TITLE:	**LONG-TERM SURVEILLANCE OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS (MANUSCRIPT STUDY)**
PROTOCOL NUMBER:	BA39730
VERSION NUMBER:	1.0
AUTHOR:	[redacted] F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
DATE FINAL:	See electronic date stamp below
EU PAS REGISTER NUMBER:	Study not registered
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STUDIED MEDICINAL PRODUCT:	OCREVUS®
PRODUCT REFERENCE NUMBER:	RO4964913
PROCEDURE NUMBER:	EMEA/H/C/004043
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES:	The research question is to assess and characterize the long-term safety data from the use of ocrelizumab in patients with multiple sclerosis (MS) overall and by MS type (e.g., relapsing forms of multiple sclerosis [RMS], primary progressive multiple sclerosis

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	31-Oct-2018 14:02:34
	Deputy QPPV	31-Oct-2018 09:38:33

	[PPMS], other). The primary objective is to estimate (overall and by MS type) the event rates of serious adverse events (SAEs), including malignancy and serious infections, following ocrelizumab treatment in patients with MS. The secondary objective is to compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs; overall, and by individual DMTs if possible), within the same data source. If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.
COUNTRIES OF STUDY POPULATION:	Denmark, France, Germany, Italy, Sweden, and countries determined to be contributing safety data to MSBase
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	[redacted] Roche Products Ltd 6 Falcon Way Welwyn Garden City AL7 1TW United Kingdom

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ARTIS	Anti-Rheumatic Therapies in Sweden
BMSD	Big MS Data
BSRBR	British Society for Rheumatology Biologics Register
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
DMT	disease modifying therapy
eCRF	electronic case report form
EC	Ethics Committee
EDC	electronic data capture
EDMUS	European Database for Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
E.U.	European Union
FDA	(United States) Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
HR	hazard ratio
IgG1	immunoglobulin G1
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
JCV	John Cunningham virus
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSDN	(Italian) Multiple Sclerosis Database Network
MSDS3D	Multiple Sclerosis Documentation System 3D
NI-PASS	non-interventional post-authorization safety study
NMSC	non-melanoma skin cancer
OFSEP	Observatoire Français de la Sclérose en Plaques
PASS	post-authorization safety study
PBRER	periodic benefit-risk evaluation report

Abbreviation	Definition
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRAC	Pharmacovigilance Risk Assessment Committee
PS	propensity score
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SPMS	secondary progressive multiple sclerosis
U.K.	United Kingdom
U.S.	United States

3. RESPONSIBLE PARTIES

Protocol Development Responsible

[redacted]
F. Hoffmann-La Roche Ltd
4070 Basel Switzerland

[redacted]
F. Hoffmann-La Roche Ltd
4070 Basel Switzerland

[redacted]
80637 Munich Germany

Registry Investigators

[redacted], Germany
E-Mail: [redacted]

[redacted]
E-mail: [redacted]

[redacted] France
E-mail: [redacted]

[redacted]
[redacted] Denmark
E-mail: [redacted]

[redacted]
[redacted]
[redacted]
[redacted]
[redacted] Sweden
E-mail: [redacted]

[redacted]
[redacted]
[redacted]
[redacted]
[redacted] Italy
E-mail: [redacted]

4. ABSTRACT

TITLE: **LONG-TERM SURVEILLANCE OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS (MANUSCRIPT STUDY)**

PROTOCOL NUMBER: BA39730

VERSION NUMBER: 1.0

DATE OF SYNOPSIS: See electronic date stamp on the cover page

Rationale and Background

Ocrelizumab, a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively targets CD20-expressing B cells, received European Medicines Agency (EMA) approval in January 2018 for the treatment of relapsing forms of multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS) (OCREVUS® Summary of Product Characteristics).

Ocrelizumab has demonstrated superior efficacy in a double-blind, randomized Phase II trial (Study WA21493) compared with placebo in relapsing-remitting multiple sclerosis (RRMS) (Kappos et al. 2011); in a double-blind, randomized, placebo-controlled Phase III trial in PPMS (ORATORIO [Study WA25046]) (Montalban et al. 2017); and in two double-blind, randomized Phase III trials compared with interferon β-1a in RMS (OPERA I [Study WA21092] and OPERA II [Study WA21093]) (Hauser et al. 2017). Frequencies of adverse events (AEs) and serious adverse events (SAEs) in the ocrelizumab group were similar to interferon β-1a or placebo (OPERA studies and ORATORIO study, respectively). Pooled trial data indicated an imbalance in malignancies in the ocrelizumab treatment group versus pooled interferon β-1a and placebo. The only cluster of events that could be identified was for female breast cancer; incidences remained within the range of placebo data from clinical trials in multiple sclerosis (MS) and epidemiological data. Thus, no firm conclusion could be made concerning malignancy risk, due to the low number of events and limited follow-up.

This longitudinal observational study is part of the European Union (E.U.) risk management plan and is designed to further assess the long-term safety profile of ocrelizumab in the real world setting. The study will provide safety data for a 10 year period after ocrelizumab launch, specifically targeting the rate of SAEs, including serious infections and malignancies.

Research Question and Objectives

The research question is to assess and characterize the long-term safety data from the use of ocrelizumab in patients with MS (overall and by MS type [e.g, RMS, PPMS, other])

The primary objective for this study is:

- to estimate (overall and by MS type) the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment in patients with MS.

The secondary objective for this study is:

- to compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease

modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source.

If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.

Study Design

This post-authorisation safety study (PASS) is a multi-source, multi-country, non-interventional, longitudinal cohort study based on secondary use of data captured for patients with MS who have newly initiated treatment with ocrelizumab or another DMT after the marketing authorization date of ocrelizumab in the target country. Patients on ocrelizumab or another DMT will be followed for up to a maximum of 10 years following their first exposure to the DMT.

Comparisons of the incidence of SAEs including malignancies and infections will be made between patients with MS initiating ocrelizumab treatment and those initiating treatment with other approved DMTs. As there are no approved DMTs for certain forms of MS (e.g., PPMS), the comparison will also involve patients with MS not treated with any DMTs, if feasible.

Population

This study will include patients with MS who have initiated treatment with ocrelizumab or another DMT during the study period, or patients with MS not on DMT therapy in routine clinical practice.

Patients must meet the following criteria for inclusion in the study:

- A diagnosis of MS
- Aged 18 years or older
- Ocrelizumab group:
  - Patient must be newly treated with ocrelizumab during the study observational period
- DMT comparator group:
  - Patient who has never received treatment with ocrelizumab (at any time in the complete available history) and must be newly treated with an approved DMT other than ocrelizumab during the study observational period
- Non-DMT comparator group:
  - Patient who has never received ocrelizumab or any other DMT within the complete history recorded within available medical records and during individual follow-up in the study observational period

Patients who meet the following criterion will be excluded from study participation:

- Patient who has received ocrelizumab in the context of a previous clinical trial or Compassionate Use program, if information is available

Variables

Primary Safety Variables

- Serious adverse events, including death (date of onset and detail)
- Non-melanoma skin cancer (NMSC)

Secondary Variables

- Patient-specific information (date of birth, date of death, sex, country of residence)

- Disease-specific information (date of MS onset, MS type, Expanded Disability Status Scale [EDSS], relapses, John Cunningham virus [JCV] antibody status and, if available, index)
- MS treatment information (all previous and current DMTs)
- If available in data source:
    - Patient-specific information (employment status, smoking status, weight, height, ethnicity)
    - Disease-specific information (date of MS diagnosis, MS diagnostic criteria used, MRI information, lab test results, comorbid diseases, past major disease, family history of malignancies)
    - Treatment information (MS symptomatic medications and any other medications)
    - Pregnancy (Y/N)

Data Sources

This PASS will use data from the following MS-specific registry sources:

- Multiple Sclerosis Documentation System 3D (MSDS3D) in Germany
- Big MS Data (BMSD) Group, a collaboration of MS registries from Denmark, France, Italy, Sweden, and the international registry MSBase

Study Size

The target study size for this study will be approximately 5000 patients with MS exposed to ocrelizumab and 3500 patients with MS treated with other DMTs across all data sources. Assuming ocrelizumab does not increase the risk of malignancy excluding NMSC (true hazard ratio [HR] = 1.0, incidence rate of 3.7 per 1000 patient-years), an overall study duration of 10 years with a 2 year patient selection period and a follow-up period of at least 8 years, a drop-out rate of 5% per year in each arm, and a one-sided type-I error of 0.025, the study (expecting 278 malignancies) could rule out a HR ≥1.43 with 80% power.

