OBSERVATIONAL STUDY PROTOCOL IM047-009

ORION (OZANIMOD REAL-WORLD SAFETY - A POST-AUTHORISATION MULTI-NATIONAL LONG-TERM NON-INTERVENTIONAL STUDY)

Title	ORION (Ozanimod Real-World Safety - A Post-authorisation Multi-National Long-term Non-Interventional Study)
Protocol Version Identifier	IM047-009 (Version 5.0 [Amendment 1.0])
Date of Last Version of Protocol	26-Oct-2021
EU PAS Register Number	EUPAS44615
Active Substance	Ozanimod (ATC code: L04AA38)
Medicinal Product	ZEPOSIA®
Product Reference	EMEA/H/C/004835
Procedure Number	EMEA/H/C/004835/MEA/001.2
Joint PASS	No
Research Question and Objectives	**Research Question:** What are the rates of adverse events of interest (AEIs) in a real-world population of patients with relapsing remitting multiple sclerosis (RRMS) receiving newly marketed product ZEPOSIA® (ozanimod), an oral sphingosine 1 phosphate (S1P) receptor modulator (exposed) compared to the rates of these events in 2 populations of patients (not exposed to ozanimod) with RRMS who have received treatment with other S1P receptor modulators or non-S1P receptor disease-modifying treatments (DMTs)? **Primary Objectives:** The primary objectives of this study will be carried out through multinational distributed data sources that include secondary databases, such as Optum Research Database (ORD) and Clinical Practice Research Datalink (CPRD) and multiple sclerosis (MS) cohort and registry data sources in United Kingdom (UK) and Europe: • To describe the incidence rate and the hazard ratio of major adverse cardiovascular events (MACE) within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat MS. • To describe the incidence rate and hazard ratio of serious opportunistic infections (SOI) within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of MS.

	• To describe the incidence rate and hazard ratio of serious acute liver injury (SALI) without predisposing risk factors within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of MS. • To describe the incidence rate and hazard ratio of macular edema within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat MS. • To describe the incidence rate and hazard ratio of malignancies within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat MS. • To describe the incidence of acute non-fatal myocardial infarction during exposure to ozanimod and exposure to other therapies used to treat MS. • To describe the incidence of acute non-fatal stroke during exposure to ozanimod and exposure to other therapies used to treat MS. • To describe the incidence of cardiovascular (CV) mortality during exposure to ozanimod and exposure to other therapies used to treat MS. • To evaluate the study outcomes among patients 55 years or older compared to patients younger than 55 years. **Secondary Objectives:** • To describe the incidence of MACE during exposure to ozanimod and exposure to other therapies used to treat MS in intervals of time since initiation (ie, < 365 days and ≥ 65 days). • To describe the incidence of symptomatic bradycardia during exposure to ozanimod and exposure to other therapies used to treat MS. • To describe the incidence of progressive multifocal leukoencephalopathy (PML) during exposure to ozanimod and exposure to other therapies used to treat MS. • To describe the incidence of SALI with and without predisposing factors within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of MS. • To describe the incidence rate of SALI during exposure to ozanimod and exposure to other therapies used to treat MS. • To describe the incidence rate of Posterior Reversible Encephalopathy Syndrome (PRES) during exposure to ozanimod and exposure to other therapies used to treat MS.
Countries of Study	United States, UK, Germany, and other European countries.
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This protocol has been reviewed and approved by the marketing authorization holder's Qualified Person for Pharmacovigilance. The electronic signature is available on file.

CONFIDENTIAL

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEI	adverse event of interest
AISM	Associazione Italiana Sclerosi Multipla
ALC	absolute lymphocyte count
ALI	acute liver injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMI	acute myocardial infarction
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AV	atrioventricular
BMI	body mass index
bpm	beats per minute
CD	Crohn's disease
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CPRD	Clinical Practice Research Datalink
CVD	cardiovascular disease
DBP	diastolic blood pressure
DILI	Drug-induced liver injury
DMSG	Deutsche Multiple Sklerose Gesellschaft Bundesverband e.V
DMT	Disease-modifying treatment
ED	Emergency Department
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EMIS	Egton Medical Information Systems
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union

Abbreviation	Definition
FDA	Food and Drug Administration
GGT	gamma-glutamyltransferase
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HES	hospital episode statistics
HCl	hydrochloride
HR	hazard ratio
IBD	inflammatory bowel disease
ICD-10 or ICD10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IFN β-1a	interferon β-1a
IPR	Swedish National Inpatient Register
ISAC	Independent Scientific Advisory Committee
JCV	John Cunningham virus
MAC	Mycobacterium avium complex
MACE	major adverse cardiac events
MAH	Marketing Authorisation Holder
MA-PD	Medicare Advantage and Medicare Part D Data
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
MS	multiple sclerosis
NCHS	National Center for Health Statistics
NDI	National Death Index
NHS	National Health Service
NPR	National Patient Register
OFSEP	Observatoire Français de la Sclérose en Plaques
OLE	open-label extension
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures
ORD	Optum Research Database

Abbreviation	Definition
ORION	Ozanimod Real-World Safety - A Post-Authorisation Multi-national Long-Term Non-Interventional Study
PAS	post-authorisation studies
PASS	post Authorisation Safety Study
PB	Privacy Board
PML	progressive multifocal leukoencephalopathy
PRES	posterior reversible encephalopathy syndrome
PY	patient-year
RRMS / RMS	relapsing remitting multiple sclerosis
SALI	serious acute liver injury
SAS	Statistical Analysis Software
SBP	systolic blood pressure
S1P	sphingosine-1 phosphate
SMQ	standardized MedDRA queries
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
SOI	serious opportunistic infections
SOP	standard operating procedure
TIA	transient ischemic attack
TNF	tumor necrosis factor
UC	ulcerative colitis
UK	United Kingdom
ULN	upper limit of normal
US	United States of America

2 RESPONSIBLE PARTIES

Company Address

[redacted]
Bristol-Myers Squibb
[redacted]

Collaborating Institutions

Optum Research Database (ORD)
UK Clinical Practice Research Datalink (CPRD)
Deutsche Multiple Sklerose Gesellschaft (DMSG)
MS Optimise (UK)
Observatoire Français de la Sclérose en Plaques (OFSEP) – French MS registry
Associazione Italiana Sclerosi Multipla (AISM) – Italian MS registry
National Patient Register of Sweden

3 ABSTRACT

Title: ORION (ORION (Ozanimod Real-World Safety - A Post-Authorisation Multi-National Long-term Non-Interventional Study)) (IM047-009, v5.0)

Rationale and Background:

This study will be conducted following the initial marketing authorization of ZEPOSIA® (ozanimod) for the treatment of multiple sclerosis (MS) to observe incidence rates of specific adverse events of interest (AEIs).

The AEIs in this Post-Authorisation Safety Study (PASS) were selected based on the mechanism of action of ozanimod (sphingosine 1 phosphate [S1P] receptor modulation), ozanimod nonclinical data, possible class effects and safety issues identified with currently marketed S1P receptor modulator compounds in the MS indication based on AEIs observed in the clinical trials for ozanimod (marketed as ZEPOSIA®).

Research Question and Objectives:

Research question:

What are the rates of AEIs in a real-world population of patients with relapsing remitting multiple sclerosis (RRMS) receiving newly marketed product ZEPOSIA® (ozanimod), an oral S1P receptor modulator (exposed) compared to the rates of these events in 2 populations of patients (not exposed to ozanimod) with RRMS who have received treatment with other S1P-receptor modulators or non-S1P receptor disease-modifying treatments (DMTs)?

Primary Objectives:

The primary objectives of this study will be carried out through multinational distributed data sources that include secondary databases, such as Optum Research Database (ORD) and Clinical Practice Research Datalink (CPRD) and RRMS cohort and registry data sources in the United Kingdom (UK) and Europe:

- To describe the incidence rate and hazard ratio of major adverse cardiovascular events (MACE) within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat RRMS.
- To describe the incidence rate and hazard ratio of serious opportunistic infections (SOI) within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of RRMS.
- To describe the incidence rate and hazard ratio of serious acute liver injury (SALI) without predisposing risk factors within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of RRMS.
- To describe the incidence rate and hazard ratio of macular edema within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat RRMS.
- To describe the incidence rate and hazard ratio of malignancies within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat RRMS.
- To describe the incidence of acute non-fatal myocardial infarction during exposure to ozanimod and exposure to other therapies used to treat RRMS.

- To describe the incidence of acute non-fatal stroke during exposure to ozanimod and exposure to other therapies used to treat RRMS.
- To describe the incidence of cardiovascular (CV) mortality during exposure to ozanimod and exposure to other therapies used to treat RRMS.
- To evaluate the study outcomes among patients 55 years or older compared to patients younger than 55 years.

Secondary Objectives:

- To describe the incidence of MACE during exposure to ozanimod and exposure to other therapies used to treat RRMS in intervals of time since initiation (ie, < 365 days and ≥ 365 days).
- To describe the incidence of symptomatic bradycardia during exposure to ozanimod and exposure to other therapies used to treat RRMS.
- To describe the incidence of progressive multifocal leukoencephalopathy (PML) during exposure to ozanimod and exposure to other therapies used to treat RRMS.
- To describe the incidence of SALI with and without predisposing factors within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of RRMS.
- To describe the incidence rate of posterior reversible encephalopathy syndrome (PRES) during exposure to ozanimod and exposure compared to other therapies used to treat RRMS.

Study Design:

This is a long-term observational study including patients exposed to ozanimod or other medications used to treat RRMS. The study will use existing multinational distributed data sources, such as administrative healthcare data, electronic health records, and potentially disease registries, which will not be collected primarily for this research but do reflect care in usual clinical practice. Exposure in the automated datasets will be based on prescription or dispensing data. As in usual practice, patients may switch between study drugs, and thus the analysis will be episode-of-use level, rather than patient level. Propensity scores (PS) based on relevant baseline demographics, clinical characteristics, and number of prior treatments at the start of each new treatment episode will be used to adjust for potential confounding in comparative analyses.

For each outcome, a separate PS will be calculated.

The primary endpoints of interest are MACE (composite and the individual components of MACE), SOI, and SALI, macular edema, and malignancy. The study will estimate the incidence rates of these events in one exposed (ozanimod), and two comparator cohorts, defined by selected DMTs for MS. Hazard ratios will be considered the main measure of effect.

A cohort design will allow direct estimation of the incidence rates, rate differences, and relative risk or hazard ratios of multiple outcomes of interest among new users of ozanimod compared with new users of other DMTs. A cohort study design will also allow accurate chronologic confounder assessment and assessment of the outcomes at multiple time points. The covariate information will be assessed during the time preceding treatment initiation and will include all relevant demographic and clinical characteristics available for each patient.

Population(s):

The study population will include men and women at least 18 years old who have a diagnosis of MS and are new users of ("initiate") treatment with one of three cohort-defining treatments.

Patients will be grouped into the following cohorts:

- Exposed: Starting ozanimod
- Non-exposed: Starting another S1P receptor modulator
- Non-exposed: Starting a DMT other than an S1P receptor modulator

Variables:

Primary outcomes:

- Composite measure of MACE, defined as the first acute myocardial infarction (AMI), stroke, or CV mortality
- Individual components of MACE
- SOI
- SALI
- Macular edema
- Malignancy

Secondary outcome:

- Symptomatic bradycardia
- PML
- PRES

Data Sources:

The study cohorts include multinational distributed data sources that will be drawn from electronic databases from health systems in which ozanimod is launched and in countries where reimbursement status is anticipated to be granted or has been granted. The primary sources of data will include the:

- United States: Optum
- UK:
  - Clinical Practice Research Datalink Aurum, linked to hospital episode statistics (HES) and national death statistics
  - Optimise (UK)
- European Union (EU): MS cohorts and registries, which include, but may not be limited to:
  - Deutsche Multiple Sklerose Gesellschaft Bundesverband e.V (Germany)
  - Observatoire Français de la Sclérose en Plaques (France)
  - Associazione Italiana Sclerosi Multipla (Italy)
  - National Patient Register (NPR) + Electronic Medical Record (EMR) (Sweden)

Study Size: The size of the study cohorts will be determined by the uptake of ozanimod and comparator drugs in the countries and populations included in the data sources during the study period, and the amount of person-time each patient will contribute will depend on how long they remain on specific treatments.
Data Analysis: When ozanimod-treated patients reach 1,000 patient-years in at least one data source, the study will conduct the PS-based analyses for the primary objectives in that data source as described below. Selective removal of observations, known as "trimming," will be implemented at both ends of the PS weight range. At the low end of the range, all patient episodes with a PS weight below the 2.5 percentile value of the distribution of scores in the exposed group (ie, ozanimod) will be excluded. At the upper end of the range, we will exclude all patients, exposed and unexposed to ozanimod, with PS weights greater than the 97.5 percentile.

4 AMENDMENTS AND UPDATES

Table 4-1: Information on Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or Update	Reason
Minor amendment 1.0	29-Nov-2023	Title page	Added EU PAS register number, update to author and Marketing Authorisation Holder contact details.	Administrative update.
		3	Update to contact details.	Administrative update.
		6	Updated milestone dates.	Updated due to delayed EU launch of ozanimod.
		9.2.1	Added monomethyl fumarate.	For consistency with Section 8.2.3.
			Ponesimod removed from other S1P cohort, ofatumumab removed from other DMT cohort.	Approved after ozanimod approval.
			Rituximab removed from other DMT cohort.	Rituximab not approved for treatment of MS.
		9.2.2	Added text to clarify time periods during which treatment episodes are eligible for inclusion.	Improve clarity.
		9.2.3	Updated washout periods in Table.	Correct omissions.
		9.2.5	Updated exclusion criteria: exclude the new indication for ozanimod (ulcerative colitis / Crohn's disease).	To avoid exposure misclassification.

Table 4-1: Information on Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or Update	Reason
		9.3.2.1	Update the definition for angina pectoris to I20.xx.	Broader definition for angina pectoris.
		9.3.2.4	Update the definition of macular edema.	Improve accuracy.
		9.3.3	Changed 12 months to 6 months.	To align with inclusion criterion of patients having at least 6 months of continuous enrollment in the data source.
		9.7.1	Apply inverse probability of treatment weighting, rather than stratification on the propensity score.	Improve covariate balance; IPTW has been shown to outperform stratification.[a]
		Multiple	Editorial changes to text.	Improve clarity and consistency.

[a] Lunceford JK, Davidian M: Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Stat Med. 2004, 23 (19): 2937-2960. 10.1002/sim.1903.

5 STUDY MILESTONES

Milestones for this study are summarized in Table 5-1.

Table 5-1: Milestones

	US	Germany	France	Italy	Spain	UK	Sweden
Anticipated Start of Data Accrual in Each Data Source[a]	2020	2020	2022[b]	2021	2022[b]	2021[c]	2022
Planned Study Period	2020-2030	2020-2030	2022-2032	2021-2031	2022-2032	2021-2031	2022-2032
Anticipated End of Data Collection	2030	2030	2032	2031	2032	2031	2032
Study Progress Reports	Annually						
Interim Report 1	Q4 2024						
Interim Report 2	Q4 2026						
Registration in the EU PAS Register	Within 1 month of protocol approval						
Final Report of Study Results	Q4 2033						

[a] Defined as the year of commercial availability (based on internal company projections).
[b] Anticipated.
[c] Full launch.

6 RATIONALE AND BACKGROUND

6.1 Rationale

The pivotal clinical trial programme of 2 Phase 3 studies compared the efficacy and safety of ozanimod versus IFNβ-1a.[1,2]

Adverse events of interest (AEIs) were defined for the ozanimod clinical trial programme, based on a knowledge of events observed with, fingolimod, another member of the sphingosine 1-phosphate (S1P) class, which gained initial approval in the United States (US) in 2010.[3,4,5,6] The following is a description of the findings of the ozanimod clinical development programme.

The safety profile of ozanimod, a selective S1P receptor modulator, has been examined in a clinical development program including a subject population of more than 3400 with over 8000 person-years of follow-up in relapsing multiple sclerosis (RMS) and inflammatory bowel disease (IBD). In the large active-controlled Phase 3 RMS clinical program in 1774 patients, ozanimod demonstrated a favorable safety profile as compared to IFNβ-1a, a well-characterized standard of care treatment for multiple sclerosis (MS).

In the active-controlled Phase 3 RMS studies, the overall incidence of AEs was lower in ozanimod treatment groups compared with an active comparator (IFN β-1a) which was driven by the high rate of influenza-like illness seen with IFN β-1a. The most frequently reported AE in ozanimod-treated patients was nasopharyngitis, which occurred in 11.1% of patients in the ozanimod HCl 1 mg group (equivalent to ozanimod 0.92 mg, hereafter referred to as ozanimod 1 mg), 11.5% of patients in the ozanimod HCl 0.5 mg group (equivalent to ozanimod 0.46 mg, hereafter referred to as ozanimod 0.5 mg), and 9.5% of patients in the IFN β-1a group. Other frequently reported AEs with ozanimod (≥ 2% of patients in any ozanimod group at an incidence ≥ 1% higher versus IFN β-1a) were ALT increased, gammaglutamyltransferase (GGT) increased, orthostatic hypotension, urinary tract infection, back pain, hypertension, pharyngitis, viral respiratory tract infection, and upper abdominal pain. The incidences of severe AEs were low and similar across treatment groups. The incidence of serious AEs in the Phase 3 RMS program was similar across treatment groups (4.6%, 5.3%, and 4.4% in the ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a groups, respectively), with no discernable trends noted in any type of serious adverse event (SAE) across the treatment groups. No dose effects were observed. Adverse events leading to permanent discontinuation of the study drug or to withdrawal from the study were infrequent in all treatment groups and reported at a slightly lower incidence in the ozanimod treatment groups compared with the IFN β-1a group. The most frequent AE leading to study drug discontinuation with ozanimod was ALT increased (0.5% and 0.1% with 1 mg and 0.5 mg, versus 0.3% with IFN β-1a).

Based on the known biology of S1P receptor modulators and prior clinical information on drugs that have an effect on the S1P receptors, special attention was directed at assessing cardiac effects, including symptomatic bradycardia, hepatic effects, infections, consequences of lymphopenia, macular edema, malignancies, and pulmonary effects.

Ozanimod is associated with transient dose-related reductions in heart rate and does not appear to affect cardiac repolarization. Implementation of the dose escalation regimen starting ozanimod HCl at an initial dose of 0.25 mg (equivalent to ozanimod 0.23 mg, hereafter referred to as ozanimod 0.25 mg) successfully attenuated the negative chronotropic and dromotropic effects of S1P receptor modulation. In the active-controlled Phase 3 RMS studies which implemented dose escalation, during the first 6 hours post-dose on Day 1, there was a modest (1.2 bpm) reduction from baseline in heart rate that was not associated with clinically significant bradycardia or conduction effects (eg, second- or third-degree atrioventricular [AV] block). No heart rate < 40 bpm was observed.

