMPLICATIONS ☐ NO ☐ YES*

IF YES, SPECIFY

☐ SINGLE GESTATION ☐ MULTIPLE GESTATION (# ☐ of ☐)

COMPLETE AN OUTCOME FORM FOR EACH FETUS/INFANT

DATE PREGNANCY ENDED: Click here to enter a date.

GESTATIONAL AGE AT OUTCOME ☐☐ WEEKS ☐ UNKNOWN

ASSESSED BY: ☐ OBSTETRICAL DATES ☐ FETUS/INFANT PHYSICAL EXAM

DID OBSTETRICAL COMPLICATIONS OR MATERNAL/PATERNAL MEDICAL CONDITIONS OCCUR DURING THIS PREGNANCY?

☐ NO ☐ YES*

☐ UNKNOWN IF YES, SPECIFY:

*FOR ANY COMPLICATIONS NOTED ABOVE, REPORT THE ADVERSE EVENT APPROPRIATELY (FOR STUDIES, REFER TO STUDY-SPECIFIC INSTRUCTIONS)

GENDER:

☐ MALE ☐ FEMALE

☐ UNKNOWN

BIRTH WEIGHT:

☐☐ / ☐☐ lbs/oz

☐☐☐☐ grams

BIRTH LENGTH:

☐ inches ☐ cm

HEAD CIRCUMFERENCE:

☐ inches ☐ cm

APGAR SCORE:

1 MIN. ☐ 5 MIN. ☐

☐ LIVE BIRTH NORMAL (PROCEED TO PART III)

☐ LIVE BIRTH ABNORMAL ☐ FETAL DEATH ☐ NEONATAL DEATH (IF ANY ARE CHECKED, COMPLETE SECTIONS BELOW)

☐ PRE-TERM ☐ TERM ☐ POST TERM

☐ SMALL FOR GESTATIONAL AGE

☐ INTRAUTERINE GROWTH RETARDATION

☐ DRUG WITHDRAWAL SYNDROME IN THE NEONATE

☐ MALFORMATION (SPECIFY BELOW)

☐ POST-NATAL/NEONATAL COMPLICATIONS (E.G. PERINATAL ASPHYXIA, INFECTION, RESPIRATORY DISTRESS) (SPECIFY):

FETAL DEATH

☐ ECTOPIC ☐ MISCARRIAGE/SPONTANEOUS ABORTION ☐ STILLBIRTH

☐ INDUCED ABORTION/ELECTIVE TERMINATION

AUTOPSY/PATHOLOGY REPORT ☐ NO ☐ YES ☐ UNKNOWN

NEONATAL DEATH:

CAUSE: DATE: Click here to enter a date.

PLACENTAL ABNORMALITIES ☐ NO ☐ YES ☐ UNKNOWN

IF YES, SPECIFY:

PATHOLOGY REPORT AVAILABLE ☐ NO ☐ YES ☐ UNKNOWN

FAMILY HISTORY OF CONGENITAL ABNORMALITIES/BIRTH DEFECTS:

☐ NO ☐ YES ☐ UNKNOWN

IF YES, SPECIFY:

PRIOR PREGNANCIES WITH CONGENITAL ABNORMALITIES/BIRTH DEFECTS: ☐ NO ☐ YES

IF YES, SPECIFY #/TYPE :

PRIOR STILLBIRTHS: ☐ NO ☐ YES

IF YES, SPECIFY # :

PRIOR SPONTANEOUS ABORTIONS: ☐ NO ☐ YES

IF YES, SPECIFY #:

SPECIFY ANY PRIOR PREGNANCY COMPLICATIONS:

HISTORY OF FERTILITY TREATMENTS (E.G. IVF):

☐ NO ☐ YES IF YES, SPECIFY:

DESCRIBE ANY CONGENITAL MALFORMATIONS/ABNORMALITIES, STRUCTURAL DEFECTS AND OTHER FETAL/NEONATAL COMPLICATIONS:

CAUSALITY (MANDATORY FOR STUDIES)

IN THE INVESTIGATOR'S OPINION, WAS THE DEFECT/MEDICAL PROBLEM RELATED TO MEDICATION UNDER STUDY? : ☐ NOT RELATED ☐ RELATED