For female breast cancer and serious infections, the outcome and HR (incidence rate per 1000 person years, expected number of events) expected to be ruled out are as follows: breast cancer, 1.79 (2.1,111); progressive multifocal leukoencephalopathy (PML), 10 (0.04, not estimable); herpes-related infection, 2.6 (0.4, 47); candida-related infections, 1.59 (2.1, 171); respiratory infections, 1.20 (16.6, 1052); and urinary tract infections, 1.16 (26.6, 1582).

Data Analysis

For semi-annual safety reports, data will be analyzed every 6 months. These reports will have aggregated data from each observational source on safety events occurring in each treatment group, which includes analysis of the primary objective.

- The total number of safety events (incident and recurrent) and unadjusted rates per 100 patient-years with 95% confidence intervals (CIs) will be provided for each treatment group, ocrelizumab and other DMTs (all DMTs combined and individual DMTs). Information on other DMTs will be provided only from registries which allow sharing of such data.
- For analyses of malignancy and PML, an ever-exposed model will be applied that includes all person-time observed since the first drug dose in the study until censorship. For all other SAEs, the analysis will be based on a time-on-drug approach. For analyses of death, both approaches will be used.
- First, event rates (i.e., accounting for multiple events) will be estimated based on the Poisson distribution and presented over the cumulative follow-up period and

stratified into one-year periods. Then, incidence rates (i.e., accounting for first event only) will be estimated.

Interim and final comparative safety reports addressing the secondary objective will be prepared 4, 6, 8, and 10 years after the study start.

- Within each data source, the ocrelizumab group will be compared to each DMT comparator group using propensity score (PS) based methods (inverse probability of treatment weighting or PS adjustment) using variables likely to include, but not limited to: age, sex, calendar time, disease duration prior to treatment initiation, proportion of disease duration spent treated with DMT, EDSS, comorbidities, prior DMT exposure, concomitant drugs (e.g., other concomitant immunomodulators/ suppressants), pre-baseline relapse activity, and (if appropriate) country.
- Unadjusted and adjusted HRs will be presented from Cox proportional hazard models or appropriate causal inference methods.
- Meta-analyses of results across the data sources will be conducted using aggregated data from each source.

Milestones

Start Date of Study

The study start date will be the date of the study dataset creation at the first data source. The planned start date is in 2018, following the launch of ocrelizumab in the E.U. in January 2018.

End of Study

The end of the study will be the date from which analysis of data required to fulfil study objectives is complete. The planned end of study date is in 2028. The final report will be provided in 2029.

Length of Study

This study will last approximately 10 years.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study milestones are given in Table 1. All study reports will be submitted to the Health Authorities through scheduled periodic benefit-risk evaluation reports (PBRERs).

Table 1 Study Milestones

Milestone	Planned Date
Registration of protocol in the E.U. PAS register	After approval of protocol
Start date of study	2018
End of study	2028
Semi-annual safety reports	Scheduled regulatory safety reporting every 6 months
Interim report 1 (Comparative safety report)	2022
Interim report 2 (Comparative safety report)	2024
Interim report 3 (Comparative safety report)	2026
Final report of study results	2029
Registration of the results in the E.U. PAS register	After approval of final study report

E.U. = European Union; PAS = post-authorization study.

Data will be extracted from the selected data sources biannually for semi-annual safety reports on new and cumulative safety events. For registries using linkage to other national registers to collect information, the linkage may not be performed for every semi-annual safety report. However, all information will be included in the interim and final reports. The interim and final comparative safety reports will be prepared 4, 6, 8, and 10 years after the study start.

The reporting periods for the study will differ by data source due to differences in launch date in each country, as seen in Table 2.

Table 2 Reporting Periods by Data Source and Country for Comparative Safety Interim Reports and Final Report

Data source	Country	Expected Launch Date Ocrelizumab	Interim Report 1 2022	Interim Report 2 2024	Interim Report 3 2026	Final Report 2029
MSDS3D	Germany	January 2018	Up to 4 years after launch date	Up to 6 years after launch date	Up to 8 years after launch date	Up to 10 years after launch date
MSBase[a]	Several European countries[b], Australia, Canada, and U.S.	Varies by country				
OFSEP[a]	France	Q2 2019				
Danish MS Registry[a]	Denmark	January 2018				
Swedish MS Registry[a]	Sweden	Q3 2018				
Italian MS Registry[a]	Italy	Q3 2018				

MSDS3D = Multiple Sclerosis Documentation System 3D; OFSEP = Observatoire Français de la Sclérose en Plaques; MS = multiple sclerosis.
[a] A member of the Big MS Data Group of registries (see Section 9.4.2)
[b] Including Czech Republic, Netherlands, Spain, UK

7. RATIONALE AND BACKGROUND

7.1 RATIONALE

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, the prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 respectively) (MSIF 2013). MS is commonly diagnosed between 20 to 40 years of age (Tullman 2013). Overall, women are affected approximately twice as often as men, except in individuals with the primary progressive form of the disease, where there is no gender difference in prevalence (MSIF 2013; Tullman 2013). The reasons for these observed differences are unclear.

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (relapsing-remitting MS [RRMS]). If left untreated, the majority of these patients will transition to a progressive form, characterized by worsening neurologic disability either with or without occasional superimposed relapses (relapsing or non-relapsing secondary progressive MS [SPMS]). Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression (Tullman 2013). Primary progressive MS (PPMS) is a less common form of MS, accounting for approximately 10% of all cases. It is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (Lublin 2014).

Evidence suggests that inflammation is present in the CNS throughout all MS clinical courses, from RRMS to SPMS and in PPMS (Frischer et al. 2009). Differences between disease phenotypes are due to the differential contribution of each of the inflammatory and neurodegenerative processes to the pathophysiology of CNS damage over time (Frischer et al. 2009; Frischer et al. 2015).

OCREVUS® (ocrelizumab) was approved by the European Medicines Agency (EMA) on January 12, 2018 for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease and for the treatment of adult patients with early PPMS in terms of disease duration and level of disability (see the OCREVUS® Summary of Product Characteristics for further details). In the United States (U.S.), OCREVUS® was approved by the U.S. Food and Drug Administration (FDA) on March 28, 2017 for the treatment of adult patients with RMS or PPMS (OCREVUS® U.S. Prescribing Information).

Ocrelizumab is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody that selectively targets CD20-expressing B cells. Ocrelizumab has demonstrated superior efficacy in a double-blind, randomized Phase II trial (Study WA21493) compared with placebo in RRMS (Kappos et al. 2011); in two identical, randomized, active-controlled Phase III trials (OPERA I [Study WA21092] and OPERA II [Study WA21093]) compared with interferon β-1a in RMS (Hauser et al. 2017); and in another double-blind randomized,

placebo-controlled Phase III trial (ORATORIO [Study WA25046]) versus placebo in PPMS (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of the disease, including disability progression, in addition to an impact on magnetic resonance imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss.