The cardiac experience from the Phase 3 RMS studies indicates that ozanimod, administered with a dose escalation regimen, can be administered without the need for first-dose cardiac monitoring in patients who do not have significant cardiovascular disease within the past 6 months.

Ozanimod was associated with elevations in ALT and GGT. These hepatic enzyme abnormalities occurred more frequently in patients with underlying hepatic conditions and in males. In the active-controlled Phase 3 RMS clinical trials, ALT elevations of ≥ 3 times the upper limit of normal (ULN) occurred in 5.5% of patients on ozanimod 1 mg, 3.8% of patients on ozanimod 0.5 mg, and 3.1% of patients on IFN β-1a. The median time to elevation was 6 months. Of these patients, the majority (approximately 79% on ozanimod 1 mg and 77% on ozanimod 0.5 mg) continued treatment with ozanimod, with values returning to < 3 x ULN within approximately 2 to 4 weeks. Elevation of ALT to ≥ 5 x ULN occurred in 1.6% of patients on ozanimod 1 mg, 1.0% of patients on ozanimod 0.5 mg, and 1.3% of patients on IFN β-1a. The majority of ALT elevations were isolated cases, as evidenced by the low incidence of consecutive elevations ≥ 3 x ULN (2.1%, 1.1%, and 1.4% of patients treated with ozanimod 1 mg and 0.5 mg versus IFN β-1a, respectively) or ≥ 5 x ULN (0.5%, 0.3%, and 0.8%, respectively). Similarly, the incidence of total bilirubin elevations > 2 x ULN was low with ozanimod 1 mg and 0.5 mg and slightly higher than with IFN β-1a (1.6%, 1.6%, and 0.2%, respectively), with few patients having consecutive elevations > 2 x ULN (0.2%, 0.2%, and 0, respectively).

Ten patients in the entire ozanimod clinical development program (RMS + IBD) had concurrent elevations of ALT or AST ≥ 3 x ULN and bilirubin > 2 x 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.

Most hepatic-related events were mild to moderate in intensity and resolved while continuing treatment. Discontinuations due to hepatic-related AEs occurred in 1.2%, 0.4%, and 0.8% of patients on ozanimod 1 mg, ozanimod 0.5 mg, and IFN β-1a, respectively. There were no cases of severe drug-induced liver injury identified in the clinical development program for ozanimod.

The incidence of infections was approximately 35% in each treatment group and most frequently included viral respiratory tract infections, nasopharyngitis, and urinary tract infection. The incidence of serious infections was low and similar across treatment groups.

No disseminated or serious opportunistic infections (SOI) occurred. Herpes zoster infections occurred in all treatment groups: 0.6% with ozanimod 1 mg, 0.3% with ozanimod 0.5 mg, and

0.2% with IFN β-1a. Herpes zoster infections were nonserious, infrequent, had a benign clinical course, and were not treatment-limiting.

Dose-dependent reductions in absolute lymphocyte count (ALC) to values < 0.2 x 10^9/L of 3.3% and 0.4% were observed in the ozanimod 1 mg and 0.5 mg treatment groups, respectively. Among patients with an ALC < 0.2 x 10^9/L, there were only 2 cases of nonserious opportunistic infections (herpes zoster and oral herpes), both in the ozanimod 1 mg group. Within the limits of the methodology employed, an association between ALC < 0.2 x 10^9/L and serious or opportunistic infections was not detected; however, an increased risk of infection cannot be ruled out. After discontinuing ozanimod 1 mg, the median time to recovery of ALC to the normal range (≥ 1 x 10^9/L) was 30 days, with approximately 90% of patients recovering to normal within 3 months. No cases of progressive multifocal leukoencephalopathy (PML) have been identified in the ozanimod clinical program.

The S1P1 receptor is highly expressed in atrial, septal, and ventricular cardiomyocytes. After initial agonism, continuous dosing results in functional antagonism and down-regulation of S1P. Activation of S1P receptors on cardiac cells provides an explanation for the transient effects on heart rate (bradycardia) and AV conduction.

In the clinical trial population with ozanimod, bradycardia has been observed, although there have been no cases of clinical consequences.

Ozanimod was associated with small increases in blood pressure relative to IFN β-1a. Patients treated with ozanimod had an average increase of approximately 1 to 2 mm Hg in systolic blood pressure (SBP) over IFN β-1a with a minimal effect on diastolic blood pressure (DBP). The increase in SBP was first detected after approximately 3 months of treatment initiation and remained stable throughout treatment. Hypertension was reported as an adverse reaction in 3.4% of patients treated with ozanimod 1 mg and in 2.0% of patients with IFN β-1a.

Patients treated with ozanimod did not show an increased incidence rate of malignancies compared to rates reported in the general population. Ozanimod is a potent S1P receptor modulator that binds with high affinity to S1P 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 multiple sclerosis and ulcerative colitis (UC) is unknown but may involve the reduction of lymphocyte migration into the central nervous system (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 are key components of immunosurveillance.[7] A comprehensive review of disease-modifying therapies that have received marketing authorization for MS does not suggest an increased cancer risk with these agents.[8]

The nonselective S1P receptor modulators have been shown to affect vascular endothelial barrier function, thereby potentially compromising the blood-retina barrier.[9] In clinical trials, ozanimod

did not show an increased rate of macular edema over the background rate, and patients experiencing macular edema had predisposing risk factors.

One case of posterior reversible encephalopathy syndrome (PRES) was seen in clinical trials in RMS in a patient with Guillain-Barre syndrome; its relationship to ozanimod is unknown. Posterior reversible encephalopathy syndrome may 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.[10]

The long-term adverse effects seen with ozanimod in patients with RMS was examined comparing the incidence and study duration-adjusted incidence rate (IR; per 1000 patient-years [PY]) of AEs in patients treated with ozanimod in the parent Phase 3 RMS studies with data from the open-label extension (OLE) study with longer term exposure to ozanimod for up to 68 months. No increase in overall rates of AEs or specific types of AEs (except for nonserious herpes zoster) was observed.

All enrolled patients were initially required to have a follow-up visit 28 days after discontinuation of study drug. Given the approximate 11-day mean half-life of the major active metabolites, the protocols were amended to extend the follow-up period to 90 days. An assessment of available data beyond 28 days post-treatment did not reveal any emerging safety signal.

In conclusion, ozanimod had an acceptable safety profile and was generally well tolerated, with completion rates of approximately 90% in the pivotal Phase 3 trials, and high retention rates in the OLE. Both the 1 mg and 0.5 mg doses of ozanimod demonstrated a favorable safety profile in the Phase 3 trial program when compared to IFN β-1a, a well-established standard of care for the treatment of relapsing remitting multiple sclerosis (RRMS). The approved maintenance dose of ozanimod is 1 mg.

This post-approval safety study is being conducted to further describe Important Potential Risks and Missing Information identified in the Risk Management Plan for ozanimod including but not limited to: long-term cardiovascular effects, SOI including PML (recently categorized as an Important Identified Risk), SALI, bradycardia, macular edema, malignancies, PRES; and to characterize the safety of ZEPOSIA® (ozanimod) in use in patients 55 years and older.

6.2 Background

There is strong evidence suggesting that MS is associated with a high prevalence of comorbidities. However, in a systematic review [11] of comorbidities in MS, considerable heterogeneity in comorbidities was identified between studies. 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. Metaanalysis estimates for the prevalence of these comorbidities were depression 23.7 (95% confidence interval [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: 020.9).[11]. 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 chronic obstructive pulmonary disease and asthma (19.7%) and hypertension (14.5%).[12]

Using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD),[13] comorbidities and medication use at the time of and after the MS diagnosis date were compared between 6,932 MS patients and 68,526 non-MS patients. Over a median follow-up of 5 years post-diagnosis, MS patients 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 MS patients.[14]

Conflicting information exists regarding the risk of cardiovascular disease (CVD) in MS ranging from no risk to high risk in various studies.[15] Cardiovascular disease is considered to be highly prevalent amongst patients with MS, relative to individuals without MS.[16] In this study, the rate ratio for myocardial infarction (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 7,667 patients with MS, in which an increased CVD risk (1.31 [95% CI: 1.22-1.41]) was reported.[17] Using the UK CPRD, 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 MS patients were identified and compared with 57,331 non-MS patients. Rates of transient ischaemic attack (TIA), angina or unspecified ischaemic heart disease, heart failure, bradycardia/heart block, other arrhythmias, or pericardial disease were similar; however, MS patients 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 non-MS patients, rates of MI were increased in women (incidence rate ratio 2.55; 95% CI, 1.40–4.37.[18]

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.[19] In addition, several MS treatments also increase the rates of infections amongst MS patients.[20] Large epidemiologic studies have found that infection is a common comorbidity amongst MS and MS patients are two to four times more likely to be hospitalised for infection compared to the general population.[21,22] The most commonly types of infections are infections of the respiratory tract, including pneumonia, and the urinary system. Other common infections include skin infections.[22,21]

The comorbidities described above will provide a background to events expected in the MS population and those observed in the current PASS. The comparator groups in this PASS will provide a comparison between different categories of MS treatment and insights into the comparative safety of ozanimod in patients with MS in real-world usage.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 Research Question

What are the rates of AEIs in a real-world population of patients with RRMS receiving newly marketed product ZEPOSIA® (ozanimod), an oral S1P receptor modulator, (exposed) compared to the rates of these events in two populations of patients (not exposed to ozanimod) with RRMS who have received treatment with other S1P-receptor modulators or non-S1P receptor disease-modifying treatments (DMTs)?

7.2 Research Objectives

7.2.1 Primary Objective

The primary objectives of this study will be carried out through multinational distributed data sources that include secondary databases, such as Optum Research Database (ORD) and CPRD and RRMS cohort and registry data sources in UK and Europe:

- To describe the incidence rate and hazard ratio of major adverse cardiovascular events (MACE) within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat RRMS.
- To describe the incidence rate and hazard ratio of SOI within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of RRMS.
- To describe the incidence rate and hazard ratio of SALI without predisposing risk factors within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of RRMS.
- To describe the incidence rate and hazard ratio of macular edema within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat RRMS.
- To describe the incidence rate and hazard ratio of malignancies within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used to treat RRMS.
- To describe the incidence of acute non-fatal MI during exposure to ozanimod and exposure to other therapies used to treat RRMS.
- To describe the incidence of acute non-fatal stroke during exposure to ozanimod and exposure to other therapies used to treat RRMS.
- To describe the incidence of CV mortality during exposure to ozanimod and exposure to other therapies used to treat RRMS.
- To evaluate the study outcomes among patients 55 years or older compared to patients younger than 55 years.

7.2.2 Secondary Objectives

- To describe the incidence of MACE during exposure to ozanimod and exposure to other therapies used to treat RRMS in intervals of time since initiation (ie, < 365 days and ≥ 365 days).
- To describe the incidence of symptomatic bradycardia during exposure to ozanimod and exposure to other therapies used to treat RRMS.

- To describe the incidence of PML during exposure to ozanimod and exposure to other therapies used to treat RRMS.
- To describe the incidence of SALI with and without predisposing factors within the person-time of exposure to ozanimod and the person-time of exposure to other therapies used in the treatment of RRMS.
- To describe the incidence rate of PRES during exposure to ozanimod and exposure compared to other therapies used to treat RRMS.

7.2.3 Exploratory Objectives

Not applicable.

8 RESEARCH METHODS

8.1 Study Design

This is a long-term observational study including patients exposed to ozanimod or other medications used to treat RRMS. The study will use a new-user design and will follow patients longitudinally. The study will use existing multinational distributed data sources, such as administrative healthcare data, electronic health records, and disease registries, which will not be collected primarily for this research but do reflect care in usual clinical practice. Exposure will be based on prescription or dispensing data, in the automated datasets, or physician report (ie, registry). As in usual practice, patients may switch between study drugs, and thus the analysis will be episode-of-use level, rather than patient level. Propensity scores (PS) based on relevant baseline demographics, clinical characteristics, and number of prior treatments at the start of each treatment episode will be used to adjust for potential confounding in comparative analyses. For each outcome, a separate PS will be calculated.

The primary endpoints of interest are MACE (composite and the individual components of MACE), SOI, SALI, macular edema, and malignancy. The study will estimate the incidence rates of these events in one exposed (ozanimod) cohort, and two comparator cohorts, defined by DMTs for MS (see Section 8.2.1). Hazards ratios will be considered the main measure of effect.

A cohort design will allow direct estimation of the incidence rates, rate differences, and relative risk or hazard ratios of multiple outcomes of interest among new users of ozanimod compared with new users of other DMTs. A cohort study design will also allow accurate chronologic confounder assessment and assessment of the outcomes at multiple time points. The covariate information will be assessed during the time preceding treatment initiation and will include all relevant demographic and clinical characteristics available for each patient.

8.2 Setting

8.2.1 Study Population

The study population will include men and women at least 18 years old who have a diagnosis of multiple sclerosis and are new users of ("initiate") treatment with one of three cohort-defining treatments. There will be two unexposed comparator cohorts, based on initiation of active treatments.

- The *exposed cohort* will comprise patients initiating treatment with ozanimod.
- The *other S1P cohort* will comprise patients initiating an S1P modulator, including siponimod. or fingolimod.
- The *other DMT cohort* will comprise patients initiating oral agents such as teriflunomide, dimethyl fumarate, diroximel fumarate, monomethyl fumarate and cladribine; intravenous infusion agents such as alemtuzumab, mitoxantrone, ocrelizumab, and natalizumab; and agents that can be injected such as interferon beta -1a, interferon beta 1b, glatiramer acetate, and pegylated interferon beta-1.

If new DMT or other relevant medications are approved after ozanimod, they will not be added to the study as part of the comparator cohorts; their inclusion may induce confounding as there would not be enough time to ensure the representativeness of that new treatment in the study population. However, these drugs will be considered for defining treatment lines, switching, and censoring. Also, as new drugs for MS become available throughout the study period, ozanimod's prescription patterns may change over time due to more alternative options becoming available. An analysis approach allowing for changing prescription patterns for ozanimod over the study period will be considered and is further described in Section 8.7.1 below.

The study population will be drawn from data sources in the US, UK, Germany, and other countries, including other EU member states, where ozanimod is granted reimbursement. This protocol focuses the study description on preidentified data sources, including two sources of automated data, the CPRD in the UK and the ORD in the US, and prospective MS disease registries from the UK and EU (Section 8.4.3).

8.2.2 Study Period

The study observation period will begin on 01-Jun-2020, the date of first commercial availability of ozanimod in the US. The study end date (when observation period ends) will be approximately 10 years after the start date.

Treatment episodes will be eligible for inclusion if they start on or after the first date of commercially availability of ozanimod in the region covered by the data source. This criterion will apply to all 3 cohorts. Treatment episodes that start within 6 months of the end of available data in the data source will be excluded.

8.2.3 New User Definition

New users will be patients who have a recorded prescription or dispensing for a medication in 1 of the 3 cohorts (see cohort-defining exposures, Section 8.2.1), with no prior prescription or dispensing of any medication from that same cohort during the lookback period. The date of the first prescription or dispensing will be the patient's 'index date' for that cohort.

Within each comparator cohorts, switching from one drug to another in the same cohort (eg, from interferon beta 1a to dimethyl fumarate) will be considered a continuation of the same treatment episode.

Subsequent to their initial index date, patients may switch to a treatment that qualifies them for a different cohort. Patients are eligible for entry into multiple cohorts as exposure is at the treatment level rather than the patient level. A patient will be allowed to enter each cohort only once during the study period (new user). A washout period equivalent to five times the half-life of the discontinued drug will be required before entry into a different cohort (see Table 8.2.3-1).

In clinical practice patients may switch medications before the washout period is concluded. Attrition tables will be provided in interim and final study reports to quantify the number of patients excluded due to this shorter washout period. If the change in sample size is greater than 10%, a sensitivity analysis will be conducted using the shorter washout period. Details will be provided in the statistical analysis plan.

Table 8.2.3-1: Drug-specific Washout Periods

MS DMT	Days Equivalent to 5 Times the Half-Life
Alemtuzumab	70 days
Dimethyl fumarate	1 day
Diroximel fumarate	1 day
Glatiramer acetate	10 days
Interferon beta	2 days
Avonex	4 days
Betaferon	1 day
Extavia	1 day
Rebif	15 days
Rebif Titration Pack	15 days
Rebif Rebidose	15 days
Monomethyl fumerate	1 day
Natalizumab	55 days
Ocrelizumab	130 days
Ozanimod	90 days
Siponimod	7 days
Fingolimod	45 days
Cladribine	5 days
Teriflunomide	95 days
Peginterferon beta-1a	17 days
Mitoxantrone	16 days

8.2.4 Inclusion Criteria

The study will include treatment episodes from men and women. The patient episodes in the study will be required to meet all of the following inclusion criteria as ascertained from each of the automated data sources:

- Be aged 18 years or older at the time of the index prescription or dispensing qualifying the patient for cohort entry
- Have a diagnosis of MS recorded on or before the index prescription or dispensing
- Have at least 6 months of continuous enrollment in the data source (thereby providing medical and dispensing/prescription history data, along with an operational definition of new use) before the index date

8.2.5 Exclusion Criteria

The study will exclude patients with:

- Prescription or dispensing of more than one cohort-defining drug on the index date (dual therapy).This exclusion criterion will be assessed for each potential treatment episode.
- An outpatient or inpatient diagnosis of Crohn's disease (CD) or UC any time prior to or on the index date, as the use of cohort-defining drug may not be related to RRMS.

8.2.6 Baseline and Lookback Period

To characterise the ozanimod and comparator cohorts on the index date, all information available during the lookback time period (pre-index or before the start of each treatment episode) will be collected. The lookback time period is defined as the time period ending on the index date, ie, will include the index date, unless otherwise specified. As all cohort members are required by inclusion criteria to have at least 6 months of data before the index date (baseline period), the lookback period will include at least 6 months during which covariates can be evaluated. For some of the cohort members, more data on covariates might be available beyond 6 months, and all available information will be considered for covariate classification related to MS and concomitant chronic conditions. Nevertheless, for comedications (ie, for diseases other than MS), the lookback time period will be limited to 180 days before or at the index date. Lookback time periods for a small number of specific covariables may be adapted in each data source, eg, to define BMI in the CPRD, the closest data in the 3 years before or at the index date will be used.

8.2.7 Follow-up Time and Censoring Criteria

Follow-up of eligible treatment episodes will start on the day after the index prescription or dispensing. There are two types of discontinuation criteria for this study: censoring of a treatment episode (ie, person-time within a particular cohort) and censoring of study follow-up. Within each patient treatment episode, follow-up for each study outcome will end at the earliest of the following dates:

- Occurrence of the individual study endpoint (counted separately for each endpoint).