IF RELATED, PLEASE COMMENT ON SPECIFIC EVENT(S) AND MEDICATION(S) BELOW:

IF NOT RELATED, INDICATE WHAT THE DEFECT/MEDICAL PROBLEM WAS ATTRIBUTED TO:

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Pregnancy Surveillance Form Part III (Infant Follow-up)

PATIENT IDENTIFIER: *(FOR STUDIES, MUST INCLUDE PROTOCOL, SITE & SUBJECT NUMBERS)*	CASE # (BMS ONLY)	LOCAL COUNTRY NUMBER: (BMS ONLY)

CURRENT INFANT AGE: ☐ AGE UNITS: ☐ DAYS ☐ WEEKS ☐ MONTHS

☐ NO PROBLEMS ☐ MEDICAL PROBLEMS NOTED (SPECIFY AND DESCRIBE FINDINGS AND/OR PLANNED EVALUATIONS; E.G. DIAGNOSTIC TESTING, CONSULTATIONS, ETC)

CAUSALITY (MANDATORY FOR ALL STUDIES): IN THE INVESTIGATOR'S OPINION WERE ANY PROBLEMS NOTED ABOVE RELATED TO THE MEDICATION UNDER STUDY? ☐ NOT RELATED ☐ RELATED (PLEASE SPECIFY):

MATERNAL BREASTFEEDING: ☐ NO ☐ YES HOW LONG:

MATERNAL DRUGS TAKEN WHILE BREASTFEEDING: ☐ NO ☐ YES (IF YES, SPECIFY)

REPORTER INFORMATION: ☐ BMS STUDY INVESTIGATOR ☐ NON-BMS STUDY SPONSOR ☐ OTHER*

*QUALIFICATION: (COMPLETE ONLY IF "OTHER" IS CHECKED)

☐ PHYSICIAN ☐ PHARMACIST ☐ NURSE/NURSE PRACTITIONER ☐ OTHER HEALTH PROFESSIONAL
☐ CONSUMER ☐ ATTORNEY ☐ OTHER NON-HEALTH PROFESSIONAL

PERSON COMPLETING THE FORM (IF DIFFERENT FROM INVESTIGATOR/SPONSOR) :	DATE:
PRINTED NAME	Click here to enter a date.
SIGNATURE	

INSTITUTION/ORGANIZATION:

STREET ADDRESS:	CITY:	STATE/PROVINCE:

POST CODE:	COUNTRY:	PHONE NUMBER:

Email address

INVESTIGATOR/SPONSOR/OTHER:

LAST NAME
FIRST NAME MIDDLE INITIAL

SIGNATURE:	DATE:
	Click here to enter a date.

Pregnancy Surveillance Form - Quick Reference Guide

The Pregnancy Surveillance Form will be completed for all prospective (confirmed pregnancy, prior to delivery or confirmation of congenital anomaly) and retrospective (when congenital anomaly/malformation is confirmed or after delivery has occurred) reports of pregnancy and pregnancy outcomes (live births: normal or abnormal, fetal death, neonatal death etc.) It functions as a data collection and query tool to report pregnancies and related pregnancy information. AE/SAEs for all subjects/patients reported in association with the pregnancy (obstetric complications, maternal medical complications, etc.) are to be reported separately on the clinical or non-interventional SAE form or spontaneous AE/SAE form.

Pregnancy Surveillance Form Part I	Pregnancy Surveillance Form Part II	Pregnancy Surveillance Form Part III
When a pregnancy is confirmed	When the pregnancy outcome is known	When the infant outcome is known.

Site Monitor: When a pregnancy is confirmed, collaborate with the site manager or clinical scientist to ensure that the Investigator has notified the IRB/IEC or Health Authority (if required by local law).

- Ensure that documentation of pregnancy notifications sent by the Investigator to the IRB/IEC are filed in the On-site Investigator File (OSIF) and R&D Study File.
- In countries where notification of the IRB/IEC is handled by the sponsor, the site manager is responsible for ensuring that the documentation of all pregnancy notifications sent to the IRB/IEC are filed within the R&D Study File.
- **Note**: for Paternal Drug Exposure in Interventional Study Reports: If pregnant partner informed consent is not signed, Part I, Part II and Part III information needs to come from the male subject, and not from the female partner herself.