This longitudinal observational study is part of the risk management plan and designed to further assess the long-term safety profile of ocrelizumab in the real world setting. The study will provide safety data for a 10 year period after ocrelizumab launch in Europe by assessing rates of serious adverse events.

7.2 BACKGROUND

Ocrelizumab has demonstrated a favorable safety profile in RMS and patients with PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events (AEs) was similar in ocrelizumab-treated patients compared with interferon β-1a (both 83.3%) or placebo-treated patients (95.1% [ocrelizumab] vs. 90.0% [placebo]). The most common AEs were infusion-related reactions, nasopharyngitis, and urinary tract infections. Patients treated with ocrelizumab (versus interferon β-1a or placebo) reported more herpes virus-associated infections than patients who received interferon β-1a or placebo (RMS trials: 5.9% vs. 3.4%; PPMS trial: 4.7% vs. 3.3%), infusion-related reactions (RMS trials: 34.3% vs. 9.7%; PPMS trial: 39.9% vs. 25.5%), and upper respiratory tract infections (RMS trials: 15.2% vs 10.5%; PPMS trial: 10.9% vs. 5.9%). The overall percentage of patients reporting a serious infection was lower in ocrelizumab-treated patients in the RMS trials compared to interferon β-1a-treated patients (1.3% vs. 2.9%), and similar in the PPMS trial (6.2% [ocrelizumab] and 5.9% [placebo]) (Hauser et al. 2017; Montalban et al. 2017).

Eight deaths occurred during the controlled treatment periods of the pivotal Phase III ocrelizumab trials (RMS trials: 2 interferon β-1a-treated patients [suicide and mechanical ileus] and 1 ocrelizumab-treated patient [suicide]; PPMS trial: 1 placebo patient [road traffic accident] and 4 ocrelizumab-treated patients [pulmonary embolism, pneumonia, pancreatic carcinoma, and pneumonia aspiration]) (Hauser et al. 2017; Montalban et al. 2017). Although the proportion of patients experiencing serious adverse events (SAEs) was similar between ocrelizumab and the comparator groups (RMS trials: 6.9% [ocrelizumab] and 8.7% [interferon β-1a]; PPMS trial: 20.4% [ocrelizumab] and 22.2% [placebo]), data are needed to confirm the safety and efficacy of ocrelizumab over a long treatment duration and, importantly, in a clinical practice setting.

In controlled studies, the pooled overall incidence of a first neoplasm among patients with MS who were treated with ocrelizumab (Phase II study, OPERA I and II, and ORATORIO) was 0.40 per 100 patient-years of exposure (6467 patient-years of exposure), as compared with 0.20 per 100 patient-years for pooled comparator groups (interferon β-1a or placebo, 2053 patient-years of exposure) (Montalban et al. 2017).

In Phase II trials, two neoplasms were reported in patients with RRMS treated with ocrelizumab; none in patients receiving placebo (Kappos et al. 2011; Genentech, Inc. 2017). In RMS trials (OPERA I and II), neoplasms occurred in 4 patients (0.5%, n=4/825) treated with ocrelizumab (including 2 patients with invasive ductal breast carcinoma) during the controlled treatment period, and 2 patients (0.2%, n=2/826) treated with interferon β-1a (Hauser et al. 2017). In the controlled treatment period of the PPMS trial (ORATORIO), neoplasms occurred in 2.3% of patients (n=11/486) who received ocrelizumab (including two events of invasive ductal breast carcinoma and one event each of breast cancer and invasive breast carcinoma), and 0.8% of patients (n=2/239) who received placebo (Montalban et al. 2017).

Pooled data from the Phase II study, OPERA I and II, and ORATORIO indicated an imbalance in malignancies in the ocrelizumab treatment group versus pooled interferon β-1a and placebo. The only cluster that could be identified was for female breast cancer, and although cancer incidences remained within the range of placebo data from clinical trials in MS and epidemiological data, no firm conclusion could be made concerning the risk due to the low number of events and the limited follow-up period.

For updated safety information refer to the current ocrelizumab Investigator's Brochure.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

The research question is to assess and characterize the long-term safety data from the use of ocrelizumab in patients with MS overall and by MS type (e.g., RMS, PPMS, other).

8.2 OBJECTIVES

The primary objective is:

- to estimate (overall and by MS type) the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment in patients with MS.

The secondary objective is:

- to compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source.

If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This post-authorisation safety study (PASS) is a multi-source, multi-country, non-interventional, longitudinal cohort study based on secondary use of data captured for patients with MS in existing disease registries.

Approximately 5000 patients who have initiated treatment with ocrelizumab and 3500 patients exposed to other DMTs will be followed up to a maximum of 10 years following their first exposure to the DMT of interest, until censoring, until lost to follow-up, or until death, whichever comes first. Follow-up is planned regardless of whether patients discontinue treatment with DMT (ocrelizumab or another DMT).

Newly treated by ocrelizumab or other DMT is defined as those patients who initiate treatment with ocrelizumab or another DMT after the marketing authorization date of ocrelizumab in the target country. All available information on previous and current DMT treatment will be extracted for all patients. Within each dataset, a specific DMT comparator cohort will be compared using propensity score (PS) methods (inverse probability of treatment weighting and/or adjusting for the PS as a model covariate) to the ocrelizumab cohort in order to provide an internal comparator. The PS model will utilize baseline characteristics, and the populations will be restricted so that the necessary assumptions (i.e., positivity) of the PS-based methods are satisfied. Baseline characteristics' measurement periods will vary according to the nature of the variable and will be defined in the analysis plan. The non-treatment cohort will be matched to the ocrelizumab cohort with derived index dates.

Data on SAEs, including malignancies and infections, will be analysed to meet the primary and secondary study objectives.

Comparisons will be made between patients with MS initiating ocrelizumab and those initiating other DMTs. As there are no approved DMTs for certain forms of MS (e.g., PPMS), the comparison will also involve patients with MS not treated with any DMTs, if feasible.

This PASS will include data from the following sources (for details see Section 9.4):

- Multiple Sclerosis Documentation System 3D (MSDS3D) in Germany
- The Big MS Data (BMSD) Group, a collaboration of MS registries from Denmark, France, Italy, Sweden and the international registry MSBase

Data sources selected for this PASS have combined access to over 100,000 patients with MS, which is expected to be sufficient to provide the required sample size (see Section 9.5 for details). However, if one of the listed data sources fails to contribute a sufficient number of patients for the study, additional data sources may be added or substituted.

9.2 SETTING

9.2.1 Study population

This study will include patients with MS who have initiated treatment with ocrelizumab or another DMT during the study period, or patients with MS not on DMT therapy in routine clinical practice.

The study population covers a broad range of countries including Denmark, France, Germany, Italy, Sweden, and countries determined to be contributing safety data to MSBase such as Netherlands, Spain, U.K., Australia, Canada, and U.S.

Selection criteria

Patients who fulfill the following selection criteria will be included:

- A diagnosis of MS
- Aged 18 years or older
- Ocrelizumab group:
    - Patient must be newly treated with ocrelizumab during the study observational period
- DMT comparator group:
    - Patient who has never received treatment with ocrelizumab (at any time in the complete available history) and must be newly treated with an approved DMT other than ocrelizumab during the study observational period
- Non-DMT comparator group:
    - Patients who has never received ocrelizumab or any other DMT within the complete history recorded within available medical records and during individual follow-up in the study observational period

Patients who meet any of the following criteria will be excluded:

- Received ocrelizumab in the context of a previous clinical trial or Compassionate Use program, if information is available

Patients with prior or concomitant conditions relevant to serious infections or malignancies (e.g., concomitant disease or prior malignancy) will not be excluded from the study. Medically relevant prior and/or concomitant diseases will be considered at the analysis stage.