  - Once an individual study endpoint occurs within a given treatment episode, patients will no longer be followed for subsequent occurrences of that same endpoint, within that treatment episode or subsequent treatment episodes.
  - Patients may experience multiple types of cardiovascular events. For example, a patient who experiences an AMI event may still be followed for stroke or CV mortality (within that treatment episode and subsequent treatment episodes). Similarly, a patient who experiences a stroke may still be followed for AMI, or CV mortality.
  - The occurrence of CV mortality will censor both the treatment episode and study follow-up.
  - For the composite MACE outcome, both the treatment episode and study follow-up will be censored at the date of occurrence of the first targeted CV event (AMI, stroke, or CV mortality).
- End of the study period.
- Last date of data with validated CV or death outcomes within each of the data sources.
- Disenrollment from the data source (eg, change of insurance plan, emigration, death).
- Dispensing or prescription of more than one study medication on the same day.

Throughout the study period, patients will be eligible to contribute additional episodes (if they qualify to enter other cohorts) until the earliest of the following dates:

- End of the study period.
- Last date of data with validated CV outcomes (or death) within each of the data sources.
- Disenrollment from the data source (eg, emigration, death).

8.3 Variables

The below sections describe the variables that define the exposures, outcomes, and covariates of interest. To account for potential changes in the medical dictionaries that define these variables, the medical dictionaries and code lists will be reviewed in advance of the preparation of the interim reports.

8.3.1 Exposures

For this study, eligible patients will be identified from prescriptions/dispensing of the study medications of interest listed in the data sources included in the study. Cohort-defining drugs are listed in Section 8.2.1. Ascertainment of these exposures will be customized to the drug coding system of participating data sources (eg, NDCs for the ORD, ATCs for the other data sources).

8.3.1.1 Exposure and Time at Risk

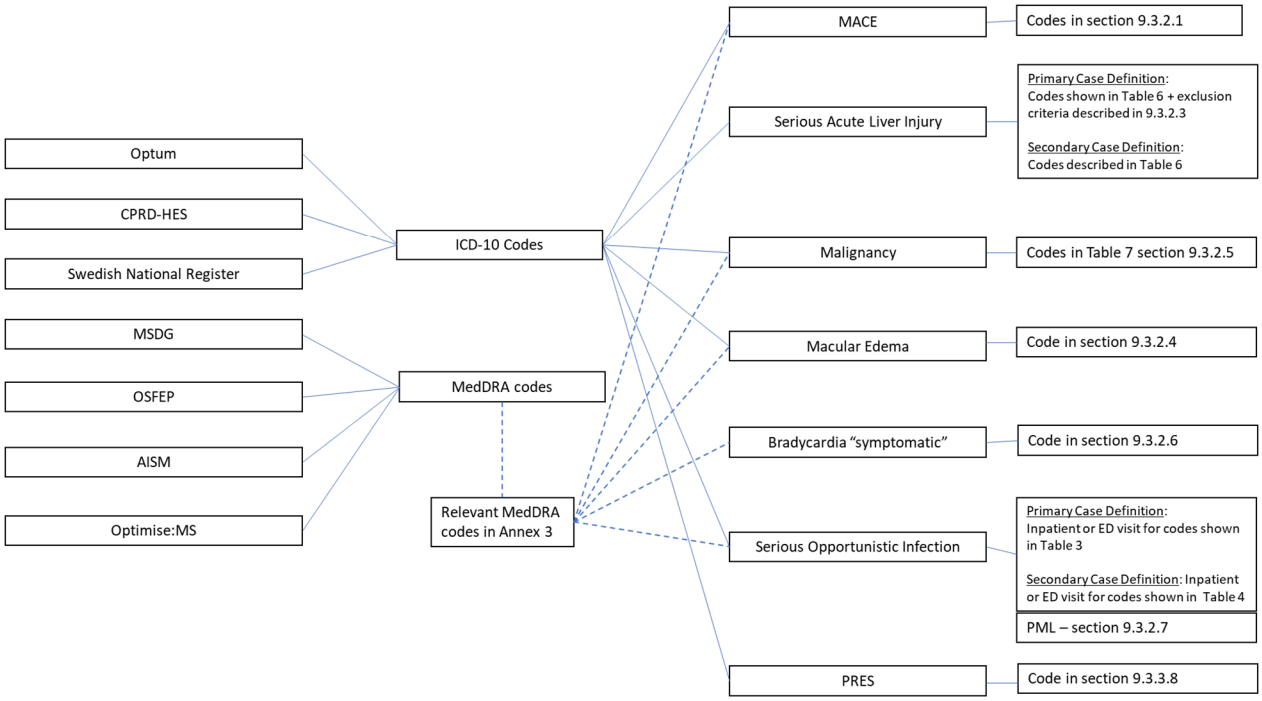
For this study, time at risk ("exposure") for each outcome is assumed to begin one day after cohort entry and continue until 30 days after the presumed end of drug supply. Only use in first continuous treatment episode will be considered. For hematologic malignancy, time at risk will continue until 1 year after presumed end of drug supply; for solid tumors, 2 years after end of drug supply. This choice takes into account median follow-up time of data sources. A continuous episode will be defined as person-time with presumed continual drug supply, allowing for gaps of no more than

30 days (ie, 30 days not covered by a prescription or dispensing). Days of drug supply will be inferred from prescription or dispensing data. If prescriptions/dispensing of the index drug repeat before the presumed end of drug supply, the overlapping day's supply will be added to the end of the concatenated exposure period. Adding 30 days to the end of the days' supply to the risk window accounts for imperfect adherence and allows for the possibility of a drug effect that may extend beyond its discontinuation. For the hematologic and solid malignancy sensitivity analysis, the time at risk will be extended from 1 year to 2 years, and from 2 to 5 years, respectively after end of drug supply. In a sensitivity analysis for all other outcomes, the time at risk will be extended from 30 to 90 days after end of drug supply.

8.3.2 Outcomes

The discussion of endpoints is organized into those associated with each of the primary and secondary objectives. A description of each outcome follows, with a focus on the automated data sources (Medical Dictionary for Regulatory Activities [MedDRA] codes for the outcomes are provided in Appendix 3). During statistical analysis plan development, primary data collection data sources will be mapped to a common data model.

Figure 8.3.2-1: Reference to Outcome Definitions by Data and Code Type



8.3.2.1 Major Adverse Cardiovascular Events

The clinical and operational definitions for MACE can be found in Table 8.3.2.1-1. Because CV outcomes have similar mechanisms and risk factors, the composite MACE outcome will be examined in addition to the individual outcomes. The MACE composite outcome will be defined as the first event of AMI, stroke, or CV death for each patient.

In addition, linkage to death registry data will be used for ascertaining mortality and cause of death. Data source-specific considerations for defining MACE are described in the subsections below.

Table 8.3.2.1-1: MACE Endpoint Definition

Composite Endpoint	Endpoint Components		Clinical Description	Operational Definitions for the CPRD and ORD
MACE	AMI diagnosed in hospital (inclusive of fatal and non-fatal events)		AMI will be defined clinically as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, including ST-elevation MI and non– ST-elevation MI. Almost one third of the patients suffering an AMI die suddenly before arriving at the hospital, and the diagnosis cannot be completed (eg, no electrocardiogram is obtained to show the typical changes or no autopsy is performed). Any AMI noted with death certificates will be categorized as Coronary heart disease death.	≥ 1 ICD-10-CM code for AMI (I21.xx) in the principal or primary diagnosis position on at least one facility claim for inpatient hospitalization[23][a]
	Stroke diagnosed in hospital (inclusive of fatal and non-fatal events)		An acute stroke is defined as the rapid onset of a persistent neurological deficit attributed to an obstruction or rupture of the arterial system. Patients with stroke can die before reaching the hospital; a complete assessment of acute stroke events requires the identification of community stroke deaths. Both hemorrhagic and ischemic strokes will be included in the case definition.	≥ 1 ICD-10-CM code for stroke (I60.xx, I61.xx, I63.xx, or I64.xx) in the principal or primary diagnosis position on at least one facility claim for hospitalization
	CV mortality	Coronary heart disease mortality	Fatal episode of AMI or CHD death.	The following ICD-10 codes in the primary cause of death position will define CV mortality: I20.xx, I21.xx, I60.xx, I61.xx, I63.xx, or I64.xx.
		Cerebrovascular disease mortality	Fatal episode of stroke or cerebrovascular disease death.	

[a] Claims for AMI from emergency departments will not be included in the case identification as they are likely to lead to misclassification.

CPRD The study will include only those CPRD Aurum practices that can be linked with the National Health Service (NHS; 2020)[24] hospital episode statistics (HES) and Office for National Statistics (ONS) vital statistics (Section 8.4). The HES data is coded using ICD-10; diagnoses and causes of death will be ascertained using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10 or ICD-10-CM) codes. Diagnoses identified using HES and causes of death from the vital statistics registry will be considered valid, as these sources are often used

as reference standard to validate information in the General Practitioner (GP) electronic medical record.

ORD For the assessment of mortality outcomes and the MACE composite outcome, identification of all-cause and CV mortality among cohort members will be ascertained via linkage to the National Death Index (NDI).[25] The NDI contains information on date and cause of death. Cause of death is coded using ICD-10 codes. Complete death records for a particular calendar year are available for NDI searches approximately 12 months following the end of the calendar year.

8.3.2.2 Serious Opportunistic Infection

Primary Case Definition

The primary case definition for SOIs for this study is: inpatient hospitalization or Emergency Department (ED) encounter due to the SOIs most commonly described in association with MS treatments, including herpes viruses (including herpes simplex, varicella, cytomegalovirus [CMV]), mycobacterium tuberculosis, and PML.[26,27,28] The medical concept of serious will be operationalized as presence of relevant diagnosis code in inpatient records, ED records, or entered as such in prospective registry. The primary case definition for SOIs will be defined using the below ICD-10-CM codes (MedDRA terms are shown in Appendix 3).

Table 8.3.2.2-1: Serious Opportunistic Infections for Primary Case Definition

Description	ICD-10-CM Code
PML	A81.2
tuberculosis	A15-A19
atypical mycobacterial infections	A31.9
listeria meningitis	A32.11
nocardiosis	A43
herpesvirus	B00
herpesviral meningitis	B00.3
CMV infections	B25
mucocutaneous candidiasis (candidas of skin and nail)	B37.2
systemic candidasis	B37.7
cryptococcal meningitis	B45.1
disseminated cryptococcus	B45.7
ocular toxoplasmosis	B58.0
pneumocystis jiroveci	B59
cellulitis of eyelid	H00.0
cellulitis of lacrimal apparatus	H04.3
cellulitis of external auditory canal	H60.1
pneumonia due to Streptococcus pneumoniae	J13

Table 8.3.2.2-1: Serious Opportunistic Infections for Primary Case Definition

Description	ICD-10-CM Code
pneumonia due to Hemophilus influenzae	J14
bacterial pneumonia, not elsewhere classified	J15
pneumonia due to other infectious organisms, not elsewhere classified	J16
pneumonia in diseases classified elsewhere	J17
pneumonia, unspecified organism	J18
cellulitis of nose	J34.0
cellulitis of mouth	K12.2
cellulitis of anal and rectal region	K61.-
cellulitis of the finger	L03.01
cellulitis of the toe	L03.03
Cellulitis of other parts of limb	L03.11
Cellulitis and acute lymphangitis of face	L03.21
Cellulitis of trunk	L03.31
cellulitis of other sites	L03.81
cellulitis, unspecified	L03.90
UTI	N39.0
cellulitis of male external genital organs	N48.2, N49.-
cellulitis of female external genital organs	N76.4

Secondary Case Definition

The secondary case definition for SOI will include infections in the primary case definition plus those that have been less commonly reported in association with MS treatments. Appendix 3 includes the MedDRA terms for opportunistic infections that appear in the Risk Management Plan for Zeposia, which will be included in the secondary case definition of SOI.

Table 8.3.2.2-2: Serious Opportunistic Infections for Secondary Case Definitions

ICD-10-CM Code	Description
A00–B99	Certain infectious and parasitic diseases
D73.3	Abscess of spleen
E06.0	Acute thyroiditis
E32.1	Abscess of thymus
G00	Bacterial meningitis NEC
G01	Meningitis in bacterial diseases classified elsewhere
G02	Meningitis in other infectious and parasitic diseases classified elsewhere

Table 8.3.2.2-2: Serious Opportunistic Infections for Secondary Case Definitions

ICD-10-CM Code	Description
G04.2	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified
G05	Encephalitis
G06	Intracranial and intraspinal abscess and granuloma
G07	Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere
H00.0	Hordeolum and chalazion
H44.0	Purulent endophthalmitis
H60.0–H60.3	Abscess of external ear, Cellulitis of external ear, Malignant otitis externa, Other infective otitis externa
H65	Nonsuppurative otitis media
H66	Suppurative and unspecified otitis media
H67	Otitis media in diseases classified elsewhere
H68	Eustachian salpingitis and obstruction
H69	Other and unspecified disorders of Eustachian tube
H70	Mastoiditis and related conditions
H71	Cholesteatoma of middle ear
H72	Perforation of tympanic membrane
H73	Other disorders of tympanic membrane
H74	Other disorders of middle ear mastoid
H75	Other disorders of middle ear and mastoid in diseases classified elsewhere
I30.1	Infective pericarditis
I40.0	Infective myocarditis
J00-J06	Acute upper respiratory infections
J09-J18	Influenza and pneumonia
J20-J22	Other acute lower respiratory infections
J32	Chronic sinusitis
J34.0	Abscess, furuncle, and carbuncle of nose
J36	Peritonsillar abscess
J38.3	Other diseases of vocal cords
J39.0	Retropharyngeal and parapharyngeal abscess
J39.1	Other abscess of pharynx
J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection
J85	Abscess of lung and mediastinum
J86	Pyothorax
K04.4	Acute apical periodontitis of pulpal origin

Table 8.3.2.2-2: Serious Opportunistic Infections for Secondary Case Definitions

ICD-10-CM Code	Description
K04.6	Periapical abscess with sinus
K04.7	Periapical abscess without sinus
K10.2	Necrosis of pulp
K11.3	Abscess of salivary gland
K12.2	Cellulitis and abscess of mouth
K14.0	Glossitis
K57.2	Diverticulitis of large intestine with perforation and abscess
K57.4	Diverticulitis of both small and large intestine with perforation and abscess
K57.8	Diverticulitis of intestine, part unspecified, with perforation and abscess
K61	Abscess of anal and rectal regions
K63.0	Ischiorectal abscess
K65.0	Generalized (acute) peritonitis
K65.1	Peritoneal abscess
K65.2	Spontaneous bacterial peritonitis
K65.9	Peritonitis, unspecified
L00–L08	Infections of the skin and subcutaneous tissue
L30.3	Infective dermatitis
M00	Pyogenic arthritis
M01	Direct infections of joint in infectious and parasitic diseases classified elsewhere
M46.2	Osteomyelitis of vertebra
M46.3	Infection of intervertebral disc (pyogenic)
M46.4	Discitis, unspecified
M46.5	Other infective spondylopathies
M60.0	Infective myositis
M65.0	Abscess of tendon sheath
M71.0	Abscess of bursa
M71.1	Other infective bursitis
M72.6	Necrotizing fasciitis
M86	Osteomyelitis
N10	Acute pyelonephritis
N11	Chronic tubulo-interstitial nephritis
N12	Tubulo-interstitial nephritis, not specified as acute or chronic
N13.6	Pyonephrosis
N15.1	Renal and perinephric abscess

Table 8.3.2.2-2: Serious Opportunistic Infections for Secondary Case Definitions

ICD-10-CM Code	Description
N15.9	Renal tubulo-interstitial disease, unspecified
N30.0	Acute cystitis
N30.8	Other cystitis
N30.9	Cystitis, unspecified
N34.0	Urethral abscess
N34.1	Nonspecific urethritis
N34.2	Other urethritis
N39.0	Urinary tract infection, site not specified
N41.2	Abscess of prostate
N43.1	Infected hydrocele
N45.2	Orchitis
N45.3	Epididymo-orchitis
N45.4	Abscess of epididymis or testis
N48.2	Other inflammatory disorders of penis
N61	Inflammatory disorders of breast
N70	Salpingitis and oophoritis
N73	Other female pelvic inflammatory diseases
N75.1	Abscess of Bartholin's gland

Endpoint Identification and Ascertainment

Cases will be ascertained from inpatient hospital data using ICD-10-CM codes in the automated data sources. In the CPRD, these diagnoses will appear in linked HES inpatient data, which will be accepted as valid at face value. In the ORD, the diagnosis needs to appear in the principal diagnosis position on at least 1 facility claim for hospitalization. The rationale for using only the primary or principal discharge diagnosis is that this diagnosis represents the reason, which after study, led to the inpatient stay. Diagnoses that appear in secondary positions are coincidental diagnoses that by themselves may not have led to hospitalization. In ongoing prospective MS registries, endpoint identification and ascertainment will be based on information provided by participating health care provider.

8.3.2.3 Serious Acute Liver Injury

The primary case definition for SALI is hospitalization due to acute liver injury in patients without predisposing factors. Predisposing factors include chronic liver disease, chronic pancreatic disease, alcohol abuse, intra- or extrahepatic biliary obstruction, primary or secondary hepatic, biliary, or pancreatic cancer, metastatic cancer on or before the start of that episode. Additionally, if during the 6 months preceding or on the index date there is a diagnosis of acute infectious

hepatitis, acute cholelithiasis or cholecystits, acute pancreatic disease, or decompensated congestive heart failure (CHF) (ie, CHF prompting ED or hospital care), patients will be considered predisposed to SALI.

Acute liver injury has been defined in terms of an elevation in the serum concentration of ALT or AST, conjugated bilirubin, or ALP. It has been considered that elevations of ALT/AST are indicators of liver injury, whereas increases of conjugated bilirubin are measures of overall liver function. Liver injury alone may not lead to clinically significant liver damage, whereas impaired liver function is a marker of (though not diagnostic of) severe drug-induced hepatotoxicity. Thus, a combined elevation of ALT or AST and conjugated bilirubin without evidence of intra- or extra-biliary obstruction (ie, no significant elevation of ALP) could be used to define potentially clinically significant elevations of serum liver enzyme levels.[29] The concept of combining markers of liver injury and function evolved from the observation of Hyman Zimmerman [30] that "drug-induced hepatocellular jaundice is a serious lesion." Zimmerman noted that the combination of pure hepatocellular injury (ALT elevation without much ALP elevation) and jaundice among patients with drug-induced liver injury had a poor prognosis, with a mortality of 10% to 15%.[30,31,32,33] This observation is referred to as "Hy's Law" by the Food and Drug Administration and has been used by the FDA over the years to assess the potential for a drug to cause severe liver injury— that is, irreversible liver failure that is fatal or requires liver transplantation.[31,32,33]

According to the international Expert Working Group on drug-induced liver injury,[34] acute liver injury is defined by abnormal liver function test results as summarised in Table 8.3.2.3-1. According to the Working Group, persistent drug-induced liver injury is defined as evidence of continued liver injury more than 3 months after hepatocellular or mixed liver injury and more than 6 months after cholestatic liver injury; increases of these parameters for more than 1 year are compatible with chronic liver injury.