All Pages Header Information

- For studies the "Patient Identifier" is the same as that used throughout the CRF, and populated with the protocol, site and subject numbers i.e. CV131-345-234-1134
- For spontaneous reports, enter local country number (if applicable) at the top left and/or enter a patient identifier (i.e. initials) if available or leave blank
- Parts I, II and III will be completed with all appropriate identifying header information on each page
  Part I - Page 1
  Complete all questions for "PREGNANCY" as the only adverse event; other SAEs reported in association with the pregnancy (obstetric complications, maternal medical complications etc.) are reported separately either on the clinical/non-interventional study SAE form or the Spontaneous AE/SAE forms.
  Part I - Page 2: Medication:
- Include each medication reported as a separate entry.
- Indicate if the drug was associated with maternal or paternal exposure.
- Indicate if the drug was identified as a non - study medication or study medication by the investigator or reporter.
  Study medications include the medications under study (for non-interventional studies), the Investigational Medicinal Product (IMP), comparator medications and background therapy identified in the protocol.
  "Pregnancy Related to Medication" Column: Check whether or not the pregnancy was related to the medication.
  Dosing Information: For route and period(s) of drug exposure, use the codes indicated at the bottom of the page.
  For period(s) of drug exposure, include all that apply.
  Part I - Page 3: Prenatal Diagnostic Testing: Indicate if the results are baseline by checking under "baseline"; otherwise leave this box blank when providing the relevant details. Specify the test results (including any relevant units or other data), use the space below this section to describe results in more detail if needed.
  Part II - Pregnancy Outcome: Complete delivery and outcome data as requested at the top of the page. If the outcome involved multiple gestations, please complete a separate outcome form for each fetus/infant. If the pregnancy/outcome involved labor or delivery complications, obstetric complications, or maternal medical conditions, briefly specify them.
  NOTE: If any complications reported above meet the definition of an SAE (or an AE for non-study patients) they should be reported separately on either the clinical or non-interventional SAE form or the spontaneous AE/SAE form. If the outcome is "live birth- normal" check this box, and proceed to the next page or any adverse outcome (live birth abnormal, fetal or neonatal death) complete all requested information to the fullest extent
  For any adverse outcome (live birth abnormal, fetal or neonatal death) complete all requested information to the fullest extent possible. A detailed causality assessment by the investigator is required for any reports from trials and must be provided as noted at the bottom of this page.

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

[Case_ ID]

Adverse Event Report Questionnaire
TL PML

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:

Patient Demographics:

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female
Age: _____

Race/Ethnicity: _____ ☐ Aboriginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product #1	Suspect Product #2	Suspect Product #3
Product name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD-MMM-YYYY)			
Stop date (DD-MMM-YYYY)			
Lot/Batch number(s)			
Expiration date(s)			
Action Taken with the suspect product			

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

Adverse Event (AE) Description: Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4

Add Diagnosis Here →				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect product(s):				
Required Hospitalization (Yes/No)				
Life-Threatening (Yes/No)				
Persistent or significant disability (Yes/No)				
Congenital abnormality (Yes/No)				
Cause of Death (Yes/No)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				
Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No)				
Did the event recur after reintroducing (Yes/No)				

Please summarize course of reported events including signs and symptoms in chronological order:

Diagnostic tests (use additional pages if needed)**:** Please indicate test unit where applicable.

Date	Test Name	Pre-treatment valu	AE onset value	AE resolution value	Normal low	Normal high
	WBC					
	Absolute lymphocyte count					
	HIV serology					
	Other:					

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

Concomitant Medications (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date DD-MMM-YYYY	Stop date DD-MMM-YYYY

Other Etiological Factors: ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

Additional questions:

Please confirm diagnosis of PML. ☐Yes ☐No

- ☐Clinical
- ☐Imaging
- ☐Laboratory

Did the patient have any of the below sign(s) of neurological deficit that led to a diagnosis/suspected diagnosis of PML? Check all that apply and specify the first identified sign.

- ☐Fever
- ☐Headaches
- ☐Hemiparesis
- ☐Cortical dysfunction:
  - ☐aphasia
  - ☐dysphasia
  - ☐agnosia
- ☐Cerebellar deficits :
  - ☐clumsiness
  - ☐ataxia
- ☐Brainstem deficits :
  - ☐visual disturbances (hemianopia)
  - ☐dysphagia
  - ☐dysarthria

- ☐ weakness
- ☐ coordination problems
- ☐ sensory loss

☐ Cognitive decline
☐ Personality changes
☐ Seizures
☐ Other to specify_____

Please describe relevant clinical examination results for the event of PML/suspected PML (mental status changes, gait, seizures, coma (stage), etc.).