Patients with MS who switch treatments during the follow-up will not be excluded from the study. These patients will be followed until the end of the study, until lost to follow-up, or until death. Patients included in the DMT comparator group who then receive ocrelizumab can be included in the ever-exposed analysis for both ocrelizumab and the comparator groups and will also be included in the time-on-drug analysis of the ocrelizumab group.

The study population will include patients with MS who are treatment naïve to DMTs (ocrelizumab or other DMTs) and patients with MS already treated with DMTs other than ocrelizumab before switching to ocrelizumab or to another DMT (prevalent patients). Data on previous treatments will be extracted to assess exposure 'overlap' periods.

The ocrelizumab-exposed RMS patient group is expected to have differential MS severity compared to patients with RMS exposed to other DMTs. The label indication for ocrelizumab treated patients with RMS requires evidence of disease activity within the previous 24 months prior to treatment, while the label indication varies for other DMT comparators (e.g., alemtuzumab is indicated only in patients with active RRMS, while the label for interferon β-1a does not restrict to patients with active RRMS). Failure to adequately control for group differences in disease activity could lead to differential apparent AE rates for ocrelizumab as the rates for various AEs are associated with disease severity. Such AEs include infections, cardiovascular events, or metabolic events, and the latter two could manifest as study outcomes as deaths or other SAEs. A channeling effect is a similar concern when comparing PPMS ocrelizumab patients to the non-DMT comparator, as PPMS patients treated with ocrelizumab may have differential MS severity compared with those undergoing other treatments or no treatment. Note that the comparator for PPMS patients is the non-DMT group as no DMTs other than ocrelizumab are approved to treat patients with PPMS. See Section 9.7 for details on the analysis and Section 9.9 for further comments on limitations of the research method.

Only patients who have either previously given informed consent for secondary data use or reside in a country with national regulations allowing secondary use of data for research purposes will be included in the study population.

9.2.2 Study period

The overall observation period of the study is 10 years and will cover the period from Q1 2018 (launch of ocrelizumab in the E.U.) up to Q1 2028 to allow a maximum patient follow-up of 10 years. However, ocrelizumab-treated patients with MS in MSBase countries in which ocrelizumab was launched before Q1 2018 (e.g., Australia, Canada) may also be considered for the study. Patients with an MS diagnosis will be followed from the first treatment with ocrelizumab or with another approved DMT until the end of the follow-up period, until death, or until lost to follow-up, whichever comes first.

Due to different market launch dates for ocrelizumab in different European countries, the start of follow-up will vary across participating registries and countries. Estimates of local launch dates are provided in Table 2. Within each country, the maximum possible follow-up time for ocrelizumab exposed patients depends on the first patient treated with ocrelizumab being recorded in the registry after market launch.

The reporting periods for the study will differ by data source due to differences in launch date in each country, as seen in Table 2.

9.2.3 Follow-up (exposure periods)

Index date: For both the ocrelizumab group and the DMT comparator group, the index date is defined as the first dose of the medication and denotes the start of the follow-up observation period. If patients start multiple DMTs, each DMT initiation is a potential index date. For the untreated group, the index dates will be derived from that of the respective ocrelizumab patients being used for the comparison.

For ocrelizumab and each DMT, there will be two types of exposure follow-up periods. The exposure period used will depend on the outcome that is analyzed (see Section 9.7.1; Llung et al. 2014; Kearsley-Fleet et al. 2016):

- **Ever-exposed follow-up period:** total patient-years observed (irrespective of treatment received) will be calculated from the index date until either the event (when analyzing first events), death, lost to follow-up, or the end of the study, whichever occurs first. Because different outcome events are being evaluated, ever-exposed follow-up period may vary for each analysis because date of event may vary. There will be no adjustment for competing risks.
- **Time-on-drug follow-up period:** total patient-years exposed from first drug dose of index drug up to a risk window after the last administration of the index drug. Risk windows will depend on the DMT and will be based on the half-life as well as the mechanism of action, including lymphocyte count recovery, as described in the Summary of Product Characteristics and the literature. Sensitivity analyses will vary the risk window to assess the robustness of findings, including but not limited to 1) 364 days for ocrelizumab and a proportionate increase for other DMTs (see Table 3), and 2) up until the date of switch to another DMT. The half-life and risk window for each DMT are listed in Table 3 below. Time-on-drug exposure periods will only be created for the index drug in a group.

Table 3 Half-Life and Risk Windows for DMTs

MS DMT	Half-life	Primary Risk Window (days)	Larger Risk Window (days) for Sensitivity Analysis
Ocrelizumab[a]	26 days	182	364
Interferon β-1b[b]	5 hrs	91	182
Interferon β-1a[c]	50-60 hrs	91	182
Glatiramer acetate[d]	<24 hrs	91	182
Natalizumab[e]	16 +/- 4 days	91	182
Fingolimod[f]	6-9 days	91	182
Teriflunomide[g]	19 days	121	242
Alemtuzumab[h]	4-5 days	364	1820
Dimethyl fumarate[i]	1 hr	91	182
Cladribine[j]	1 day	364	1456
Mitoxantrone[k]	23-215 hrs	91	182

DMT = disease modifying therapy; hrs = hours
[a] OCREVUS® (ocrelizumab) Summary of Product Characteristics
[b] EXTAVIA® (interferon β-1b) Summary of Product Characteristics
[c] Rebif® (interferon β-1a) Summary of Product Characteristics
[d] Medicines and Healthcare Products Regulatory Agency product details (glatiramer acetate)
[e] Tysabri® (natalizumab) Summary of Product Characteristics
[f] GILENYA® (fingolimod) Summary of Product Characteristics
[g] AUBAGIO® (teriflunomide) Summary of Product Characteristics
[h] LEMTRADA® (alemtuzumab) Summary of Product Characteristics
[i] Tecfidera® (dimethyl fumarate) Summary of Product Characteristics
[j] MAVENCLAD® (cladribine) Summary of Product Characteristics; Protocol MS 700568-0002
[k] Scott and Figgitt 2004

9.3 VARIABLES

9.3.1 Primary Safety Variables

Outcome variables will be described according to Medical Dictionary for Regulatory Activities (MedDRA) classification or another standard coding system along with the date of each outcome event:

- SAEs, including:
    - Malignancy (overall and categorized by subtype, including breast cancer)
    - Serious infections (overall and categorized by subtype, including progressive multifocal leukoencephalopathy [PML], herpetic infections, candida infections, urinary tract infection, respiratory tract infections, etc.)
    - Any other SAEs, including death (categorised by major type)
- Non-melanoma skin cancer (NMSC)

9.3.2 Secondary Variables

Data elements which are key to conduct this PASS and will be extracted from all data sources are:

- Patient-specific information
    - Date of birth
    - Date of death, if applicable
    - Primary and underlying causes of death, if applicable
    - Sex
    - Country of residence
- Disease-specific information
    - Date of MS onset (first clinical manifestation)
    - MS type
        - RMS
            - Relapsing remitting
            - Secondary progressive
        - PPMS
        - Other
    - Expanded Disability Status Scale (EDSS) scores (including dates of assessment) or a proxy measure (e.g., Patient Determined Disease Steps) if EDSS is not available
        - For up to 2 years prior to index date
        - During study follow-up
    - Relapses (including dates of onset), including glucocorticoid treatment (yes/no)
        - For up to 2 years prior to index date
        - During study follow-up
    - John Cunningham virus (JCV) antibody status (Pos/Neg with index) (including date of sample), if available
- MS treatment information
    - All previous and current DMTs, including all known immunosuppressants for the treatment of MS
        - Drug name
        - Start date
        - Stop date (e.g., date of last administration) (for medications ceased)