Table 8.3.2.3-1: Clinical Criteria for "Clinically Significant" or "Severe" or "Liver Injury"

Endpoint[a]	Definition
Clinically significant ALI[b]	Any of the following criteria: ALT or AST ≥ 5 × ULN, *or* ALT or AST ≥ 3 × ULN *and* total bilirubin ≥ 2 × ULN *or* *ALP* ≥ 2 x ULN
Severe ALI[b]	Clinically significant ALI, bilirubin concentration >2× ULN, and one of the following: International normalized ratio ≥ 1.5 Ascites and/or encephalopathy, disease duration < 26 weeks, and absence of underlying cirrhosis

ALI, acute liver injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal range.

[a] Censoring for the study period will occur if any of the endpoint-specific exclusion criteria are recorded after cohort entry.

[b] Sources: adapted from.[34]

The secondary case definition for SALI is more inclusive than the primary definition: hospitalization due to acute liver injury in patients with or without predisposing factors.

Endpoint Identification and Ascertainment

Potential cases of liver injury will be identified by the same process in the CPRD and ORD data sources through inpatient hospitalizations with a principal or primary discharge diagnosis with an ICD-10-CM code suggestive of SALI. Relevant ICD-10 codes appear in Table 8.3.2.3-2. The MedDRA codes are shown in Appendix 3.

Table 8.3.2.3-2: ICD-10-CM Codes to Identify Suspected SALI From Hospital Diagnoses

ICD-10 code	Description
K71.1	Toxic liver disease with hepatic necrosis
K71.2	Toxic liver disease with acute hepatitis
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.9	Toxic liver disease, unspecified
K72.0	Acute and subacute hepatic failure
K72.9	Hepatic failure, unspecified
K76.8	Other specified diseases of liver
K76.9	Liver disease, unspecified
R17	Unspecified jaundice, excludes neonatal
Z94.4	Liver transplant

Validation

The algorithm used to identify SALI using the primary case definition in automated data sources will be evaluated based on review of clinical records or laboratory data, using the criteria for "clinically significant" acute liver injury (ALI) listed in Table 8.3.2.3-1.

Validation of SALI: Optum will conduct a validation study of the algorithm used to identify SALI. A random subset of patients with the outcome identified on the basis of specified claims codes in the source database will have medical records sought through an approved process within Optum. The medical records obtained through this process will be blinded with respect to patient-identifying information and to exposure status. In cases obtained in registry/cohort studies,

cases will be verified by reviewing the source data (redacted patient medical charts). The validation plan will is described in detail in a separate document.

8.3.2.4 Macular Edema

In the automated data sources, macular edema will be identified based upon the presence of at least 1 ICD-10-CM diagnosis code for macular edema (H35.81 or H59.03*).

8.3.2.5 Malignancy

Malignancies will be identified based upon the presence of at least 1 ICD-10-CM diagnosis code for malignancy associated with an inpatient hospitalization in the principal or primary diagnostic position. Malignancies will be defined as a composite and by type, according to the following groupings in Table 8.3.2.5-1.

Table 8.3.2.5-1: ICD-10-CM Codes to Identify Malignancy From Hospital Diagnoses

ICD-10 code	Description
C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
C15-C26	Malignant neoplasms of digestive organs
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
C40-C41	Malignant neoplasms of bone and articular cartilage
C43-C44	Melanoma and other malignant neoplasms of skin
C45-C49	Malignant neoplasms of mesothelial and soft tissue
C50-C50	Malignant neoplasms of breast
C51-C58	Malignant neoplasms of female genital organs
C60-C63	Malignant neoplasms of male genital organs
C64-C68	Malignant neoplasms of urinary tract
C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
C73-C75	Malignant neoplasms of thyroid and other endocrine glands
C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites
C7A-C7A	Malignant neuroendocrine tumors
C7B-C7B	Secondary neuroendocrine tumors
C81-C96	Malignant neoplasms of lymphoid, hematopoietic and related tissue
D00-D09	In situ neoplasms
D37-D48	Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes
D49-D49	Neoplasms of unspecified behavior

8.3.2.6 Symptomatic Bradycardia

Symptomatic bradycardia will be defined by the presence of at least 1 ICD-10-CM code (R00.1) associated with an ED encounter or an inpatient hospitalization in any diagnostic position.

8.3.2.7 Progressive Multifocal Leukoencephalopathy

PML will be defined by the presence of at least 1 ICD-10-CM code (A81.2) listed as principal or primary diagnoses for inpatient hospitalizations, unless MS is the principal or primary discharge diagnosis, in which case the PML diagnosis does not have to be principal or primary.[26]

Validation of PML: In health claims data sources, medical records will be sought in a subset of patients for validation of PML diagnoses to assess information bias. This subset of patients is subject to the availability of linkage to patient medical data. Due to patient privacy reasons, the data partner will conduct PML verification.

In ongoing MS registries, the PML cases will be based on information collected as routine part of registry data process in accordance with the data holder's privacy policies.

This process will be in parallel to external expert review as part of routine pharmacovigilance activities described in the Risk Management Plan.

8.3.2.8 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome will be defined by the presence of at least 1 ICD-10-CM diagnosis code (I67.83) in any diagnostic position associated with either an ED encounter or an inpatient hospitalization.

8.3.3 Other Patient Demographics and Clinical Characteristics

This section describes additional variables that will be obtained from the data sources beyond exposures and outcomes. These variables will be used to determine study eligibility, describe cohorts at baseline[1], adjust for confounding, and describe patients at the time of the event to ensure that the current status of the patient at the time of the event is as accurate as possible. Definitions of specific variables will be adapted to the type and availability of data in each data source, and they will be detailed in the statistical analysis plan. Not all variables will be present in every data source (eg, smoking or BMI). Except for factors that serve to determine eligibility and censoring, all variables will be considered as potential confounders in the analysis (Section 8.7.1). Medical conditions may be identified through diagnoses or treatment-specific medications or procedures. Operational definitions and parameterization of covariates will be detailed in the statistical analysis plan prior to data extraction.

- Demographics: age at start of a new treatment episode and gender
- Lifestyle and socioeconomic variables: smoking, obesity, alcohol use, social deprivation index (where available)
- Healthcare utilization in the 6 months prior to start of a new treatment episode: number of outpatient visits to general physicians and specialists; number of hospitalisations, and numbers of days hospitalized[35,36,37,38]
- Comorbidity score any time prior to index (using conditions identified by ICD-10-CM codes)

[1] As this is a treatment level analysis, the patient demographic and clinical characteristics will be described at the time of new therapy.

- Multiple sclerosis treatment history: number of prior treatment episodes and type of all DMTs, number of flares in the 6 months prior to index
- Inclusion criteria and censoring criteria (Section 8.2.7)

8.3.3.1 Risk Factors to be Considered in the Propensity Score Model for Each of the Outcomes

The following covariates will be included in the PS model for all outcomes:

- Age (with cutpoints to be determined based on sample size and distribution of age),
- Number of MS diagnosis billing codes during the 6 months lookback time period (relevant to US claims Optum data source only),
- Steroid use, and
- Line of therapy (eg, first line [US approval] or second line [EU approval]).

Additional outcomes-specific covariates that will be considered for inclusion in the PS models are listed in the following sections.

MACE: variables include risk factors for constituent elements, AMI, stroke, and CHD death. They include traditional risk factors such as smoking, hypertension, hyperlipidemia, and diabetes mellitus. They also include chronic inflammatory conditions associated with increased risk of disease, including rheumatoid arthritis, psoriasis, systemic lupus erythematosus, and IBD. Patients with demonstrated atherosclerotic disease are at particularly increased risk; markers include diagnoses of angina pectoris, TIA, or procedures to treat these conditions, including angioplasty, surgical bypass grafting, or amputation. Atrial fibrillation is a risk factor for stroke. Risk factors for cardiovascular death, which includes sudden cardiac death, include (in addition to factors mentioned) schizophrenia, epilepsy, and ventricular tachyarrhythmias.

SOI: history of opportunistic infections not requiring hospitalization, latent tuberculosis infection, previous hepatitis B or C, sustained use of systemic corticosteroids, use of nonbiological immunosuppressants other than cohort-defining drugs (eg, methotrexate, cyclosporin), and biologic agents other than cohort-defining drugs (eg, tumor necrosis factor (TNF)-inhibitors, anti-cytokines, and monoclonal antibodies targeting T-cell and B-cell lymphocytes).

SALI: major predisposing factors are exclusion and censoring criteria (Section 8.2.5). Potentially hepatotoxic medications will be considered as potential confounders (refer to Table 13-5 in Appendix 3).

Macular Edema: uveitis or diabetes mellitus will be considered confounders and added to PS model.

Malignancy: predisposition factors include smoking and obesity (BMI $\geq$ 30.0).

Symptomatic Bradycardia: no additional risk factors applied to PS model.

PML: HIV and prior natalizumab treatment will be added to PS.

PRES: predisposing factors included will be renal failure, and hypertension. 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.[39]

8.4 Data Sources

The study cohorts will include multinational distributed data sources that include electronic databases from health systems in which ozanimod is launched and in countries where reimbursement status is anticipated to be granted or has been granted. The specific data sources found suitable for inclusion include:

- US: ORD (administrative insurance claims database)
- UK:
  - CPRD Aurum, linked to HES and national death statistics (medical record database)
  - Optimise (UK)
- EU: MS cohort and registries, which include, but may not be limited to:
  - DMSG (Germany)
  - OFSEP (France)
  - Associazione Italiana Sclerosi Multipla (Italy)
  - National Patient Register (NPR) + Electronic Medical Record (EMR) (Sweden)

The Market Authorisation Holder (MAH) will continue to evaluate relevant data sources within the EU for feasibility through the study duration. If reimbursement of ozanimod is granted in a given country and study patient group / outcomes of interest can be collected by the relevant data holder in that country, then the MAH will work with the data holder to investigate participation in the ORION study.

Potential, additional data sources will be evaluated using the following criteria.

- Ozanimod exposure and other MS related drug exposure can be accurately captured.
- Number of ozanimod exposed MS patients.
- The outcomes and relevant patient demographic and clinical characteristics can be described using relevant diagnosis code or algorithm in electronic database or data entered by participating center into the registry or cohort studies.

8.4.1 Summary of Feasibility Assessment

A feasibility assessment of the potential data sources was performed to evaluate their suitability for the proposed study (Table 8.4.1-1).

Among the factors considered were the number of patients included, type of data collection, and completeness of the key study variables within the data source. Additional feasibility assessment criteria from the European Medicines Agency (EMA) Guideline (2020)[40] on registry-based studies

(page 7) were considered specifically for the EU data sources, as summarized in Appendix 4. Participation in this study is also subject to registry interest.

Table 8.4.1-1: Key Characteristics of the Data Sources[a]

	Database, MS Cohort, or Registry Data Source						
Variables in Study	**OPTUM**	**CPRD**	**NPR+EMR**	**DMSG**	**Optimise**	**OFSEP**	**AISM**
Country	**US**	**UK**	**Sweden**	**Germany**	**UK**	**France**	**Italy**
Number of MS patients (as of April 2021)	82,630	[redacted]	[redacted]	48,000	1,500	61,000	[redacted]
Start year for registry or cohort data source	1993	1987	1964	2001	2017	2011	2015
Type of data source	Insurance claims database	Medical record database	Medical record database	MS registry	MS cohort study	MS registry	MS registry
Type of data collection	ICD-10-CM codes, NDC/GPI codes	READ/ICD-10 codes	ICD-10 codes	Primary data collection	Primary data collection	Primary data collection	Primary data collection

Abbreviations: AISM, Associazione Italiana Sclerosi Multipla; DMSG, Deutsche Multiple Sklerose Gesellschaft Bundesverband e.V, MRI, Magnetic resonance imaging.

[a] Data as of November 2020 and based on publically available data.

Table 8.4.1-2: Availability of Covariates by Data Source[a]

	Database, MS Cohort, or Registry Data Source						
Variables in Study	**OPTUM**	**CPRD**	**NPR+EMR**	**DMSG**	**Optimise**	**OFSEP**	**AISM**
Country	**US**	**UK**	**Sweden**	**Germany**	**UK**	**France**	**Italy**
Baseline Characteristics (y/n)	yes	yes	yes	yes	yes	yes	yes
Age	yes	yes	yes	yes	yes	yes	yes
Gender	yes	yes	yes	yes	yes	yes	yes
Year of Diagnosis	yes	yes	yes	yes	yes	yes	yes
MS Type	yes	yes	yes	yes	yes	yes	yes
Previous DMTs	yes	yes	yes	yes	yes	yes	yes
Mean follow-up time	2.6 years	9.1 years	High	Lifetime	5 years	1 year	lifetime
Concomitant Medications	yes	yes	yes	yes	yes	yes	yes

Table 8.4.1-2: Availability of Covariates by Data Source[a]

	Database, MS Cohort, or Registry Data Source						
Number of Previous Relapses	yes	yes	yes	yes	yes	yes	yes
Medical History	yes	yes	yes	yes, in PV cohort	yes	yes[b] (says history of serious disease)	yes
Cardiac disease	yes	yes	yes	yes, in PV cohort	yes	yes	no
Hepatic disease or injury	yes	yes	yes	yes, in PV cohort	yes	yes	no
Diseases of the eye (any)	yes	yes	yes	yes, in PV cohort	yes	yes	yes
CNS diseases (any)	yes	yes	yes	yes, in PV cohort	yes	yes	yes
Opportunistic disease	yes	yes	yes	yes, in PV cohort	yes	yes	no
Malignancy	yes	yes	yes	yes, in PV cohort	yes	yes	no
Comorbidities			yes		yes	yes	yes
Cardiac disease	yes	yes	yes	yes, in PV cohort	yes	yes	no
Hepatic disease or injury	yes	yes	yes	yes, in PV cohort	yes	unknown	no
Diseases of the eye (any)	yes	yes	yes	yes	yes	unknown	yes
CNS diseases (any)	yes	yes	yes	yes	yes	yes	yes
EDSS	no	yes	no	yes	yes	yes	yes
Anti-JC antibody status	no	yes	no	no	unknown	yes	No
MRI status	No	yes	no	yes, in PV cohort	yes	yes	yes
Lab test values	no	yes	no	yes, in PV cohort	yes	yes	yes

Abbreviations: AISM, Associazione Italiana Sclerosi Multipla; DMSG, Deutsche Multiple Sklerose Gesellschaft Bundesverband e.V, EDSS, Expanded Disability Status Scale; MRI, Magnetic resonance imaging; PV, pharmacovigilance.

[a] Data as of November 2020 and based on publically available data.

[b] Data source says history of serious disease.

Table 8.4.1-3: Availability of Outcomes by Data Source

	Database, MS Cohort, or Registry Data Source[a]						
Variables In Study	**OPTUM**	**CPRD**	**NPR+EMR**	**DMSG**	**Optimise**	**OFSEP**	**AISM**
Country	**US**	**UK**	**Sweden**	**Germany**	**UK**	**France**	**Italy**
	Approach to collection of outcomes of Interest Prespecified / structured data collection form [b,c]						
MACE	ICD-10codes or algorithm	ICD-10codes or algorithm	ICD-10codes or algorithm	MedDRA	MedDRA	MedDRA	MedDRA
SOI	ICD-10codes or algorithm	ICD-10codes or algorithm	ICD-10codes or algorithm	MedDRA	MedDRA	MedDRA	MedDRA
SALI	ICD-10codes or algorithm	ICD-10codes or algorithm	ICD-10codes or algorithm	MedDRA	MedDRA	MedDRA	no
Macular Edema	ICD-10codes or algorithm	ICD-10codes or algorithm	ICD-10codes or algorithm	MedDRA	MedDRA	MedDRA	MedDRA
PRES	ICD-10codes or algorithm	ICD-10codes or algorithm	ICD-10codes or algorithm	MedDRA	MedDRA	no	yes
Symptomatic Bradycardia	ICD-10codes or algorithm	ICD-10codes or algorithm	ICD-10codes or algorithm	MedDRA	Unknown	MedDRA	unknown

Abbreviations: AISM, Associazione Italiana Sclerosi Multipla; DMSG, Deutsche Multiple Sklerose Gesellschaft Bundesverband e.V, MRI, Magnetic resonance imaging .

[a] Data as of November 2020 and based on publically available data.

[b] Ability to collect data points based on sponsor request.

[c] Outcome case definition defined by individual data source holder.

8.4.2 Optum Research Database and the Optum Medicare Advantage and Medicare Part D Database (US)

8.4.2.1 Optum Administrative Insurance Claims Data

Optum Research Database (ORD)

The patients included in this study will be drawn from a proprietary research database containing eligibility and pharmacy and medical claims data from a large US health insurance plan affiliated with Optum. For 2018, data are available for approximately 14.3 million individuals with medical and pharmacy coverage. On average, individuals are enrolled in the health plan for 2.6 years. Underlying information is geographically diverse across the country and fairly representative of the US population. Optum research activities utilize de-identified data from the research database. In limited instances, patient identifiers may be accessed where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

Medicare Advantage and Medicare Part D Data (MA-PD)

Beginning in 2006, complete medical and pharmacy information is available for Medicare enrollees in the US government sponsored Medicare program with medical and Medicare Part D

(pharmacy) coverage. The pharmacy claims contain sufficient information to trace patients' pharmacy expenditures through the multiple phases of the Medicare Part D plans. For 2018, data are available for approximately 4.3 million individuals with both medical and pharmacy benefit coverage. Underlying information is geographically diverse across the country and fairly representative of the US Medicare population. Optum research activities utilize de-identified data from MA-PD. In limited instances, patient identifiers may be accessed where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

For both the ORD and MA-PD, pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications.

Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of provided services, including specialty, preventive and office-based treatments. Medical claims include information such as diagnoses (International Classification of Diseases, 10th revision since 1-Oct-2015), procedures (Current Procedural Terminology or Healthcare Common Procedure Coding System), site of service, provider specialty, revenue codes, and paid amounts. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, eg, physicians, use the HCFA-1500 or CMS-1500 formats. Claims for facility services submitted by institutions, eg, hospitals, use the UB-82, UB-92, UB-04, or CMS-1450 formats.

Supplemental Data Source: National Death Index Database

The NDI database (US Department of Health and Human Services, 2020) is a central computerized index of death record information comprised of data on file in the state vital statistics offices. The US National Center for Health Statistics (NCHS) maintains the database, which contains both date and cause of death for adults and children. Records from 1979 through 2018 are available and contain a standard set of identifying information on each death, and they are updated annually. Death records are added to the NDI file annually, approximately 12 to 16 months after the end of a particular calendar year. Early release files for a particular calendar year will be available for NDI routine searches when approximately ≥ 90% of the year's death records have been received and processed, but no later than 6 months after the end of the calendar year. However, completion status may vary by state (70% to 100%), and the early release file is subject to additions and corrections. The NDI data may be linked to a subset of the ORD or MA-PD following necessary approvals.