Please name any underlying condition(s) /previous history, or current/previous medications that may be relevant to the reported/suspected event of PML:

☐ Previous history of infection, including HIV (AIDS)
☐ History of SLE or RA or psoriasis
☐ Neutropenia
☐ Lymphopenia
☐ History of lymphoproliferative diseases (Hodgkin's lymphoma), please specify_____
☐ Exposure to monoclonal antibodies (natalizumab, rituximab, ocrelizumab, efalizumab, and/or alemtuzumab), please specify_____
☐ Immunosuppressant (methotrexate, cyclophosphamide, azathioprine, mycophenolate and Fludarabine), please specify_____
☐ Immunomodulatory therapy (ozanimod, fingolimod, siponimod, interferon, other), please specify_____
☐ History of transplants, please specify_____
☐ In elderly patients - history of liver or renal impairment, please specify_____

Have any serology tests (e.g., JC virus DNA in CSF on PCR assay, blood JCV antibodies) been performed for this patient? ☐ Yes ☐ No

If yes, what were the test results (include dates and ranges)?

What were the patient diagnostic imaging results (e.g., Brain imagery MRI (particularly T2-weighted sequences such as fluid attenuated inversion recovery FLAIR), CT angiography, magnetic resonance angiography, catheter cerebral angiogram) (include dates)?

Did the patient have a stereotactic brain biopsy for detection of JCV DNA/proteins by in situ hybridization or immunohistochemistry (if applicable)? ☐Yes ☐No
If yes, what was the biopsy result (include date)?

Have any additional diagnostic tests (e.g., Chest X-Ray, CT scan, ultrasound) been performed for this patient?

☐Yes ☐No

If yes, could you provide the test results (include dates and reason for the testing)?

Please provide the treatment/intervention measures given for the PML. Please include therapy dosages and dates.

Please specify action taken with suspect product in response to the event of PML/suspected PML.

☐ Permanently Discontinued Stop date: _____
☐ Temporarily Interrupted Stop date: _____
☐ Dose Reduced Date and dose: _____
☐ None (no action taken)

If temporarily interrupted, did neurological deficit or PML recur after reintroducing suspect product?
☐Yes ☐No

Please specify current neurologic findings if the outcome of reported neurological event(s) or PML (confirmed or suspected) diagnosis is not recovered/resolved or recovered/resolved with sequelae

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Prior to the launch of Zeposia in each Member State, the 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 NCA.

The MAH shall ensure that in each Member State where Zeposia is marketed, all Healthcare Professionals who intend to prescribe Zeposia are provided with a Healthcare Professional Information Pack, containing the following:

1. Information on where to find latest SmPC;
2. Healthcare Professional checklist;
3. Patient/Caregiver's guide;
4. 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 QD on Days 1-4, then increase the dose to 0.46 mg QD on Days 5-7. Following the 7-day dose escalation, the QD dose is 0.92 mg, starting on Day 8.
  - Patients with mild or moderate chronic hepatic impairment (Child-Pugh class A or B) are recommended to complete the 7-day dose escalation regimen, and then take 0.92 mg once every other day.
- 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 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 or UC 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 MI 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 if at hour 6 post-dose:
  - Heart rate is 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;
  - There is 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, unstable angina, stroke, transient ischaemic attack, decompensated heart failure requiring hospitalisation or 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. Complete blood cell count should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior MS or UC 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 antineoplastic non-corticosteroid 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 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.
- Patients 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;
- What ulcerative colitis 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 and/or psychiatric symptoms/signs (such as sudden onset of severe headache, confusion, seizures, progressive weakness, clumsiness 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. Patients should inform their doctor if they notice yellowing of their skin or the whites of their eyes, abnormally dark urine, pain on the right side of the stomach area, tiredness, loss of appetite or unexplained nausea and vomiting as these can be signs of liver injury;
- 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 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 possibly return when treatment with Zeposia is stopped due to pregnancy or planning a pregnancy.