        - Major reason for discontinuation/switch (if available) (for medications ceased)

Data elements considered important but not mandatory for conduct of this PASS will be extracted if collected by a data source:

- Patient-specific information
    - Employment status
    - Smoking status (never, former, current)
    - Weight, height, ethnicity
- Disease-specific information
    - Date of MS diagnosis
    - MS diagnostic criteria used
    - Brain MRI information (including date of assessment)
    - Lab test results (e.g., lymphocyte counts, liver enzymes), including date of test. Classification can be provided as normal and value if abnormal.
    - Current comorbid disease (e.g., none, cardiovascular, respiratory, gastrointestinal, psychiatric, metabolic, malignancies, musculo-skeletal, other auto-immune conditions, other)
    - Past major disease (e.g., malignancies)
    - Family history of malignancies
    - Any available personal or family genetic testing for malignancy risk factors (e.g., BRCA1 and 2)
- Treatment information (non-MS disease modifying and immunotherapy)
    - MS symptomatic therapy
        - Drug name
        - Start date
        - Stop date and reason of discontinuation (for medications ceased)
        - Dose, schedule
    - Other therapies
        - Drug name
        - Indication
        - Start and stop dates
        - Dose, route, schedule
- Pregnancy (Y/N)
    - If yes, date of last menstrual period or other estimated date of start of pregnancy

9.4 DATA SOURCES

European healthcare registries have been previously used to assess the long-term safety in post-marketing commitments requested by the FDA and EMA (Neovius et al. 2011; Xue and Ma 2013). Furthermore, EMA began a patient registry initiative in 2015 to facilitate the use of registry data for informing regulatory decisions. In July 2017, EMA hosted the MS registries workshop and released a set of recommendations (Report on Multiple Sclerosis Registries). Subsequently, the BMSD Group, industry partners, and EMA had a follow-up meeting in February 2018 to discuss the implementation of the recommendations, including development of a safety core protocol (Section 9.4.2).

As such, data received in this study will be obtained through the BMSD Group, a collaboration of MS registries from Denmark, France, Italy, Sweden, and the international registry MSBase, as well as through MSDS3D in Germany. Both the BMSD Group and MSDS3D are led by academic institutions that prospectively collect high quality data allowing for the safety monitoring of ocrelizumab over the long-term.

Post-marketing safety studies can have greater efficiency and faster data generation when based on established high-quality data sources. Advantages over site-based prospective data collection include:

- Less potential for selection bias and greater generalizability of findings because many registries are population-based (e.g., Nordic registries)
- Greater credibility of study findings because registries complement prospective non-interventional studies from industry. Furthermore, Nordic registries have the ability to collect additional data through linkage with their other population-based registries (e.g., cancer registry and death registry) and, therefore, allow for malignancy follow-up, even in the event a patient stops treatment with the product of interest and/or has been lost to follow-up in the disease-specific registry. It has been argued that disease registries, rather than specific product registries, are more likely to be successful in systematically collecting interpretable long-term safety data, thereby allowing comparisons, to the extent possible, across types and generations of drugs (Gliklich et al. 2014)
- 'Automatic' generation of comparator data within the same data source, thus same source population, in order to contextualize a product's safety profile (for those data sources from which comparator data will be drawn)

The next sections provide details on the different registries considered for this study.

9.4.1 Multiple Sclerosis Documentation System 3D (MSDS3D)

MSDS3D is an internet-based patient management and documentation system in Germany which allows the management of patient visit schedules and documentation of diagnostic, clinical, and safety data via different modules. It was reengineered in 2010 based on a previous MS documentation system (Ziemssen et al. 2013).

Data can be entered into MSDS3D software through an internet or computer-based electronic case report form (eCRF) / electronic data capture (EDC) system and uploaded into a central database. Anonymized data exports can be provided on an ad-hoc basis. Adverse events are captured through a custom safety module that uses MedDRA and WHO-DD coding systems and that has been used in previous studies (Ziemssen et al. 2015; Haase 2018).

Data collected in MSDS3D for a longitudinal, observational study in patients with MS exposed to ocrelizumab and other DMTs will be used as secondary data for the objectives of this PASS. This study will start data collection in 2018 and is expected to enroll 3000 ocrelizumab-treated patients and 1500 patients exposed to approved MS DMTs other than ocrelizumab (Roche Study ML39632) from approximately 250 sites across Germany.

9.4.2 Big MS Data (BMSD) Group

The BMSD Group is following up on guidance recommendations from the EMA Initiative for Patient Registries MS Workshop (Report on Multiple Sclerosis Registries) and collaborating to develop standards for registry safety data collection and reporting. This protocol BA39730 is aligned with a core study protocol "*A prospective observational long-term safety surveillance study in the Big MS Data (BMSD) Group network*," developed jointly by industry partners and the BMSD Group.

9.4.2.1 MSBase

MSBase is a longitudinal, observational registry that collects clinical, therapeutic, imaging, and safety data from routine clinical practice for patients with MS. MSBase was started with an overall objective to facilitate the collection of epidemiological information through its unique web interface and to use the collected information to answer epidemiological questions that aim to improve the quality of care of patients with MS (Butzkueven et al. 2006; MSBase 2017).

MSBase was started in 2003 and contains data on >50,000 patients from 115 centers across over 72 countries. In Europe, the largest contributors are Italy, Spain, and Netherlands with approximately 10,000, 4,000 and 3,000 patients respectively. To avoid patient duplication, patient data from clinics who contribute to both MSBase and a country-specific registry in Section 9.4.2.2 – 9.4.2.5 will only be extracted from one data source.

Data is imported into the MSBase registry from a number of sources: MSBase web-based data entry system, iMed software application, or through local registry integration. Safety data will be collected through an MSBase-specific safety module using a MedDRA coding system (Haartsen et al. 2015).

9.4.2.2 Observatoire Français de la Sclérose en Plaques (OFSEP)

OFSEP is a longitudinal observational registry that collects clinical, therapeutic, imaging, and safety data as well as biological samples from routine clinical practice for patients with MS or related diseases in France. OFSEP is based on European Database for Multiple

Sclerosis (EDMUS) software and was started to promote research that aims to improve the diagnosis and treatment of people with MS and to advance the understanding of the causes and mechanisms of the disease (OFSEP 2016).

OFSEP was started in 2011 and contains data on >50,000 patients and 23,000 active patients (with consultation in the last two years) from 35 centers (hospital and hospital outpatient departments) across France. Approximately 57% of total patients have the relapse remitting form of MS and 11% have PPMS. Of the patients with RRMS, 23% are currently on no DMT, 41% are on first-line treatment and 32% are on second-line treatment. Median length of follow-up for patients is over 12 years and as of December 2016, 35% of patients had a consultation within the last year.

Data is collected via the EDMUS data collection system and reported on a biannual basis. Adverse events are collected through a safety module.

9.4.2.3 Danish MS Registry

The Danish MS Registry is a population-level registry that collects clinical, therapeutic, and safety data via different modules (Brønnum-Hansen et al. 2011; Koch-Henriksen et al. 2015). The Danish MS Registry started with a nationwide population-based MS prevalence survey and continues as a means of promoting research on high-quality real-world data in MS.

The registry contains data at a near population level (26,300 patients of which 16,000 were alive at end of 2017). Of the 16,000 active patients, approximately 59% currently receive DMT. As reporting of all patients on DMTs is mandatory (Koch-Henriksen and Sørensen 2000; Koch-Henriksen et al. 2015), data completeness is estimated at above 90% and lifetime follow-up can be expected for all patients, as long as they remain in the country.