8.4.3 UK Clinical Practice Research Datalink

In the UK, most of the population is registered with an NHS-funded general practice. General practitioners' service is free for the patient at the point of use. General practitioners provide primary care, order tests, issue prescriptions and referrals to specialists. General practitioners also issue prescriptions for some long-term treatments started by specialists. Approximately 55% of general practices in England use the electronic patient record system, Egton Medical Information

Systems (EMIS) Web. The electronic medical records from general practices that use EMIS Web and agreed to contribute to CPRD are collected in CPRD Aurum.[41]

CPRD Aurum was launched in October 2017[41] and its size has been increasing as practices transition from other software to EMIS Web. When practices start contributing to CPRD Aurum, CPRD receives historical (coded) data from patients, including patients who died or who left the general practice, and makes this historical data available for research. The CPRD Aurum data include year of birth, sex, lifestyle factors (eg, smoking and drinking habits), signs, symptoms, clinical measurements (eg, weight, height, BMI, blood pressure), diagnoses, referrals, immunizations, tests requested and their results, and prescriptions issued for medications or devices. A variable proportion of missingness can be expected in lifestyle factors, clinical measurements and other data elements, as recording of this information is decided by the GP during routine practice. The CPRD Aurum data are coded using Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT), and local EMIS Web codes. Drugs and devices are coded in using the Dictionary of Medicines and Devices, nested within SNOMED CT. The CPRD Aurum is updated monthly.

Prescriptions written by physicians outside the general practice and records of drugs administered in specialty care are not systematically recorded in the CPRD.[42] Specialists typically inform GPs about care of their patients, including treatment, and GPs may manually enter such information into their records. Because neurologists, rather than GPs, typically make prescribing decisions about DMTs for MS, many or all of the study medications may not be systematically captured in the GP record. However, NHS Digital, has plans to make data about prescribing in secondary care available for linkage, although no firm time lines have been provided[24,43] (NHS Digital has responsibility for standardising, collecting and publishing data from across the health care system in England). Validation of specific AEIs will take place through comparison of a subset of identified AEs in the CPRD with the linked HES database. Previous researchers have used this approach to validate the CPRD (Quality and Completeness of Myocardial Infarction Recording in Clinical Practice Research Datalink Aurum - PubMed (nih.gov)). As of November 2020, investigators at the University of Oxford are piloting linkage of specialty prescribing information to primary care data in the context of ongoing research into Covid-19 (personal communication, Professor Ben Goldacre, University of Oxford, 10-Nov-2020).

Within the NHS, patients are issued a unique patient identifier used in primary, secondary and tertiary care. This identifier allows linking patient level data from general practices to various other data sets, including the HES, ONS, and cancer and other disease registries, and other data sources. Linkage between general practice data and these NHS data sets is conducted by a trusted third party using the NHS number, exact date of birth sex and patients' postcode. The HES data contain details of all admissions or attendance to hospitals; data do not include inpatient medications. Diagnoses are coded in the ICD coding system (currently ICD-10) and procedures are coded in Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS). As of November 2020, recent HES release covered the period from April 1997 to March 2020. The ONS data is considered the gold standard source for mortality data and contain date, place and cause of death, starting in 1998. Cause of death is coded in the ICD coding system

(currently ICD-10). The most recent release of ONS data covered the period from January 1998 to April 2020. All CPRD Aurum practices consented to participating in these linkages. Primary care data can also be linked to datasets with information on socioeconomic status at the general practice or patient level.[41]

Patient identifiers (name, date of birth, post code and NHS patient number) are removed from the data before the data are sent to CPRD. Patients can opt out of having their information used for research purposes; as of September 2018, 2.7% of patients registered with a general practice in England had done so. Researchers who want to use CPRD Aurum must have the study approved by the Independent Scientific Advisory Committee (ISAC) to ensure that the proposed research is viable, does not raise governance concerns, and attains an acceptable scientific. [41]

As of October 2020, 1,350 practices were contributing data to CPRD Aurum, and they contribute data from 12.9 million currently registered patients (19% of the UK population). The median follow-up is 9.1 years for current patients. Patients in CPRD Aurum are considered to be representative of the English population in terms of geographical distribution, deprivation, age, and gender.[44] The duration of available follow-up for each patient is expected to be high.

8.4.4 Other EU MS Cohort or Registry Data Sources

The MAH has initiated discussions with each of the following MS cohort or registry data sources to be included in this study based upon key data sources for MS described in.[45]

8.4.4.1 German MS Registry - DMSG

Created in 2001, the DMSG houses information for more than 48,000 German MS patients contributing data from approximately 190 centres. In the last year, 15,000 patients have received an update to their record. Over the last 3 years, median annual recruitment for the registry was 3,500 patients per year. The DMSG expects to follow patients longitudinally until death. Interruptions or loss in follow-up may occur if patients switch centers or centers cease participation in the registry. 30 centers have already been onboarded for the newly established pharmacovigilance module (forming the basis for PASS surveillance). The sponsor takes part in the multi-stakeholder funding of the pharmacovigilance module of the registry enabling the use of the registry for this PASS. Ozanimod is already marketed in Germany and first patients are followed up in the registry. The DMSG performs a constant monitoring of the verbatim terms entered by the centers in the AE-Description field. In case of unclear descriptions, the DMSG raise queries via the eCRF-Systems. If the DMSG find terms relating to AEIs these are escalated manually. Some terms (like leukozytopenie) automatically trigger requests eg, for lab data or upgrade to SAE-Status. Further feasibility information is included in Appendix 4.

8.4.4.2 UK Optimise: MS

Optimise: MS is conducted in the UK and collects data from participating neurologists and MS centers. The registry focuses on data collection to assist in monitoring of benefits and risks of disease-modifying therapies for prospective pharmacovigilance monitoring and allows for the addition of free text data entry. All AE data captured in Optimise is collected by the clinical staff at the participating sites. In addition to their clinical assessment, study subjects are interrogated at

each site visit regarding any events experienced since the previous visit; events are classified by the interviewing clinician. The data is uploaded to the central database where validity checks on the event dates and classifications are performed. The same process is used for all AEs. The relative frequency AEIs and AEs in Optimise then will be compared with pooled, publicly available results from the clinical development program. A feasibility assessment shows that outcomes of interest are currently collected among the data points. Mean patient level follow-up is approximately 5 years. Limitations of this data source include 1) ozanimod is currently not reimbursed in the UK; 2) this data source currently has less than 2,000 MS patients, which will limit the sample size of ozanimod-treated patients as well as events of rare outcomes.

8.4.4.3 France Observatoire Français de la Sclérose en Plaques (OFSEP)

OFSEP is an observational cohort of MS and related disorders in France. It was initiated in 2011 and consists of a consortium of three entities: Lyon University Hospital, Lyon 1 University and EDMUS Foundation. The study collects data regarding mechanisms of MS, the prognostic factors of disease progression, the effectiveness and safety of therapeutic drugs, the impact of the disease on patients and society. The study covers approximately 47% of MS patients in France and currently houses data on over 61,000 MS patients (median follow-up time = 1 year). MedDRA are populated centrally in the database after receipt from centers. Any ambiguity is validated by OFSEP. A feasibility assessment shows that cardiovascular outcomes, bradycardia, SALI, malignancy, and macular edema are currently collected among the data points. Posterior reversible encephalopathy syndrome is not collected. Ozanimod reimbursement has been granted in France. Further feasibility information is included in Appendix 4.

8.4.4.4 The Italian Sclerosi Multipla Registry

In 2015, the Italian MS Registry was officially launched as a scientific research tool welcoming epidemiological and clinical studies. The Italian MS Registry is organized as a network of MS clinical centers, and MS neurologists are in charge of the centers. Over 140 Italian Clinical Centers have joined the project, which collects the demographic and clinical data of over [redacted] MS patients. All patients with MS are referred to a specific center of their choice and if they change the center and refer to another one, the previous patient clinical data are maintained and from that time on are open to and filled in by the new center so that the patient data are not lost. Usually, a patient is followed from the neurologist/center of choice through death. The Italian MS Registry have in the national staff, a group of research assistants visiting the Centers, interacting with the Center staff, and helping them to complete all of the clinical data and assuring that the information is complete. This is a general activity going on for any information currently inserted in the Register. In addition, when a PASS study is activated and a contract is in place, the Italian MS Registry train the staff and assign a specific task to them to be confident that all the detailed information needed according to the specific PASS protocol is included. Initial feasibility of the registry shows that macular edema is currently the only outcome of interest collected among the data points. However, as of September 2021, ozanimod reimbursement has not been granted in Italy. Further feasibility information is included in Appendix 4.

8.4.4.5 National Patient Register of Sweden

The NPR in Sweden is a non-disease specific registry. The registry covers 80% of the MS patients in Sweden and houses approximately [redacted] MS patients. The Swedish NPR - National Board of Health and Welfare (socialstyrelsen.se) is Sweden's nationalized database of diseases and treatments in specialized care, including inpatient care; specialist outpatient care; psychiatric care; and emergency care (since 2016). The clinical data contained in this database includes specialty care and hospitalization data derived from legally mandated, systematic reporting from included settings of care. Validation studies have been conducted. The database does not contain primary care. As part of this study's feasibility, it has been determined a potential limitation with respect to treatment. Data show a lower use of S1P modulators and preferential (off-label) use of rituximab in certain regions in Sweden. The Swedish National Inpatient Register (IPR), also called the Hospital Discharge Register, was established in 1964. The IPR has complete national coverage since 1987. The IPR is part of the NPR. Sweden has a single-payer, public healthcare system and patients are followed for the duration of their contact with the Swedish healthcare system. The duration of available follow-up period for each patient is expected to be high. During the preliminary feasibility assessment of the registry showed that not all outcomes were captured. Subsequent attempts to interact with the register have been unsuccessful. As of September 2021, ozanimod has not been granted reimbursement in Sweden and uptake of ozanimod in Sweden may be limited even after it is granted reimbursement in Sweden. Because the study will continually monitor new data sources for participation, the sponsor will continue to monitor this data source for potential study participation due to register size.

8.5 Study Size

The size of the study cohorts will be determined by the uptake of ozanimod and comparator drugs in the countries and populations included in the data sources during the study period, and the amount of person-time each patient will contribute will depend on how long they remain on specific treatments.

The estimated number of patients treated with ozanimod is 9,000 for the full study (see Table 8.5-1). Specifically, at least 2,020 patients treated with ozanimod (7,660 person-year of follow-up) from Germany, France, and Italy could be included in the study. In UK, the study anticipates at least 500 ozanimod-treated patients and 3,900 person-year of follow-up could be included in the study. The study anticipates at least 7,000 ozanimod-treated patients with at least 14,000 person-year of follow in the US.

Table 8.5-1: Estimated Sample Size and Person-Time

	Database, MS Cohort, or Registry Data Source						
Variables in Study	**OPTUM**	**CPRD**	**NPR+ EMR**	**DMSG**	**Optimise**	**OFSEP**	**AISM**
Country	**US**	**UK**	**Sweden**	**Germany**	**UK**	**France**	**Italy**
Number of MS Patients (as of April 2021)[a]	82,630	[redacted]	[redacted]	48,000	1,500	61,000	[redacted]
Range of Estimated Ozanimod Utilization Among all MS Patients (%)	8% - 16%	1% - 5%	0% - 1%	2% - 4.5%	1% - 5%	1% - 8%	1% - 5%
Minimum Number of Unique Patients Anticipated Ozanimod Patients During 5 year Accrual Period	7000	350	0	960	150	610	450
Mean Follow-up Time[a]	2.6 years	9.1 years	High	Lifetime	5 years	1 year	Lifetime
Anticipated Person-year Contribution	14,000	3150	0	4,800[b]	750	610	2,250[b]

[a] data as reported by the data holder.

[b] assumes 5-year follow-up.

The MAH will continue to monitor the number of ozanimod-treated patients. Enrollment progress will be included in annual study reports.

The implications of various study sizes on precision of results for various endpoints are based on incidence rate observed in published studies. Table 8.5-2 shows the probability, given a hazard ratio of 1, that the upper bound of the 95% CI for the hazard ratio will be less than several threshold values, across a range of potential study sizes.

- These results assume that the incidence rate for MACE endpoints in an unselected population of patients with MS is 25 per 10,000 person-years.[46]
- Table 8.5-3 shows corresponding estimates for various scenarios, also assuming the hazard ratio (HR)=1, for SOIs, for which the incidence rate in the comparator groups is approximately 10 per 10,000 person-years.[26,47]
- The incidence rate of drug-induced liver injury (a different case definition from this study) has ranged in the order of 0.7 to 3.9 per 100,000 person-years.[48,49] Given this very low anticipated background rate, no estimates about study precision have been developed for this outcome.

Results in Table 8.5-2 and Table 8.5-3 can be used to estimate the precision from analyses conducted in a single data source. The analyses conducted separately by data source will be combined in a fixed effects meta-analysis, the precision of the summary results from the meta-analysis could be greater or lesser than the estimates below, depending on the heterogeneity of the effect over data sources and the validity of the assumptions needed to carry out the analysis.

Table 8.5-2: Probability That Upper Bound of 95% CI Will be Lower Than Specified Threshold Assuming HR=1 and Incidence Rate in Unexposed Cohort is 25/10,000 PY

Range of Potential Person-year of Follow-up	Person-years		Probability That UB 95% CI is Below			
	Unexposed	Exposed	1.5	2	2.5	3
6,000	5,000	1,000	0.08	0.17	0.26	0.35
12,000	10,000	2,000	0.13	0.29	0.47	0.61
18,000	15,000	3,000	0.17	0.41	0.63	0.79
24,000	20,000	4,000	0.22	0.52	0.75	0.89
30,000	25,000	5,000	0.26	0.61	0.84	0.94
36,000	30,000	6,000	0.30	0.69	0.90	0.97
42,000	35,000	7,000	0.34	0.76	0.94	0.99
48,000	40,000	8,000	0.38	0.81	0.96	0.99
54,000	45,000	9,000	0.42	0.85	0.98	1.00
60,000	50,000	10,000	0.46	0.89	0.99	1.00

For example, with a total sample size of 30,000 person-years, the probability of observing a 100% increased risk among the exposed population is 0.61 with a hazard ratio = 1.

Table 8.5-3: Probability That Upper Bound of 95% CI Will be Lower Than Specified Threshold Assuming HR=1 and Incidence Rate in Unexposed Cohort is 10/10,000 PY

Range of Potential Person-year of Follow-up	Person-years		Probability That UB 95% CI is Below:			
	Unexposed	Exposed	1.5	2	2.5	3
6,000	5,000	1,000	0.06	0.09	0.13	0.17
12,000	10,000	2,000	0.08	0.14	0.22	0.29
18,000	15,000	3,000	0.09	0.19	0.30	0.41
24,000	20,000	4,000	0.11	0.24	0.39	0.52
30,000	25,000	5,000	0.13	0.29	0.46	0.61
36,000	30,000	6,000	0.15	0.34	0.54	0.69
42,000	35,000	7,000	0.16	0.39	0.60	0.76
48,000	40,000	8,000	0.18	0.43	0.66	0.81
54,000	45,000	9,000	0.20	0.48	0.71	0.85
60,000	50,000	10,000	0.22	0.52	0.75	0.89

For example, with a total sample size of 30,000 person-years, the probability of observing a 100% increased risk among the exposed population is 0.29 with a hazard ratio = 1.

Accrual of unique patients exposed to ozanimod will be monitored annually in each data source. Feasibility to include additional data sources will be summarized at year 5. Annual progress reports will include number of data sources and total number of patients included. If the projected sample size is smaller than the sample size required to achieve sufficient power for planned analyses, mitigation approaches could include the following: recommendation to perform the analysis using the sample size available at the time, consideration of including additional or alternative data sources (eg, adding automated databases for retrospective study in Europe), using the Optum database as the primary database as it has a larger sample size, continuation of monitoring in the data source to accrue additional data thus extending the study period, or pooling country-specific data sources or pooling country-specific data sources.

Optum

The Optum data source is broadly based geographically in the US, so it reflects MS patients and MS care across a wide range of providers and care settings in the US. Accordingly, it will be representative of insured people in the US. Optum has prepared updated sample size and power calculations. Assumptions are still needed to project the numbers of MS patients who will be prescribed ozanimod. Based on fingolimod uptake in the Optum database, Optum projects nearly 9,000 patients will receive ozanimod in the Optum database over the course of the study, and application of eligibility criteria may reduce this somewhat. Thus, we estimate that about 7,000 patients will represent a realistic accrual. Since the indication for ozanimod is a chronic disease, it is likely that many patients will have a duration of follow-up that is close to the dwell

time of patients in the data source, and this was the foundation of the exposure estimate. The average time a person spends in the Optum database is approximately 2.6 years, so it is likely that each patient will contribute at least one and possibly as much as 2 years of follow-up. Thus, 7,000 patients will likely provide 7,000 to 14,000 person-years of study observation. At the end of the study, there will likely be 80% power to detect a relative risk of 4 for SALI and a relative risk of 2 for MACE. For the SALI outcome, the rarity of occurrence means that any study would have low power for small relative risks. The MAH chose a relative risk of 4 as a tradeoff of what is feasible, and above which would constitute a serious public health risk. One of the values of conducting the study across data sources is to increase the ability to address smaller relative risks for such rare outcomes. Accordingly, a relative risk of 2 may only be detectable by combining estimates across data sources.

8.6 Data Management

Files from the various data sources will be kept separate behind firewalls, and the patient level data will not be merged. All data management and analysis will be performed in Statistical Analysis Software (SAS) software (SAS Institute, Inc. Cary, North Carolina) or Stata (StataCorp, College Station, TX).

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. Each data source custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures (SOPs).

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except selected study staff.

Appropriate data storage and archiving procedures will be followed. All conversion of the original data to analysis variables will be performed using SAS software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina). Routine procedures include checking electronic files, maintaining security and data confidentiality, following the statistical epidemiological analysis plan, and performing quality-control checks of all programmes. Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

8.7 Data Analysis

The final approach to data analysis will be presented in a separate statistical analysis plan, to be developed before data collection. Several analyses that are specific to each data source, based upon the constraints of the individual data sources, will be conducted for the Interim and Final Reports. The details of each analysis will be outlined in the common Core Statistical Analysis Plan, but a general description of these analyses is provided below.

8.7.1 Propensity Score Approach

When ozanimod-treated patients reach 1,000 patient-years of exposure in at least one data source, the study will conduct the PS-based analyses for the primary objectives in that data source as described below.

Decisions to initiate a specific medication are influenced by demographic, medical, and clinical factors, and those same factors might be associated with the outcomes of interest. In the context of this study where the expected number of patients meeting the case definition is small for some of the outcomes (eg, SALI), the number of covariates that can be used in a regression model predicting those outcomes is limited. To overcome this problem, the set of confounding variables will be summarised into a single summary confounder score, a PS. The PS is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates. Because the models predict not the probability of experiencing the outcome but the probability of being treated with ozanimod in this study, many more variables can be used in the predicting regression model.

A generalized boosted model (GMB) will generate three sets of PS: one for probability of treatment with ozanimod, one for probability of treatment with another S1P, and one for probability of treatment with a DMT. The PS will be estimated at the start of each qualifying treatment episode, based on the values of select observed covariates (Section 8.3.3.1). For each outcome analysis, a single PS weight will be applied to each treatment episode: the inverse probability of treatment weighting (IPTW).

Prescription patterns change over time, and the confounding influence of the determinants of the prescription may also change. To allow for changing prescription patterns for ozanimod from the time it is first available through the date of receipt of the data, the model will include calendar year as a covariate and interaction terms for calendar year times with each of the other covariates. This full-interaction PS model will allow the influence of each covariate in predicting treatment to vary across time (thus accounting for potential channeling bias) and has an advantage of efficiency in providing one overall comprehensive model compared with generating separate PS models for the primary outcomes by calendar year.

Selective removal of observations, known as “trimming” will be implemented at both ends of the PS weight range. At the low end of the range, all patient episodes with a PS weight below the 2.5 percentile value of the distribution of scores for the exposed group (ie, ozanimod) will be excluded. At the upper end of the range, we will exclude all patients, exposed and unexposed to ozanimod, with PS weights greater than the 97.5 percentile.

After trimming is completed, the PS estimation model will be re-run and the PS will be recalculated. Re-estimation of the PS in the trimmed populations is important, since the PS model estimated in the untrimmed population will be mis-specified in the population remaining after trimming. Use of PSs for weighting rather than matching has the advantage of using all available data, which may improve precision of relative risk estimates.

The PS methodology to be applied in this study will be further detailed in the statistical analysis plan.

8.7.2 Primary and Secondary Objectives: Estimate Incidence Rates, and Adjusted Hazard Ratios for Each of the Study Outcomes

Incidence rates of MACE, SOI, SALI, macular edema, and malignancy for eligible new users of ozanimod and comparator agents will be estimated and compared at the treatment episode level. Incidence rates will be reported as point estimates (in cases per 1,000 person-years) and 95% CI. Incidence rates and hazard ratios of the "other DMT" cohort will also be reported stratified by route of administration (ie: oral, intravenous infusion and self-injectables).

There is variability within the different cohorts being compared with regards to malignancy risk.[1] For instance, cutaneous malignancies have been reported in patients treated with S1P receptor modulators (cohort 2 other S1P's). Another consideration is in cohort 3 given the diverse number of other DMT's included, one needs to factor in the different malignancy risk profiles known with these drugs, for instance Cladribine, which have a known increased risk of malignancy warning. Additionally, cancer type also is an important consideration, immunosuppression is a risk factor of lymphomas. Thus, disproportionate incident rates (for example, 1-3 times higher dependent on the cohort being assessed and the malignancies being determined) observed for any specific malignancies, are grouped in Table 8.3.2.5-1; this will be considered clinically meaningful and separate incidence rate and hazard ratio will be presented for the corresponding malignancies.

Ascertainment during follow-up will allow estimation of the number of new cases for each of the primary outcomes. Person-time for each treatment episode will be allocated as the time between the date of the first prescription or dispensing for either ozanimod or a comparator DMT and the end of time at risk (Section 8.3.1.1 for time at risk definitions) for each treatment episode. The total person-time of observation among individuals at risk will then be calculated.

8.7.2.1 Main Analysis

Patients meeting the study inclusion/exclusion criteria will contribute information to the analysis for each respective qualifying treatment group initiated. Thus, the unit of observation will be the treatment group episode (and not the patient). For each of the primary outcomes (primary objectives) and the secondary outcomes (secondary objectives) of interest, estimation of adjusted hazard ratios with 95% CIs will be considered the main analysis of interest, using Cox proportional hazard methods with time since cohort entry as the primary time axis with greater than 10 cases per study group.

Adjustment will be implemented by PS methodology outlined in Section 8.7.1. However, if certain characteristics remain unbalanced after stratification, those variables will be included in the outcome models. Methods to evaluate covariate imbalance and the impact of non-independent

[1] The main analysis is conducted at the treatment episode level. A sensitivity analysis will assess the risk of malignancy associated with prior treatments given the long latency period for malignancy.

nature of the data (ie, multiple episodes per person) on the estimation will be described in the common Core statistical analysis plan.

Although HRs will be estimated using two different comparison groups and for several different outcomes, no adjustment for multiple comparisons is planned for this study.

Age Stratified Analyses

Because safety of ozanimod in patients older than 55 years was not well characterized in registration trials, adjusted hazard ratios will also be stratified by age (< 55 years of age; ≥ 55 years of age).

Outcome-specific Exclusion Criteria

- For analysis of the MACE outcome (as a composite and for each individual component), any prior diagnosis of a MACE endpoint; however, patients with coronary artery or peripheral artery disease who have not experienced these endpoints are permitted.
- For analysis of the SOI outcome, any prior hospitalization due to a SOI.
- For analysis of the SALI outcome, treatment episodes will be excluded if:
  - there is any prior hospitalization due to ALI, or
  - if there is a prior diagnosis of chronic liver disease, chronic pancreatic disease, alcohol abuse, intra- or extrahepatic biliary obstruction, primary or secondary hepatic, biliary, or pancreatic cancer, or metastatic cancer on or before the start of that episode. The rationale here is that that by design only patients without chronic liver disease are at risk for acute liver disease; and that several other factors (eg, alcohol abuse) may be proxies for chronic liver disease,
  - if during the 6 months preceding or on the index date there is a diagnosis of acute infectious hepatitis, acute cholelithiasis or cholecystitis, acute pancreatic disease, or decompensated CHF (ie, CHF prompting emergency department or hospital care). The rationale here is that these conditions may predispose to or represent acute liver injury.
- Prior malignancy will be excluded from the analysis of malignancies.

8.7.2.2 Secondary Analyses

Incidence rates of PML, PRES, and symptomatic bradycardia for new users of ozanimod and comparator agents will be estimated. Incidence rates will be reported as point estimates (in cases per 1,000 person-years) and 95% CIs. In outcomes resulting in greater or equal to 10 cases per study group, hazard ratios and 95% CI will be estimated.

Secondary analyses will also evaluate whether duration of use is an effect modifier.

Duration Effects Analysis

It is conceivable that risk of MACE may vary by duration of use within each treatment episode and number of prior treatment episodes. This question will be evaluated through inspection of Kaplan-Meier curves, and separate HRs will be estimated for the first year of use, use beyond one year, and number of prior treatment episodes.

8.7.3 Imputation of Missing Values

In the CPRD, no high frequency of missing values is expected for most variables, except for lifestyle variables. If missing data are common for lifestyle variables, multiple imputation methods will be used to replace missing values during PS generation and multivariable analysis.[50,51] The method for imputation and subsequent analysis of the filled-in data involve three steps: 1) imputing data under an appropriate model and repeating the imputation to obtain *m* copies of the filled-in data set; 2) analyzing each data set separately to obtain desired parameter estimates and standard errors; and 3) combining results of the *m* analyses by computing the mean of the *m* parameter estimates and a variance estimate that includes both a within-imputation and an across-imputation component. Additional details on when and how multiple imputation methods will be used will be provided in the statistical epidemiological analysis plan.

In the ORD, no data will be available for smoking, alcohol, and BMI, but no high frequency of missing values is expected for most of the other variables. Clinical variables (diagnoses, drugs, procedures) are defined so as to ensure no missingness: an indicator variable for the condition is yes if the code is present and no if it is not. Similarly, any cost variables will be present for all costs incurred by the health insurer; cost may be incomplete and missing medical costs that were not paid for by insurance. For enrollment variables (age, sex, dates of enrollment) there is essentially no missingness, Patients are excluded with inconsistent sex in the baseline period and censor those who appear to change sex during follow-up. Effect of unmeasured confounders will be evaluated in a sensitivity analysis (Section 8.7.4 for Sensitivity Analysis). Of note, for the medical history conditions and comorbidities to be collected for inclusion in the PS, the absence of a code for a condition will be interpreted as an absence of the event.

8.7.4 Sensitivity Analyses

The following sensitivity analyses are planned.

1) In the main analysis, for all outcomes except malignancies, the exposure risk window ends 30 days after end of supply but in a sensitivity analysis it will end 90 days after end of supply. For the outcomes of hematologic and solid malignancies, the exposure risk window after end of supply will be extended from 1 to 2 years and from 2 to 5 years, respectively in a sensitivity analysis. These changes will be applied to all exposure groups. New adjusted HRs will then be estimated for ozanimod users vs. comparator DMT users.
2) Assess the potential effect of unmeasured confounders on the association between ozanimod use and MACE outcomes through bias analyses. These methods may be of special interest to evaluate how robust observed results are to varying assumptions about smoking in the ORD, where smoking is not systematically captured. More details and examples of how this bias analysis method will be used will be provided in the statistical analysis plan.
3) Characteristics of patient episodes with a PS below the 2.5 percentile value of the distribution of scores for the exposed group (ie, ozanimod) and greater than the 97.5 percentile for the comparator cohorts will be reported as a sensitivity analysis to examine the potential bias that could result from the exclusion of patient episodes at both extremes of the PS distribution.
4) Patients with contraindications found in the product information of each medication will be excluded from all cohorts as a sensitivity analysis. New adjusted HRs will then be estimated

for ozanimod users vs. comparator DMT users. Contraindications by treatment will detailed in the statistical analysis plan.

5) A sensitivity analysis of treatment changes within the same cohort will be conducted for observed risks.
6) The main analysis is conducted at the treatment episode level. A sensitivity analysis will assess the risk of malignancy associated with prior treatments given the long latency period for malignancy.

8.7.5 Analyses Combining Results from the Different Data Sources

The sponsor will take a qualitative and quantitative approach to determining whether meta-analysis is appropriate, and specific evaluation criteria will be provided in the statistical analysis plan. In brief, the results will be synthesized if the individual studies are similar in terms of population, intervention, comparators, outcomes, and study design (PICOS).[52] Planned analyses in each primary data source will be conducted according to this common protocol to facilitate future comparison and potential integration of results. While the studies in each data source are designed to be similar, external factors outside of the sponsor's control could impact the appropriateness of combining results from the different data sources (eg, if national treatment guidelines change resulting in different study populations across the different data sources).

If meta-analytic techniques are deemed appropriate based upon the PICOS criteria, meta-analytic technique will be used to combine the HRs obtained from the primary analysis performed in the cohort study in the different data sources. No individual-level data will be pooled across data sources, and an appropriate method to combine effect estimates across data sources will be applied, depending on features of the estimates, including the homogeneity of the estimates across populations. Data source-specific estimates (HRs and CIs) will be analyzed, and a summary of the data (tabular and forest plots) along with pooled estimates and CIs will be provided, as well as diagnostic measures of heterogeneity (if there are more than two data sources). Results from both random effects and fixed effects meta-analysis will be reported.

For the interim reports, no meta-analysis will be performed.

Additional details of the planned meta-analyses are outlined in the common Core Statistical Analysis Plan.

8.8 Quality Control

Within each research center, SOPs or guidelines will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Key programming modules written by a study analyst might be independently reviewed by a different analyst. The study will adhere to the 'Guideline on Good Pharmacovigilance Practices (GVP) Module VIII Post-authorisation Safety Studies'. Procedures will be consistent with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (GPP).

8.8.1 Direct Access to Source Documents

Each research partner will maintain copies of the common Core protocol and statistical analysis plan. In addition, each research partner will prepare a database-specific study protocol and any additional documentation needed to support an EMA or FDA audit, if requested.

8.9 Limitations of the Research Methods

8.9.1 Confounding

All observational studies are potentially subject to confounding. In this study, although use of PS will facilitate control of measured confounders. However, imperfectly measured, unmeasured and unidentified confounders could still introduce bias if they are differentially distributed among the exposed and comparator groups and are related to the outcome. For example, cigarette smoking, a risk factor for MACE, is not measured in the ORD (US claims) data source. A bias analysis is planned to evaluate the robustness of findings to different assumptions about smoking prevalence in the different cohorts.

Confounding by indication or severity, also known as channeling bias, is a common bias in pharmacoepidemiology. Patients starting treatment with a newly marketed drug might have more severe disease than patients not taking the medication either because of self-selection or because of physician preference. They may also have a less severe form of the disease if physicians prefer to test new drugs with a less familiar safety profile in less severely affected patients. New medications may also be prescribed differentially by physicians who are "early adopters" of new medicines and who systematically treat more severely affected patients with the new medications. Inspection of baseline characteristics between cohorts can give some indication of potential confounding by indication, as can inspection of the distribution of the PS distributions. Channeling, if present, could bias the risk estimate towards or away from the null.

The use of comparator groups that contain several drugs also raises the possibility of residual confounding. If there is considerable heterogeneity in patient characteristics within the comparator cohorts, adjustment for confounding may be limited, and the possibility of assessing a more narrowly defined comparator group will be considered.

8.9.2 Misclassification Bias

Misclassification bias can occur when exposure or outcome status are incorrectly assessed.

The main limitation of this study may arise from the fact that exposure is based on prescription or dispensing records to assess exposure to the medications that define the cohorts. The possibility of exposure misclassification could occur in this study through at least two mechanisms. Although this study will use prescribing or dispensing records to assess exposures, the study assumes that patients are adherent to their prescribed medications. The study design addresses this possibility through the use of a "grace period" of 30 days after end of drug supply when the patient is still considered exposed and at risk. The effects of drugs may persist for some time after they are no longer used. This possibility is evaluated by extending time at risk to 90 days after presumed end of drug supply. Exposure misclassification can also occur if information about the exposure is

incompletely captured in the data. This remains a possibility using CPRD data and is discussed separately in this context (Section 8.4.3).

The accuracy of outcome is also dependent on the data source, and misclassification may arise differently from the different data sources due to their specific characteristics. Outcomes in the CPRD and ORD are based on existence of relevant diagnosis codes or validated algorithm, which may be subject to misclassification bias (eg, in claims data, patients with symptomatic bradycardia could be misclassified as not having the condition if they did not have a healthcare encounter in which symptomatic bradycardia was billed for). Misclassification of the outcome will be reduced by using algorithms to identify endpoints that have been previously validated (eg, MACE) or by validating the algorithm used to ascertain the outcome (eg, SALI). Further, the MAH will periodically review the medical dictionaries for changes that may affect the coding in the database considering the long study period; this will help to ensure that the study variable definitions are kept current, thereby also potentially reducing the degree of misclassification.

The assessment of outcome is dependent on the data availability as each relevant MS cohort or registry data source will collect data based on their own internal processes and case definitions, which is subject to misclassification and under-reporting (eg, prespecified and structured data collection form vs free text field for outcome measure).

8.9.3 Random Error

All estimates are subject to random error, which will be expressed in terms of 95% CIs around point estimates. Because MS is an uncommon disease, for which multiple treatments are available, exposure to ozanimod may be limited. This, coupled with the rarity of certain outcomes (SALI), may limit the precisions of effect estimates.

8.9.4 Other Challenges

- Effects of ozanimod can only be assessed in countries where it is used. At the time of the writing of this protocol (May 2021), the reimbursement status of the drug has not been determined in several markets, and as a result, it is not possible to provide specifics about potential registry participation from countries in the EU.
- Ongoing MS registries have different approach to capturing endpoint of interests.
- Often, endpoint of interest is not captured using a prespecified study report form. Instead, endpoint of interest is captured using an open-ended question (ie, did any AE occur during the follow-up period?). Therefore, risk estimation of AEI may be under-estimated.
- The feasibility of using CPRD data for this project depends on the ability to link secondary care prescribing information to general practice data in the CPRD. While this appears technically feasible, as of November 2020, plans for implementation are not clear. Assuming that ozanimod will be used in England, delays in implementing this linkage should not imperil this study if specialty prescribing data are being captured prospectively. Information on the progress of this linkage will be included in study progress reports. Adjudicating hospitalized events where treatment with a systemic antiviral antifungal, or cytotoxic chemo would corroborate a diagnosis would be difficult.

8.10 Other Aspects

The list of European data sources in this protocol may increase. As noted, a challenge with several European databases include the lack of reimbursement of ozanimod and limited sample size for robust statistical power of outcomes. Therefore, the MAH will continue to monitor the reimbursement of ozanimod among countries throughout the study period. As ozanimod is granted reimbursement, potential data sources in said country will be investigated for study entry feasibility. If new European data sources are identified as feasible for inclusion, the sponsor will include those data sources progressively in the study progress reports, annually from the approval of the study protocol.

9 PROTECTION OF HUMAN SUBJECTS

The protect the rights of human subjects, at no time during the conduct of this study will information identifying patients or providers be provided to the sponsor. The data holder will be responsible for patient level data and statistical analysis, providing the sponsor aggregate data only, where feasible. If the data source does not have the ability to conduct study analysis, patient level data will be provided to the sponsor in anonymized fashion and the sponsor will not attempt to reidentify any patients or provider from aggregate data provided for the study. No data will be collected by the sponsor directly from individual subjects, and subjects participating in this non-interventional, observational study will already have given consent to participate in their individual country registries/healthcare data collection systems.

9.1 Clinical Practice Research Datalink

It is anticipated that the MAH's agent will serve as the coordinating center for this project (to be confirmed) and will be responsible for conducting this study using CPRD. This agent will seek approval from the CPRD ISAC for the protocol.

9.2 Optum

Optum will apply to a central institutional review board (IRB) for a waiver of authorization to use de-identified data. Approval from an IRB for this study is not guaranteed. This study will be undertaken only after the study protocol and study documents have been approved and Optum is granted a waiver of authorization. The IRB will monitor the study for the life of the project and may require formal re-review and approval on an annual basis. Changes to the project may also require re-review and approval by the IRB.

For any chart abstraction, it will be necessary to obtain health plan approval, and then apply to an IRB and affiliated privacy board (PB) for approval of the medical chart abstraction process and documents.

In addition, accessing certain data fields necessary to link data sources, such as to the NDI, requires separate IRB approval, which is not guaranteed. Approval for linking to NDI data is not guaranteed. Approved NDI users agree that no data will be published or released in any form, including for purposes of adverse event reporting to any party, if a particular individual or establishment is identifiable.

9.2.1 EU MS Cohort or Registry Data Sources

For the EU MS cohort or registry data sources, data will be accessed in a manner that complies with regional and local laws and regulations, including any related to the privacy and security of individually identifiable health information.

For the DSMG, a scientific advisory board and an executive committee approve requests for data and collaborations.

At MS: Optimise, the Study Coordination Centre has obtained approval from the London – City and East Research Ethics Committee and Health Research Authority. The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. Additionally, the cohort utilizes a Chief Investigator who will preserve the confidentiality of participants taking part in the fulfil transparency requirements under the General Data Protection Regulation for health and care research.