The Danish MS Registry uses the COMPOS® online data collection system. Data can be exported on an ad-hoc basis as required by study timelines. Safety events can also be captured by linkage to other Danish national registries using the personal identification number (CPR-number) which is used by all national registers.

9.4.2.4 Swedish MS Registry

The Swedish MS Registry is a near population-level registry (>80% coverage) that has been active since 2001 with a primary objective to collect data to assess the long-term effectiveness of disease-modifying treatments (Hillert and Stawiarz, 2015).

The Swedish MS Registry contains data on approximately 15,000 patients since 2001. All serious adverse reactions as defined by the Swedish Health Authorities will be reported to the registry. Lifetime follow-up in national patient registers can be expected due to a unique personal identification number, as long as the patient remains in the country.

The Swedish MS Registry uses the COMPOS® online data collection system. Data can be exported on an ad-hoc basis as required by study timelines. Safety events can also be captured by linkage to other Swedish national registries using the personal identification number (CPR-number) which is used by all national registers.

9.4.2.5 Italian MS Registry

The Italian Registry is active since 2000. From 2000 to 2015, the registry was in the framework of the Italian Multiple Sclerosis Database Network (MSDN). Since 2015, the framework has been altered to a near population-level registry promoted and founded by the Italian Multiple Sclerosis Society and its Italian Multiple Sclerosis Foundation in collaboration with the University of Bari, with continuity in the existing MSDN-iMed© software's database collection.

The Italian MS Registry currently contains data (clinical, therapeutic, imaging, lab and safety data) on approximately 50,000 patients from 72 MS Italian centers. About 50% of patients have a follow-up period longer than 5 years, and 30% longer than 10 years. About 70% of the population is represented by DMT-treated patients.

A data collection web-site is currently available at https://registroitalianosm.it/, where each center can enter data through a personalized password. It is possible to check the presence of a unique valid code identifier, through the patient encrypted fiscal code, in order to overcome duplications. Several quality controls have been implemented in order to increase the quality and generalizability of data collected. Safety data will be collected through a specific safety module using the MedDRA coding system.

9.5 STUDY SIZE

The target for this study will be approximately 5000 patients with MS exposed to ocrelizumab and 3500 patients with MS treated with other DMTs. Within each data source, the number of patients included in the comparator group is assumed to be at least half of the number of patients exposed to ocrelizumab.

Power calculations are presented to provide the expected precision of hazard ratio (HR) estimates for important SAEs, including malignancy (excluding NMSC) and serious infections. No formal hypothesis testing will be performed.

For malignancy excluding NMSC, an incidence rate of 3.7 per 1000 patient-years in the reference group is assumed, based on the real-world data from British Columbia, Canada (Kingwell et al. 2012). Assuming that ocrelizumab does not increase the risk of malignancy (true HR = 1.0), an overall study duration of 10 years with a 2 year patient selection period and a follow-up period of at least 8 years, a drop-out rate of 5% per year in each arm, a one-sided type-I error of 0.025 and with a sample size of 5000 patients recruited in the ocrelizumab group and 3500 patients in the non-ocrelizumab group across all data sources, the study could rule out a HR ≥1.43 with 80% power, based on expecting 278

malignancies.

For female breast cancer and serious infections, given the same assumptions of the parameters, the HRs expected to be ruled out with 80% power are listed in Table 4, which includes incidence rates and expected number of events.

Note that this power is only realized in the ideal case of unbiased treatment effect estimates across all data sources.

Table 4 Effect Size to be Ruled Out with 80% Power and Sample Size Consisting of 5000 Ocrelizumab-Treated Patients with MS and 3500 Patients with MS Treated with Approved DMTs Other Than Ocrelizumab

Outcome	Incident Rate per 1000 PY in the Reference Group	Expected Number of Events	HR Expected to be Ruled Out
Malignancy			
Malignancy (excl NMSC)[a]	3.7	278	1.43
Breast cancer (female)[b]	2.1	111	1.79
Infections[c]			
PML	0.04	not estimable	10
Herpes-related infections	0.4	47	2.6
Candida-related infections	2.1	171	1.59
Respiratory infections	16.6	1052	1.20
Urinary tract infections	26.6	1582	1.16

DMT = disease modifying therapy; HR = hazard ratio; MS = multiple sclerosis; NMSC = non-melanoma skin cancer; PML = progressive multifocal leukoencephalopathy; PY = patient-years.
Note: Assumptions underlying these calculations:
- No difference in risk between the exposed and unexposed (i.e., hazard ratio = 1)
- Proportion of females = 60%

[a] Kingwell et al. 2012, British Columbia (Canada), BC MS database linked to BC cancer registry
[b] Nielsen et al. 2006, Denmark MS Registry
[c] Swedish MS registry linked to Swedish Patient registry (unpublished)

9.6 DATA MANAGEMENT

Overall, this study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

The processes for data management differ by country and data source. 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, with periodic backup of files. Standard procedures will be in place to restore files in the event of a hardware or software failure.

MS registries

Data at BMSD registries will be extracted and analysed for this study locally by each registry holder. Extraction of data and data management will be done according to registry-specific procedures. Routine procedures pre-specified and approved by each disease registry will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. The datasets and analytic programs relevant for the execution of this PASS will be stored according to the registries' procedures to allow future analysis if needed. Statistical Analysis System (SAS) software version 9.2 or later, or other appropriate statistical software, including R, version 3.2 or later, will be utilized for access to the raw data, to manage the analytic datasets, and to conduct data analysis. Aggregated results in tables will be transferred electronically to [redacted].

Data collected via MSDS3D, including quality checking of the data, is done by a contract research organization (CRO) responsible for Roche Study ML39632. Data extracts of patient-level data for secondary use will be transferred electronically to [redacted] for analysis and meta-analysis.

[redacted]

[redacted] will receive patient-level data extracts from MSDS3D and aggregated data from the other data sources for all semi-annual and interim reports as well as the final report. Furthermore, [redacted] will conduct the meta-analyses using aggregated data from each source for the interim and final reports. Data extracts and analysis programs will be stored to allow any necessary future analysis. All analyses done by [redacted] will be performed using SAS software version 9.2 or later, or other appropriate statistical software, including R, version 3.2 or later.

9.7 DATA ANALYSIS

9.7.1 Safety Analyses

Data will be analyzed every 6 months over a study duration of 10 years. Variables (e.g., age, sex, EDSS, type and duration of prior DMTs, etc) will be summarized using mean, median, standard deviation, and range for continuous data and counts and percentages for categorical data. Missing values will be counted and presented for each variable.

Patients will be selected over a period of time and the study will end on a specific calendar date (10 years from the start of the study). Thus, patients who enroll later will be followed for a shorter period than patients who enroll early owing to administrative censoring. Other patients may be lost to follow-up in the data sources. Therefore, methods accounting for right-censored data will be used.

Two main analytical approaches will be used depending on the outcome of interest, as

described in methods used by Anti-Rheumatic Therapies in Sweden (ARTIS) and the British Society for Rheumatology Biologics Register (BSRBR) (Llung et al. 2014; Kearsley-Fleet et al. 2016). For analyses of risk of malignancy and of PML, an ever-exposed model will be applied that includes all person-time observed since the first drug dose in the study until study end. For all other SAEs, the analysis will be based on a time-on-drug approach that uses person-time as exposed from first drug dose in the study up to a risk window after the last administration of ocrelizumab or other DMT (see Section 9.2.3). Time on ocrelizumab or other DMT will be summarized, and rates of treatment cessation and switching will be calculated. An outcome of interest occurring during the defined risk window period will be allocated to the preceding treatment. The risk windows will be varied in sensitivity analyses to assess the robustness of findings, including but not limited to 72 weeks after last administration of the index drug and up until the date of switch to another DMT. For analyses of risk of death, both analytical approaches will be used − an ever-exposed and an on-drug model.