OFSEP only processes non-nominative data to which only trained, approved personnel have access. The cohort has registered an authorization request for biomedical research with France's national data protection authority. This authorization concerning the collection of clinical data and biological samples was granted under number 914066 in May 2014; the authorization concerning the collection of MRI data was granted in May 2015. The updated protocol has received a positive response of the Ile-de-France VI Ethics Committee in February 2020. Furthermore, this current project will be evaluated by the scientific committee and validated by the OFSEP steering committee [http://www.ofsep.org/en/data-access]).

The Italian MS register was approved by the Ethics Committee of the University of Bari (Italy) as coordinator center and the local ethics committee of all participant centers. Each individual with a diagnosis of MS enrolled is required to sign a written informed consensus to enter into the register. Since in some of the participant centers data were collected before the starting of the Italian MS Register, according to the local laws and regulations, data collected retrospectively can be also included without informed consent.

10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The data sources utilized in this PASS are secondary in nature and therefore not subject to individual reporting to Health Authorities. Data will be analyzed at an aggregate level and any safety signals discovered during the course of the study will be presented in Periodic Safety Update Reports, interim and final study reports.

11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual progress reports will include updates on available data sources and counts of patients in the exposed and comparator treatment in each data source.

Interim reports will include descriptive analyses of each cohort (including mean patient follow-up time) and adjusted comparative analyses for all primary outcomes by data source, if feasible. Attrition tables depicting the number of patients excluded due to shorter washout periods will also be provided. No meta-analyses are planned for the interim reports.

Patient level data will be redacted in all study reports between sponsor and data holder.

Results from this single company PASS will be disseminated at scientific meetings and in published literature.

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13 APPENDICES

APPENDIX 1 LIST OF STAND-ALONE DOCUMENTS

None.

APPENDIX 2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: ORION (Ozanimod Real-World Safety - A Post-authorisation Multi-National Long-term Non-Interventional Study)

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones		**Yes**	**No**	**N/A**	**Section Number**
1.1	Does the protocol specify timelines for				
1.1.1	Start of data collection[1]	☒	☐	☐	6
1.1.2	End of data collection[2]	☒	☐	☐	6
1.1.3	Progress report(s)	☒	☐	☐	6
1.1.4	Interim report(s)	☒	☐	☐	6
1.1.5	Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6	Final report of study results.	☒	☐	☐	6

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question		Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8.1
2.1.1	Why the study is conducted? (eg, to address an important public health concern, a risk identified in the Risk Management Plan, an emerging safety issue)	☒	☐	☐	
2.1.2	The objective(s) of the study?	☒	☐	☐	8.2
2.1.3	The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4	Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5	If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	8.1

Comments:

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (eg, cohort, case- control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	8.2
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				9.2
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)				9.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	9.5
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation substudy)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication)	☒	☐	☐	9.7, 9.9
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1	Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
9.1.2	Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
9.1.3	Covariates and other characteristics	☒	☐	☐	9.3
9.2	Does the protocol describe the information available from the data source(s) on:				
9.2.1	Exposure (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2	Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3	Covariats and other characteristics? (eg, age sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
9.3.1	Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2	Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedRA))	☒	☐	☐	9.4
9.3.3	Covariates and other characteristics?	☒	☐	☐	9.4
9.4	Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is the study size and/or statistical precision estimated?	☐	☐	☒	9.7
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of cofounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information ondata storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☐	☐	☒	
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				9.9
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.10

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: 17-May-2021

Signature:

APPENDIX 3 ADDITIONAL INFORMATION

Table 13-1: List of MedDRA Preferred Terms for MACE

MedDRA PT	MedDRA PT Code
Acute coronary syndrome	10051592
Acute myocardial infarction	10000891
Angina pectoris	10002383
Angina unstable	10002388
Anginal equivalent	10076419
Arteriogram coronary abnormal	10003201
Arteriosclerosis coronary artery	10003211
Arteriospasm coronary	10003225
Blood creatine phosphokinase abnormal	10005468
Blood creatine phosphokinase increased	10005470
Blood creatine phosphokinase MB abnormal	10005472
Blood creatine phosphokinase MB increased	10005474
Cardiac stress test abnormal	10055014
Cardiac ventricular scarring	10076898
Cardiopulmonary exercise test abnormal	10074359
Computerised tomogram coronary artery abnormal	10060806
Dissecting coronary artery aneurysm	10013428
ECG electrically inactive area	10072252
ECG signs of myocardial infarction	10075299
ECG signs of myocardial ischaemia	10058317
Electrocardiogram Q wave abnormal	10051177
Electrocardiogram ST segment abnormal	10014390
Electrocardiogram ST segment depression	10014391
Electrocardiogram ST segment elevation	10014392
Electrocardiogram ST-T segment abnormal	10052333
Electrocardiogram ST-T segment depression	10049224
Electrocardiogram ST-T segment elevation	10049225
Electrocardiogram T wave abnormal	10050380
Electrocardiogram T wave inversion	10014395
Exercise electrocardiogram abnormal	10015645
Exercise test abnormal	10015653

Table 13-1: List of MedDRA Preferred Terms for MACE

MedDRA PT	MedDRA PT Code
External counterpulsation	10067876
Haemorrhage coronary artery	10055803
Infarction	10061216
Ischaemic cardiomyopathy	10048858
Kounis syndrome	10069167
Microvascular coronary artery disease	10072685
Myocardial infarction	10028596
Myocardial ischaemia	10028600
Myocardial necrosis	10028602
Myocardial necrosis marker increased	10075211
Myocardial reperfusion injury	10051624
Myocardial stunning	10072186
Papillary muscle infarction	10033697
Postinfarction angina	10058144
Prinzmetal angina	10036759
Scan myocardial perfusion abnormal	10061501
Silent myocardial infarction	10049768
Stress cardiomyopathy	10066286
Stress echocardiogram abnormal	10070746
Subclavian coronary steal syndrome	10064994
Subendocardial ischaemia	10058145
Troponin I increased	10058268
Troponin increased	10058267
Troponin T increased	10058269
Vascular stent restenosis	10077145

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Abscess fungal	10065330
Acute pulmonary histoplasmosis	10001027
Adrenal gland tuberculosis	10001358
Allescheriosis	10001754
Alternaria infection	10054207
Anal fungal infection	10068556
Arthritis fungal	10060966
Aspergilloma	10003487
Aspergillosis oral	10003489
Aspergillus infection	10074171
Atypical mycobacterial infection	10061663
Atypical mycobacterial lower respiratory tract infection	10075026
Atypical mycobacterial lymphadenitis	10003755
Atypical mycobacterial pneumonia	10071075
Atypical mycobacterium pericarditis	10055036
Bacillary angiomatosis	10003971
Bartonellosis	10004145
Biliary tract infection cryptosporidial	10067319
Biliary tract infection fungal	10065203
Blastomycosis	10005098
Bone tuberculosis	10056377
Borderline leprosy	10006029
Bovine tuberculosis	10006049
Bronchitis fungal	10061737
Bronchopulmonary aspergillosis	10006473
Bronchopulmonary aspergillosis allergic	10006474
Candida endophthalmitis	10059449
Candida infection	10074170
Candida osteomyelitis	10064699
Candida pneumonia	10053158
Candida retinitis	10068612
Candida sepsis	10053166
Cat scratch disease	10007729
Central nervous system fungal infection	10072805

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Cerebral aspergillosis	10051597
Cerebral fungal infection	10049657
Cerebral toxoplasmosis	10057854
Choroid tubercles	10008779
Chronic pulmonary histoplasmosis	10009115
Coccidioides encephalitis	10054214
Coccidioidomycosis	10009825
Colitis herpes	10051782
Conjunctivitis tuberculous	10010754
Cryptococcal cutaneous infection	10054216
Cryptococcal fungaemia	10067112
Cryptococcosis	10011490
Cryptosporidiosis infection	10011502
Cutaneous tuberculosis	10011684
Cytomegalovirus chorioretinitis	10048843
Cytomegalovirus colitis	10048983
Cytomegalovirus duodenitis	10049014
Cytomegalovirus enteritis	10049074
Cytomegalovirus enterocolitis	10049015
Cytomegalovirus gastritis	10049016
Cytomegalovirus gastroenteritis	10051349
Cytomegalovirus gastrointestinal infection	10052817
Cytomegalovirus gastrointestinal ulcer	10075619
Cytomegalovirus hepatitis	10011830
Cytomegalovirus infection	10011831
Cytomegalovirus mononucleosis	10011834
Cytomegalovirus mucocutaneous ulcer	10065036
Cytomegalovirus myelomeningoradiculitis	10065621
Cytomegalovirus myocarditis	10056261
Cytomegalovirus oesophagitis	10049018
Cytomegalovirus pancreatitis	10049566
Cytomegalovirus pericarditis	10056721
Cytomegalovirus syndrome	10056262

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Cytomegalovirus urinary tract infection	10051350
Cytomegalovirus viraemia	10058854
Disseminated Bacillus Calmette-Guerin infection	10076666
Disseminated cryptococcosis	10013439
Disseminated cytomegaloviral infection	10049075
Disseminated tuberculosis	10013453
Disseminated varicella zoster vaccine virus infection	10076667
Ear infection fungal	10068630
Ear tuberculosis	10014027
Eczema herpeticum	10014197
Encephalitis cytomegalovirus	10014586
Encephalitis fungal	10065170
Encephalitis protozoal	10061118
Endocarditis candida	10014669
Endocarditis histoplasma	10014676
Enterocolitis fungal	10065205
Epididymitis tuberculous	10015004
Exserohilum infection	10073244
Extrapulmonary tuberculosis	10064445
Eye infection fungal	10015933
Eye infection toxoplasmal	10015939
Female genital tract tuberculosis	10061150
Fungal abscess central nervous system	10017524
Fungal cystitis	10017525
Fungal endocarditis	10017529
Fungal infection	10017533
Fungal labyrinthitis	10065174
Fungal oesophagitis	10049656
Fungal paronychia	10017540
Fungal peritonitis	10061138
Fungal pharyngitis	10076516
Fungal retinitis	10068613

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Fungal rhinitis	10065182
Fungal sepsis	10058872
Fungal tracheitis	10069508
Fusarium infection	10051919
Gastritis fungal	10061972
Gastritis herpes	10051784
Gastroenteritis cryptococcal	10011485
Gastroenteritis cryptosporidial	10017899
Gastrointestinal candidiasis	10017938
Gastrointestinal fungal infection	10049479
Gastrointestinal protozoal infection	10061175
Genital candidiasis	10018143
Genital herpes	10018150
Genital herpes simplex	10073931
Genital herpes zoster	10072210
Genital infection fungal	10061180
Hepatic candidiasis	10049653
Hepatic infection fungal	10065217
Hepatitis toxoplasmal	10019798
Hepatosplenic candidiasis	10051590
Herpes dermatitis	10062639
Herpes oesophagitis	10052330
Herpes ophthalmic	10062004
Herpes pharyngitis	10066888
Herpes sepsis	10058876
Herpes simplex	10019948
Herpes simplex colitis	10074239
Herpes simplex encephalitis	10019953
Herpes simplex gastritis	10074240
Herpes simplex hepatitis	10067389
Herpes simplex meningitis	10019956
Herpes simplex meningoencephalitis	10074247

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Herpes simplex meningomyelitis	10074250
Herpes simplex necrotising retinopathy	10074252
Herpes simplex oesophagitis	10074242
Herpes simplex otitis externa	10019959
Herpes simplex pharyngitis	10074244
Herpes simplex pneumonia	10065046
Herpes simplex sepsis	10074246
Herpes simplex visceral	10019963
Herpes virus infection	10019973
Herpes zoster	10019974
Herpes zoster cutaneous disseminated	10074297
Herpes zoster disseminated	10065038
Herpes zoster infection neurological	10061208
Herpes zoster meningitis	10074259
Herpes zoster meningoencephalitis	10074248
Herpes zoster meningomyelitis	10074251
Herpes zoster necrotising retinopathy	10074253
Herpes zoster oticus	10063491
Herpes zoster pharyngitis	10074245
Histoplasmosis	10020141
Histoplasmosis cutaneous	10049142
Histoplasmosis disseminated	10020144
Human herpesvirus 6 infection	10020431
Human herpesvirus 7 infection	10063571
Human herpesvirus 8 infection	10066435
Human polyomavirus infection	10057366
Immune reconstitution inflammatory syndrome associated tuberculosis	10072797
Infection protozoal	10021859
Intestinal tuberculosis	10075268
JC virus infection	10023163
Joint tuberculosis	10056367
Keratitis fungal	10062353

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Laryngitis fungal	10067321
Latent tuberculosis	10065048
Legionella infection	10061266
Lepromatous leprosy	10024227
Leprosy	10024229
Listeria encephalitis	10054116
Listeria sepsis	10063085
Listeriosis	10024641
Lower respiratory tract infection fungal	10065187
Lymph node tuberculosis	10025183
Lymphadenitis fungal	10065208
Malassezia infection	10054117
Male genital tract tuberculosis	10061234
Mastitis fungal	10065211
Meningitis aspergillus	10073245
Meningitis candida	10027205
Meningitis coccidioides	10027207
Meningitis cryptococcal	10027209
Meningitis exserohilum	10073246
Meningitis fungal	10027236
Meningitis herpes	10027242
Meningitis histoplasma	10027243
Meningitis listeria	10027248
Meningitis toxoplasmal	10048848
Meningitis tuberculous	10027259
Meningoencephalitis herpetic	10027285
Meningomyelitis herpes	10074249
Microsporidia infection	10053982
Microsporum infection	10054121
Mucocutaneous candidiasis	10028080
Mucormycosis	10028098
Mycetoma mycotic	10028426

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Mycobacterial infection	10062207
Mycobacterial peritonitis	10073514
Mycobacterium abscessus infection	10064789
Mycobacterium avium complex immune restoration disease	10058449
Mycobacterium avium complex infection	10058806
Mycobacterium chelonae infection	10071401
Mycobacterium fortuitum infection	10049659
Mycobacterium kansasii infection	10028447
Mycobacterium marinum infection	10028452
Mycobacterium ulcerans infection	10066289
Mycotic corneal ulcer	10028518
Mycotic endophthalmitis	10063202
Mycotoxicosis	10028520
Myocarditis mycotic	10059026
Myocarditis toxoplasmal	10028617
Nasal candidiasis	10050345
Nasal herpes	10074936
Necrotising fasciitis fungal	10052892
Necrotising herpetic retinopathy	10065119
Neurocryptococcosis	10068368
Oesophageal candidiasis	10030154
Oesophageal tuberculosis	10030200
Ophthalmic herpes simplex	10073938
Ophthalmic herpes zoster	10030865
Opportunistic infection	10030901
Oral candidiasis	10030963
Oral fungal infection	10061324
Oral herpes	10067152
Oral tuberculosis	10076879
Oro-pharyngeal aspergillosis	10053029
Oropharyngeal candidiasis	10050346
Oropharyngitis fungal	10061891

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Osteomyelitis blastomyces	10031255
Osteomyelitis fungal	10065239
Otitis externa fungal	10052557
Otitis media fungal	10065175
Pancreatitis fungal	10065190
Paracoccidioides infection	10061906
Penicilliosis	10064458
Pericarditis fungal	10065220
Pericarditis histoplasma	10034489
Pericarditis tuberculous	10055069
Peritoneal candidiasis	10056562
Peritoneal tuberculosis	10053583
Phaehyphomycosis	10034799
Pneumocystis jirovecii infection	10073756
Pneumocystis jirovecii pneumonia	10073755
Pneumonia blastomyces	10035671
Pneumonia cryptococcal	10067565
Pneumonia cytomegaloviral	10035676
Pneumonia fungal	10061354
Pneumonia herpes viral	10035703
Pneumonia legionella	10035718
Pneumonia toxoplasmal	10067566
Polyomavirus-associated nephropathy	10065381
Pontiac fever	10054161
Presumed ocular histoplasmosis syndrome	10063664
Proctitis fungal	10063201
Proctitis herpes	10036780
Proctitis monilial	10036781
Progressive multifocal leukoencephalopathy	10036807
Prostatitis tuberculous	10064743
Protozoal corneal ulcer	10054777
Pseudallescheria infection	10061919

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Pseudallescheria sepsis	10058973
Pulmonary mycosis	10037422
Pulmonary trichosporonosis	10068184
Pulmonary tuberculoma	10066927
Pulmonary tuberculosis	10037440
Pyelonephritis fungal	10065214
Pythium insidiosum infection	10074264
Renal tuberculosis	10038534
Respiratory moniliasis	10038705
Respiratory tract infection fungal	10060692
Retinitis histoplasma	10038912
Rhinosporidiosis	10039104
Salpingitis tuberculous	10039463
Scedosporium infection	10059045
Silicotuberculosis	10068876
Sinusitis aspergillus	10051016
Sinusitis fungal	10058678
Spleen tuberculosis	10041640
Splenic candidiasis	10051725
Splenic infection fungal	10065194
Sporotrichosis	10041736
Superinfection fungal	10066984
Superinfection mycobacterial	10075381
Systemic candida	10042938
Systemic mycosis	10052366
Thyroid tuberculosis	10043774
Tongue fungal infection	10075845
Tonsillitis fungal	10065236
Toxoplasmosis	10044272
Trench fever	10044582
Trichomoniasis intestinal	10044621
Tuberculoid leprosy	10044729

Table 13-2: List of MedDRA Preferred Terms for Opportunistic Infection[a]

MedDRA PT	MedDRA PT Code
Tuberculoma of central nervous system	10052883
Tuberculosis	10044755
Tuberculosis bladder	10044758
Tuberculosis gastrointestinal	10061390
Tuberculosis liver	10058120
Tuberculosis of central nervous system	10061391
Tuberculosis of eye	10044819
Tuberculosis of genitourinary system	10044828
Tuberculosis of intrathoracic lymph nodes	10044846
Tuberculosis of peripheral lymph nodes	10044965
Tuberculosis ureter	10045026
Tuberculous endometritis	10071559
Tuberculous laryngitis	10045072
Tuberculous pleurisy	10045104
Tuberculous tenosynovitis	10059161
Type 1 lepra reaction	10070516
Type 2 lepra reaction	10070517
Upper respiratory fungal infection	10062219
Urinary tract infection fungal	10049059
Urogenital infection fungal	10065582
Varicella	10046980
Varicella zoster gastritis	10074241
Varicella zoster oesophagitis	10074243
Varicella zoster pneumonia	10074254
Varicella zoster virus infection	10075611
Vorticella infection	10053696

[a] Based on MedDRA version 23.1 narrow scope SMQ for opportunistic infections.

Table 13-3: Macular Edema

MedDRA PT	MedDRA PT Code
Acute zonal occult outer retinopathy	10074444
Age-related macular degeneration	10064930
Anterior chamber angle neovascularisation	10071364
Anterior chamber cell	10053781
Anterior chamber fibrin	10054774
Anterior chamber flare	10052127
Anterior chamber inflammation	10054765
Aqueous fibrin	10054773
Autoimmune retinopathy	10071578
Behcet's syndrome	10004213
Birdshot chorioretinopathy	10072959
Chorioretinitis	10008769
Chorioretinopathy	10063118
Choroidal neovascularisation	10060823
Choroiditis	10008792
Commotio retinae	10071321
Corneal deposits	10011000
Cyclitic membrane	10052119
Cyclitis	10011715
Cystoid macular oedema	10058202
Detachment of macular retinal pigment epithelium	10071004
Diabetic retinal oedema	10012688
Diabetic retinopathy	10012689
Diabetic uveitis	10012692
Endophthalmitis	10014801
Eye infection intraocular	10054762
Eye oedema	10052139
Fibrin deposition on lens postoperative	10016590
Fungal retinitis	10068613
Herpes zoster necrotising retinopathy	10074253
Hypopyon	10021086
Infective uveitis	10074700

Table 13-3: Macular Edema

MedDRA PT	MedDRA PT Code
Iridocyclitis	10022941
Iris adhesions	10022945
Iritis	10022955
IRVAN syndrome	10073929
Macular cyst	10025407
Macular degeneration	10025409
Macular fibrosis	10071392
Macular hole	10051058
Macular oedema	10025415
Macular pigmentation	10071041
Macular pseudohole	10060815
Macular scar	10063185
Maculopathy	10025425
Metamorphopsia	10063341
Mycotic endophthalmitis	10063202
Necrotising herpetic retinopathy	10065119
Necrotising retinitis	10064997
Neovascular age-related macular degeneration	10071129
Non-infectious endophthalmitis	10069093
Noninfective chorioretinitis	10074696
Noninfective retinitis	10074699
Panophthalmitis	10033683
Phacolytic glaucoma	10034798
Polypoidal choroidal vasculopathy	10063381
Presumed ocular histoplasmosis syndrome	10063664
Retinal exudates	10038862
Retinal infiltrates	10064833
Retinal neovascularisation	10055666
Retinal oedema	10038886
Retinal pigment epitheliopathy	10038893
Retinal vasculitis	10038905
Retinal vein occlusion	10038907

Table 13-3: Macular Edema

MedDRA PT	MedDRA PT Code
Retinal vein thrombosis	10038908
Retinitis	10038910
Retinitis histoplasma	10038912
Retinitis viral	10038915
Subretinal fluid	10069356
Subretinal haematoma	10071935
Uveitic glaucoma	10072686
Uveitis	10046851
Uveitis-glaucoma-hyphaema syndrome	10068148
Viral uveitis	10071005
Vitreal cells	10066421
Vitreomacular interface abnormal	10071035
Vitreous fibrin	10052126
Vitritis	10047663
Vogt-Koyanagi-Harada syndrome	10047680

Table 13-4: MedDRA Terms for Serious Acute Liver Injury

MedDRA PT	MedDRA PT Code
Acute hepatic failure	10000804
Alanine aminotransferase abnormal	10001547
Alanine aminotransferase increased	10001551
Allergic hepatitis	10071198
Aspartate aminotransferase abnormal	10003477
Aspartate aminotransferase increased	10003481
Autoimmune hepatitis	10003827
Bilirubin conjugated abnormal	10067718
Bilirubin conjugated increased	10004685
Blood alkaline phosphatase abnormal	10059571
Blood alkaline phosphatase increased	10059570
Blood bilirubin abnormal	10058477
Blood bilirubin increased	10005364

Table 13-4: MedDRA Terms for Serious Acute Liver Injury

MedDRA PT	MedDRA PT Code
Chronic hepatic failure	10057573
Chronic hepatitis	10008909
Coma hepatic	10010075
Drug-induced liver injury	10072268
Gamma-glutamyltransferase abnormal	10017688
Gamma-glutamyltransferase increased	10017693
Hepatic enzyme abnormal	10062685
Hepatic enzyme increased	10060795
Hepatic failure	10019663
Hepatic function abnormal	10019670
Hepatic necrosis	10019692
Hepatitis	10019717
Hepatitis acute	10019727
Hepatitis chronic active	10019755
Hepatitis chronic persistent	10019759
Hepatitis fulminant	10019772
Hepatitis toxic	10019795
Hepatobiliary disease	10062000
Hepatocellular injury	10019837
Hepatotoxicity	10019851
Hyperbilirubinaemia	10020578
Hypertransaminasaemia	10068237
Jaundice	10023126
Jaundice hepatocellular	10023136
Liver disorder	10024670
Liver function test abnormal	10024690
Liver injury	10067125
Subacute hepatic failure	10056956
Transaminases abnormal	10062688
Transaminases increased	10054889
Yellow skin	10048245

Table 13-5: List of Potentially Hepatotoxic Medications

Acarbose	Estrogens	Phenytoin
Acetaminophen (prescription)	Fluoxetine	Pyrazinamide
Allopurinol	Flutamide	Rifampicin
Amiodarone	HAART drugs	Risperidone
Amitriptyline	Irbesartan	Sertraline
Amoxicillin + clavulanic acid	Isoniazid	Statins
Anabolic steroids	Ketoconazole	Sulfonamides
Azathioprine	Lisinopril	Terbinafine
Baclofen	Losartan	Tetracyclines
Bupropion	Methotrexate	Trazodone
Captopril	Mirtazapine	Trazodone
Carbamazepine	Nitrofurantoin	Tricyclics
Chlorpromazine	NSAIDs	Trimethoprim-sulfamethoxazole
Clindamycin	Omeprazole	Trovafloxacin
Clopidogrel	Oral contraceptives	Valproic acid
Cyproheptadine	Paroxetine	Verapamil
Enalapril	Phenobarbital	
Erythromycins	Phenothiazines	

Adapted from Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006;354(7):731-9.

APPENDIX 4 FEASIBILITY OF EUROPEAN UNION DATA SOURCES

Table 13-6: Feasibility Checklist From CPRD in the UK

Name of Registry/Data Source: UK Clinical Practice Research Datalink (CPRD)	
Completed (mark with X)	**Necessary Information to Include in the Analysis:**
X	1. Description of the registry or coordinated registry network. See Section 8.4.3.
X	2. Analysis of the availability of the data elements needed for this study. This includes confounding and effect-modifying variables. Also comment on if the registry can be used to collect any additional data elements or additional data collection methods if necessary. [redacted]
X	3. Analysis of the quality and completeness of the available data elements needed for the study. This includes information on missing data and possible data imputation, and the results of any audits performed. **for studies using multiple registries, an analysis of the differences between the registries and impact of these differences must be included** [redacted]
X	4. The number of centers involved in the registry, the number of registered patients and active patients, the number of new patients enrolled per month/year, duration of follow-up, and missing data and loses to follow-up. Based on this information, a comment on the time needed to complete patient recruitment for the study and if the study is feasible. [redacted]
X	5. Analysis of potential information bias, selection bias due to inclusion/exclusion criteria, time bias, and potential losses to follow-up. [redacted]

Table 13-6: Feasibility Checklist From CPRD in the UK

Name of Registry/Data Source: UK Clinical Practice Research Datalink (CPRD)	
X	6. Analysis of any potential confounding bias if some data elements are not available. Not applicable.
X	7. Any analytical issues that may arise based on the data characteristics and study design. No major issues anticipated. Endpoint measurement is expected to be valid due to linkage with HES.
X	8. Any data privacy issues and governance-related issues (ie, data sharing, funding sources, etc.) All patient data are anonymized. Linkage requests are subject to review and approval. GP practices and individual patients can opt out of sharing linked data.
	9. Comment on the overall evaluation of the suitability of the registry for the proposed study. Include a comment on any missing information from the aspects mentioned in the steps above. Based on the feasibility conducted, CPRD is deemed to be suitable for entry into the ORION MS-PASS study

Table 13-7: Feasibility Checklist From DMSG in Germany

Name of Registry: Deutsche Multiple Sklerose Gesellschaft (DMSG)	
Completed (mark with X)	**Necessary Information to Include in the Analysis:**
X	1. Description of the registry or coordinated registry network. See Section 8.4.4.1.
X	2. Analysis of the availability of the data elements needed for this study. This includes confounding and effect-modifying variables. Also, comment on if the registry can be used to collect any additional data elements or additional data collection methods if necessary. All outcomes and baseline characteristics of interest are collected from the registry holder, except JCV status. JCV status planned to be implemented in 2021.
X	3. Analysis of the quality and completeness of the available data elements needed for the study. This includes information on missing data and possible data imputation, and the results of any audits performed. The registry currently has all data points of interest for ORION, except JCV status. This data point is specifically linked to the outcome of PML. Positive JCV status is a necessary component for the diagnosis of PML. The diagnosis of a PML case will be made by the treating physician (reporting to the registry), not the sponsor, thus, this missing information should not cause any bias. The impact of this missing variable will be in the descriptive statistics only and does not cause any bias to the collection of the outcome of PML.

Table 13-7: Feasibility Checklist From DMSG in Germany

Name of Registry: Deutsche Multiple Sklerose Gesellschaft (DMSG)	
X	4. The number of centers involved in the registry, the number of registered patients and active patients, the number of new patients enrolled per month/year, duration of follow-up, and missing data and loses to follow-up. Based on this information, a comment on the time needed to complete patient recruitment for the study and if the study is feasible. There are currently 190 centers contributing to the registry, over which, 31 are on-boarded for the pharmacovigilance (PV) module (utilized in ORION). The PV-module was evaluated by the registry and was deemed to be representative of the overall registry population. As of 26-Apr-2021, there were 2,915 patients in the PV-module.
X	5. Analysis of potential information bias, selection bias due to inclusion/exclusion criteria, time bias, and potential losses to follow-up. The registry only recruits centers that fulfill a set of qualification requirements (eg, Number of MS-Patients treated p.a., years of experience in treating patients with MS (PwMS), etc.) Thus, a certain center-bias exists. Recent calculations show that the 190 centers participating in the registry cover around 90,000 PwMS (about 1/3 of the expected total German MS-population). 35,000 of those are currently recruited for the registry. The PV-Module is currently only open to centers that have a good track record in regard to follow-up. A recent analysis showed the number of patients that could be considered lost to follow-up (eg, no follow-up within 2 years) was limited to a handful of cases (eg, untreated primary progressive multiple sclerosis patients not seen regularly). In regard to death outside of the neurological scope we are currently implementing a protocol to handle / identify such cases.
X	6. Analysis of any potential confounding bias if some data elements are not available. Not applicable.
X	7. Any analytical issues that may arise based on the data characteristics and study design. Due to the nature of the registry (we only collect data on visits schedules by the centers/patients based on the physicians / patients decision) gaps between visits might exist and completeness for non-mandatory items in follow-ups. For example, certain scores, such as 9 Hole Peg Test, 25 ft Walking test or PASAT3 may be limited. As documentation is often carried out in bulks of patients by specialized personnel, some time lag between the occurrence of an event and the capturing in the database is not uncommon. As the study protocol has sufficient time between the end of data collection and the preparation of the final report we do not foresee problems caused by this.
X	8. Any data privacy issues and governance-related issues (ie, data sharing, funding sources, etc.) None identified. Data will remain in DMSG's possession. Funding has been approved by BMS.
X	9. Comment on the overall evaluation of the suitability of the registry for the proposed study. Include a comment on any missing information from the aspects mentioned in the steps above. Based on the feasibility conducted, DMSG is deemed to be suitable for entry into the ORION MS-PASS study. The data desired is largely captured by the data source. Missing JCV status (which may be available by study start) shows little/no additional bias.

Table 13-8: Feasibility Checklist From MS Optimise (UK)

Name of Registry: MS: Optimise	
Completed (mark with X)	**Necessary Information to Include in the Analysis:**
X	1. Description of the registry or coordinated registry network. See Section 8.4.4.2.
X	2. Analysis of the availability of the data elements needed for this study. This includes confounding and effect-modifying variables. Also comment on if the registry can be used to collect any additional data elements or additional data collection methods if necessary. The data registry currently has most data points desired for this analysis [redacted]
X	3. Analysis of the quality and completeness of the available data elements needed for the study. This includes information on missing data and possible data imputation, and the results of any audits performed. The data registry currently has most data points desired for this analysis. [redacted]
X	4. The number of centers involved in the registry, the number of registered patients and active patients, the number of new patients enrolled per month/year, duration of follow-up, and missing data and loses to follow-up. Based on this information, a comment on the time needed to complete patient recruitment for the study and if the study is feasible. [redacted]
X	5. Analysis of potential information bias, selection bias due to inclusion/exclusion criteria, time bias, and potential losses to follow-up. The only bias related to the inclusion and exclusion criteria relates only to patients who are enrolled onto a clinical trial of an investigational medicinal product. The collection of adverse event data relating to prescribed DMTs means that patients enrolled onto a clinical trial of an investigational medicinal product cannot participate in the study.
X	6. Analysis of any potential confounding bias if some data elements are not available. [redacted]
X	7. Any analytical issues that may arise based on the data characteristics and study design. Rare outcomes may be difficult to find.

Table 13-8: Feasibility Checklist From MS Optimise (UK)

Name of Registry: MS: Optimise	
Completed (mark with X)	**Necessary Information to Include in the Analysis:**
X	8. Any data privacy issues and governance-related issues (ie, data sharing, funding sources, etc.) None.
X	9. Comment on the overall evaluation of the suitability of the registry for the proposed study. Include a comment on any missing information from the aspects mentioned in the steps above. Based on the feasibility conducted, MS: Optimise is deemed to be suitable for entry into the ORION MS-PASS study.

Table 13-9: Feasibility Checklist From OFSEP - France

Name of Registry: OFSEP – French MS Registry	
Completed (mark with X)	**Necessary Information to Include in the Analysis:**
X	1. Description of the registry or coordinated registry network. See Section 8.4.4.3.
X	2. Analysis of the availability of the data elements needed for this study. This includes confounding and effect-modifying variables. Also comment on if the registry can be used to collect any additional data elements or additional data collection methods if necessary. [redacted]
X	3. Analysis of the quality and completeness of the available data elements needed for the study. This includes information on missing data and possible data imputation, and the results of any audits performed. **for studies using multiple registries, an analysis of the differences between the registries and impact of these differences must be included** [redacted]

Table 13-9: Feasibility Checklist From OFSEP - France

Name of Registry: OFSEP – French MS Registry	
X	4. The number of centers involved in the registry, the number of registered patients and active patients, the number of new patients enrolled per month/year, duration of follow-up, and missing data and loses to follow-up. Based on this information, a comment on the time needed to complete patient recruitment for the study and if the study is feasible. [redacted]
X	5. Analysis of potential information bias, selection bias due to inclusion/exclusion criteria, time bias, and potential losses to follow-up. [redacted]
X	6. Analysis of any potential confounding bias if some data elements are not available. Not applicable.
X	7. Any analytical issues that may arise based on the data characteristics and study design. [redacted]
X	8. Any data privacy issues and governance-related issues (ie, data sharing, funding sources, etc.) None.
X	9. Comment on the overall evaluation of the suitability of the registry for the proposed study. Include a comment on any missing information from the aspects mentioned in the steps above. Based on the feasibility conducted, OFSEP is deemed to be suitable for entry into the ORION MS-PASS study. The primary outcomes are captured by the data source. Secondary outcome (PRES) is not.

Table 13-10: Feasibility Checklist From AISM in Italy

Name of Registry: AISM – Italian MS Registry	
Completed (mark with X)	**Necessary Information to Include in the Analysis:**
X	1. Description of the registry or coordinated registry network. See Section 8.4.4.4.
X	2. Analysis of the availability of the data elements needed for this study. This includes confounding and effect-modifying variables. Also comment on if the registry can be used to collect any additional data elements or additional data collection methods if necessary.

Table 13-10: Feasibility Checklist From AISM in Italy

Name of Registry: AISM – Italian MS Registry	
X	3. Analysis of the quality and completeness of the available data elements needed for the study. This includes information on missing data and possible data imputation, and the results of any audits performed. **for studies using multiple registries, an analysis of the differences between the registries and impact of these differences must be included**
X	4. The number of centers involved in the registry, the number of registered patients and active patients, the number of new patients enrolled per month/year, duration of follow-up, and missing data and loses to follow-up. Based on this information, a comment on the time needed to complete patient recruitment for the study and if the study is feasible.
X	5. Analysis of potential information bias, selection bias due to inclusion/exclusion criteria, time bias, and potential losses to follow-up.
X	6. Analysis of any potential confounding bias if some data elements are not available.
X	7. Any analytical issues that may arise based on the data characteristics and study design.
X	8. Any data privacy issues and governance-related issues (ie, data sharing, funding sources, etc.)
X	9. Comment on the overall evaluation of the suitability of the registry for the proposed study. Include a comment on any missing information from the aspects mentioned in the steps above. The registry is interested in participating in ORION.

Table 13-11: Feasibility Checklist From NPR in Sweden

Name of Registry: National Patient Register of Sweden	
Completed (mark with X)	**Necessary Information to Include in the Analysis:**
X	1. Description of the registry or coordinated registry network. Section 8.4.4.5.
X	2. Analysis of the availability of the data elements needed for this study. This includes confounding and effect-modifying variables. Also comment on if the registry can be used to collect any additional data elements or additional data collection methods if necessary. The NPR currently has most data points desired for this analysis, with rich clinical data derived from legally required, systematic reporting from included settings of care. These include diagnostic and procedure codes; dates of care; including admission and discharge dates. (Source: information-in-the-national-patient-register.pdf [socialstyrelsen.se]).

Table 13-11: Feasibility Checklist From NPR in Sweden

Name of Registry: National Patient Register of Sweden	
X	3. Analysis of the quality and completeness of the available data elements needed for the study. This includes information on missing data and possible data imputation, and the results of any audits performed. [redacted]
X	4. The number of centers involved in the registry, the number of registered patients and active patients, the number of new patients enrolled per month/year, duration of follow-up, and missing data and loses to follow-up. Based on this information, a comment on the time needed to complete patient recruitment for the study and if the study is feasible. [redacted]
X	5. Analysis of potential information bias, selection bias due to inclusion/exclusion criteria, time bias, and potential losses to follow-up. Not applicable. The NPR is a national database and included centers and their patient populations are not subject to selection bias.
X	6. Analysis of any potential confounding bias if some data elements are not available. Not applicable.
X	7. Any analytical issues that may arise based on the data characteristics and study design. None.
	8. Any data privacy issues and governance-related issues (ie, data sharing, funding sources, etc.) All patient data are anonymized. Requests for research data are subject to review and approval by the Swedish National Board of Health and Welfare.
	9. Comment on the overall evaluation of the suitability of the registry for the proposed study. Include a comment on any missing information from the aspects mentioned in the steps above. As of September 2021, ozanimod has not been granted reimbursement in Sweden and uptake of ozanimod in Sweden may be limited even after it is granted reimbursement in Sweden.