9.7.1.1 Semi-annual safety reports

Semi-annual cumulative safety study reports will be prepared, with aggregated data from all observational sources on safety events occurring in each treatment group. In these semi-annual safety reports, the total number of safety events (incident and recurrent) and unadjusted rates per 100 patient-years with 95% confidence intervals (CIs) will be provided.

Incidence rates (involving first events only) and event rates (including all reoccurring events during the risk window) will be calculated for all events. Incidence rates (involving time to first events only) and event rates (including all reoccurring events during the risk window) will be calculated for all outcome variables.

All rates will be reported stratified by MS type (overall, RMS, PPMS, other) and sex (overall, male, female).

These reports will be based on a common reporting template used by all participating registries to relay ongoing information with regards to safety within these registries. Meta-analyses will not be conducted for biannual reports.

9.7.1.2 Interim and Final Comparative Safety Reports

In addition to the semi-annual safety reports, interim and final comparative safety reports addressing the secondary objectives will be prepared 4, 6, 8, and 10 years after the study start, respectively.

To compare incidence rates between ocrelizumab-treated and comparator patients within registries, unadjusted and adjusted HRs will be presented. The HRs comparing patients with MS exposed to ocrelizumab with patients with MS exposed to any other approved DMT (or to individual DMTs if possible) with associated CIs will be estimated using survival analysis including Cox proportional-hazard models. Additional comparative

analyses may involve comparator groups defined by line of treatments/number of switches (e.g., by number of prior DMT starts). The assumptions of the models will be tested.

Analyses will be conducted within each data source separately using ocrelizumab and DMT comparator groups. PS adjustment will be used to adjust for measured confounders. Standard regression-based covariate adjustments and/or appropriate causal inference methods (Hernán and Robins 2017) may also be applied. Potential confounders are likely to include, but will not be limited to, age, sex, calendar time, disease duration prior to treatment initiation, proportion of disease duration spent treated with DMT, EDSS, comorbidities, prior drug exposure, concomitant drugs (e.g., other concomitant immunomodulators/suppressants), pre-baseline relapse activity, and (if appropriate) country. For each registry, variables associated with ocrelizumab and other DMT use at a significance level of P<.10 will be used to generate individual propensity scores for each patient. Baseline variables will be reported for these groups. The propensity score models will be checked by examining the expected bias, which is the likely bias in the treatment estimate due to each confounder.

Further analyses involve subgroup analyses of absolute and relative risks by patient-level characteristics including age, sex, MS subtype, disease duration, EDSS, comorbidities, prior drug exposure, and concomitant drugs, if possible. If PML cases are observed in this study, descriptive analyses will be conducted taking into account duration of exposure to ocrelizumab, and type and duration of prior exposure to immunosuppressive/ immunomodulatory drugs, as well as information on JCV antibody titre, if available.

Meta-analysis of results across the data sources will be conducted using aggregated data from each source. The overall treatment effect (expressed as a HR and CI) will be estimated using a random effects model and the Hartung-Knapp estimator (Hartung 1999; Hartung and Knapp 2001a; Hartung and Knapp 2001b). Heterogeneity will be assessed using Cochran's Q and the I2 statistic. As a sensitivity analysis, the heterogeneity parameter $\tau 2$ will be estimated, and an additional sensitivity analysis will estimate the overall treatment effect and CI using a fixed effect model with the Mantel-Haenszel estimator (Wiksten, et al 2016). Results will be graphically displayed using forest plots.

Since data will be used for on-going risk characterization, results will not be adjusted for multiplicity analysis of multiple endpoints or at multiple time points.

These interim and final comparative reports may also include analysis of an exploratory objective, to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS never exposed to any DMTs. If sufficient data is available, the methods used for the secondary analyses would be applied to the exploratory analysis. The ocrelizumab group will be compared to the non-DMT comparator group using a similar methodology, with any visit on or after diagnosis in the non-DMT comparator group as a potential entry date. Since prior use of any DMTs is a confounding

variable, only patients with PPMS with no DMT treatment prior to starting treatment with ocrelizumab will be compared. If patient numbers are low, a descriptive analysis will be conducted.

All analyses will be performed based on a common core protocol and reporting template. MSDS3D will contribute patient-level data for analysis. The other registries will submit aggregated-level data. All results will then be collated and meta-analyzed in a single report for submission to Health Authorities. Pooled analyses stratified by registries comparing ocrelizumab to all DMTs combined and individual DMTs, if possible, will be presented.

Full details of planned statistical methodology, including handling of missing and censored data and sensitivity analyses to quantify the potential effect of unmeasured confounding, will be specified in the Statistical Analysis Plan (SAP) which will be developed after approval of the study protocol.

9.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

Marketing Authorization Holder

The Marketing Authorization Holder (MAH) must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms (if applicable), and documentation of Institutional Review Board (IRB)/Ethics Committee (EC) and governmental approval/notification (if required).

The MAH shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Registries

The registries' standard operating procedures, internal policies and process guidance, and/or routine practice will be used for the conduct of this PASS. These procedures may include, among others, rules for data storage, methods to maintain and archive project and study documents, quality-control procedures for programming, standards for writing analysis plans, and review of analysis programs and study documents by senior staff and internal audits.

[redacted]

All aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of the [redacted] Quality Management System and in accordance to [redacted] policies and procedures, including quality control on the study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions, and study reports.

Retention of Records

Records and documents pertaining to the conduct of this study must be retained for at least 15 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the MAH. Written notification should be provided to the MAH prior to transferring any records to another party or moving them to another location.

All data sources will comply with F. Hoffmann-La Roche Ltd procedures regarding archiving and record management.

9.9 LIMITATIONS OF THE RESEARCH METHOD

This study aims to evaluate the long-term safety of ocrelizumab and other available DMTs in patients with MS in a real-world setting. The following sections address the potential limitations:

- Sample size: Uptake of new medications such as ocrelizumab is unpredictable and has the potential to impact the feasibility of reaching the sample size over all selected data sources for this PASS. However, continuous check of patient numbers per data source will allow strategies to be employed in response to any such challenges and to reduce or eliminate the potential impact of these factors. These include potential inclusion of additional data sources (e.g., another MS registry) and/or expansion of the patient inclusion period.

  Channeling effect: Factors associated with treatment choice and also with any of the study outcomes of interest will be evaluated at baseline (index date), and will be accounted for in multivariate analyses using PS adjustment . However, if the populations being compared are too different, the PS in the ocrelizumab and comparator cohorts may have areas of non-overlap. Patients with such propensity scores would be excluded, leading to lower power than expected. If this is observed, the previously described strategies to increase the sample size will be employed to recover the lost power. Specifically, the non-DMT exposed patient group is expected to differ systematically from the DMT-exposed group with regards to MS severity and other variables that could also be associated with the outcomes of interest.

- Residual confounding between the study population and comparators: The planned analysis of baseline characteristics will examine the distributions of key variables that could cause confounding (e.g., age, sex, comorbidities), and will be accounted for using PS adjustment. However, residual confounding due to unknown and imprecisely measured confounders may still remain. Sensitivity analyses will be conducted to quantify the potential effect of unmeasured confounding, but such analyses will not be able to assess the actual amount of bias (if any) in the study results.
- There is a risk that due to switching of treatments, the DMT that caused a condition might not be the DMT in use when the condition is diagnosed. This risk is higher for diseases with long latency periods such as malignancy. For this reason, malignancy and PML are only analyzed using "ever-exposed" periods in the analysis. For other outcomes, sensitivity analyses will vary the size of the risk window used to define the "time-on-drug" exposure periods. This will allow for an assessment of the robustness of the conclusions to the risk window used. This is the reason why a pre-index observation period in the registry of up to 2 years is desired in order to allow capture of previous DMTs.

9.10 OTHER ASPECTS

None.

10. PROTECTION OF HUMAN PATIENTS

10.1 INFORMED CONSENT

Whenever possible, the MAH shall ensure that patients at the occasion of the primary data collection have explicitly agreed to any secondary use of their data if they provide patient-level data to the MAH. In case it is not possible/practical to obtain or retrieve informed consent for use of secondary data in a non-interventional study, certain other precautions must be taken, including:

- Ensuring data are anonymised / pseudonymised
- Ensuring final analysis data are anonymised / pseudonymised
- Ensuring possibility of linkage back to individual identified patients is impossible or tightly controlled
- Obtaining ethical committee approval for use of data as proposed (e.g., the review of and extraction of information from individual medical charts) ahead of study initiation

In the unusual circumstance that individual patients can be identified directly from their data received, then approval to use that data should be sought where possible.

10.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiology Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union (E.U.) requirements for ensuring the well-being and rights of participants in a non-interventional post-authorization safety study (NI-PASS).

10.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

As the study will be operating using secondary data extracted from a number of sources, additional ethical approvals are typically not required. If required by local regulations, each data source will submit this protocol and relevant supporting information to the relevant IRB/EC for review and approval before the study is initiated.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is an NI-PASS involving the use of secondary data and the reporting of adverse reactions in the form of Individual Case Safety Reports is not required.

12. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Regardless of the outcome of the study, the MAH is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

Semi-annual safety reports will be prepared over the entire 10-year study period and submitted with PBRERs.

The first interim report will be submitted 4 years after study start. The estimated year is 2022. Further interim reports will be submitted every 2 years until 2026. These reports will add cumulative data from the launch date until the end of the respective reporting period (see Table 2).

The final report will be submitted in 2029.

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

None.

Appendix 2
ENCePP Checklist for Study Protocols (Revision 4)

Doc.Ref. EMA/540136/2009

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

Study title:
LONG-TERM SURVEILLANCE OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS (MANUSCRIPT STUDY)

EU PAS Register® number: Study not registered
Study reference number (if applicable): BA39730

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:

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

[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.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. 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?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.1
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. 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; 9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.2.1
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

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? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2.3; 9.7
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2.3
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.1

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?	☒	☐	☐	9.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. 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? (e.g. confounding by indication)	☒	☐	☐	9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2; 9.4; 9.7
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7

Comments:

This study uses data from established MS registries routinely used for research.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. 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? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.1
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4.2

Comments:

Coding of covariates, if applicable, will be described in the SAP which will be developed after approval of the study protocol.

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 study size and/or statistical precision estimated?	☒	☐	☐	9.5
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 confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.2.3; 9.7

Comments:

Missing values will be counted and presented for each variable. Full methodological methods for handling missing data in the analysis will be elaborated in the statistical analysis plan.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Quality control includes independent review of study results by senior staff.

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

Comments:

Avoidance of selection bias was considered during the selection of patient population and data sources

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

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 (e.g. 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: 29/10/2018

Signatur[redacted]

Appendix 3
Description of Data Sources

Table A3-1 Description of data sources and information available

	MSDS3D	MSBase	OFSEP	Danish MS Registry	Swedish MS Registry	Italian MS Registry
Database information						
Principal Investigator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of database	MS registry	MS registry	MS registry	MS registry	MS registry	MS registry
Geographic coverage	Germany	72 countries worldwide, including Netherlands, Spain, U.K., Australia, Canada, and U.S.	France	Denmark	Sweden	Italy
Start of data collection	2001	2003	2011	2015	2004	2000 as MSDN, transition to current format in 2015
Number of prevalent patients with MS	4500 (3000 OCR / 1500comparator)	55,000	>50,000	>20,000	14,500	50,000
Median follow-up duration (years)	~8	4.05 (IQR: 0.88-8.81)	15.2 (mean)	Lifelong	Lifelong	50% of patients have >5 years of data
Inclusion of untreated patients with MS	Yes	Yes	Yes	No	Yes	TBD
Can patients be linked to additional data sources?	No	No	No	Yes	Yes	No
If yes, what linkages are possible?	Not applicable	Not applicable	Not applicable	Linkable to the National Patient Register, Causes of Death Registry, Nationa Prescription Registry, Cancer Registry, etc.	Linkable to the National Patient Register, Causes of Death Registry, National Prescription Registry, Cancer Registry, etc.	Not applicable

Table A3-1 Continued

	MSDS3D	MSBase	OFSEP	Danish MS Registry	Swedish MS Registry	Italian MS Registry
Frequency data refresh	Real time	TBD	Monthly	Ad-hoc	TBD	TBD
Comparator data available?	Yes	Yes	Yes	Yes	Yes	Yes
Comparisons to drug-specific groups feasible?	Yes	Yes	Yes	TBD	No	Yes
Patient-specific data						
Year of birth	Yes	Yes	Yes	Yes	Yes	Yes
Gender	Yes	Yes	Yes	Yes	Yes	Yes
Comorbidity	Yes	Not minimum dataset, but spontaneous reporting	Yes, history of cancer, family history of MS	Available through linkage to other registries	Available through linkage to other registries	TBD
MS-related information						
Date of onset of MS symptoms	Yes	Yes	Yes	Yes	Yes	Yes
Date of first MS diagnosis	Yes	Yes	Yes	Yes	Yes	TBD
MS type	Yes	Yes	Yes	Yes	Yes	Yes
EDSS score	Yes	Yes	Yes	Yes	Yes	Yes
MS relapse	Yes	Yes	Yes	Yes	Yes	Yes
JCV antibody status	Yes	Yes	Yes	Yes	Blood samples available	Yes
MS treatment						
DMT used	Yes	Yes	Yes	Yes	Yes	Yes
Date of first administration of each DMT	Yes	Yes	Yes	Yes	Yes	Yes

Table A3-1 Continued

	MSDS3D	MSBase	OFSEP	Danish MS Registry	Swedish MS Registry	Italian MS Registry
Date of last administration of each DMT	Yes	Yes	Yes	Yes	Yes	Yes
Type DMTs prior OCR	Yes	Yes	Yes	Yes	Yes	Yes
Duration of DMTs used prior to OCR	Yes	Yes	Yes	Yes	Yes	Yes
Adverse events						
Serious adverse events	Yes	Yes[a]	Yes[b]	Available through linkage to other quality registries[c]	Available through linkage to other quality registries[d]	Yes
Malignancy	Yes	Yes[a]	Yes[b]	Yes	Yes	Yes
Infections	Yes	Yes[a]	Yes[b]	Yes	Yes	Yes
Other SAEs	Yes	Yes[a]	Yes[b]	Yes	Yes	Yes
Reimbursement						
Expected launch date	January 2018	Varies by country	Q2 2019	January 2018	Q3 2018	Q3 2018

DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; JCV = John Cunningham virus; MS = multiple sclerosis; MSDS3D = Multiple Sclerosis Documentation System 3D; OCR = ocrelizumab; OFSEP = Observatoire Français de la Sclérose en Plaques; SAEs = serious adverse events.

[a] Full list of SAEs collected in OFSEP can be found at http://www.ofsep.org/images/CLINIQUE/FicheMinimaleOFSEP_EIG_2016-04-05.pdf.

[b] Serious adverse drug reactions, as defined by the Swedish Health Authorities are also collected in the Swedish National MS registry