TITLE:	**AN OBSERVATIONAL STUDY OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS TO DETERMINE THE INCIDENCE AND MORTALITY RATES OF BREAST CANCER AND ALL MALIGNANCIES (VERISMO STUDY)**
PROTOCOL NUMBER:	BA39731
VERSION NUMBER:	1.0
AUTHOR:	[redacted] F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
DATE FINAL:	See electronic date stamp below
E.U. PAS REGISTER NUMBER:	Study not registered
ACTIVE SUBSTANCE:	[redacted](ocrelizumab)
STUDIED MEDICINAL PRODUCT:	OCREVUS®
PRODUCT REFERENCE NUMBER:	RO4964913
PROCEDURE NUMBER:	IND 100,593; BLA 761053
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	To assess and characterize the incidence and mortality rates of breast cancer, all malignancies, and the long-term safety regarding serious adverse events

FINAL PROTOCOL APPROVAL

Approver's Name	**Title**	**Date and Time (UTC)**
[redacted]	Company Signatory	15-Apr-2019 10:05:47
	Deputy EU QPPV	12-Apr-2019 13:18:28

	(SAEs) among patients with multiple sclerosis (MS) newly exposed to ocrelizumab under routine clinical care. The primary objective for this study is as follows: • To determine the incidence rate of breast cancer and all malignancies following the first ocrelizumab treatment among patients with MS The secondary objectives for this study are as follows: • To determine the mortality rate of breast cancer and all malignancies following the first ocrelizumab treatment among patients with MS • To compare the observed incidence and mortality rates of breast cancer and all malignancies between ocrelizumab-exposed MS patients and patients newly treated with approved MS disease modifying therapies (DMTs) other than ocrelizumab as well as general populations • To determine the event rate of all SAEs in the ocrelizumab-treated patients with MS
COUNTRIES OF STUDY POPULATION:	United States and Germany
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH (RRG) 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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PROTOCOL ACCEPTANCE FORM

TITLE:	**AN OBSERVATIONAL STUDY OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS TO DETERMINE THE INCIDENCE AND MORTALITY RATES OF BREAST CANCER AND ALL MALIGNANCIES (VERISMO STUDY)**
PROTOCOL NUMBER:	BA39731
VERSION NUMBER:	1.0
E.U. PAS REGISTER NUMBER:	Study not registered
STUDIED MEDICINAL PRODUCT:	ocrelizumab (RO4964913; OCREVUS®)
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH (RRG) Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

I agree to conduct the study in accordance with the current protocol.

_____
Treating Physician's Name (print)

_____ _____
Treating Physician's Signature Date

Please return a copy of this form to [redacted]. Please retain the signed original for your study files.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMT	disease modifying therapy
eCRF	electronic case report form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
E.U.	European Union
FDA	(U.S.) Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	hazard ratio
ICF	Informed Consent Form
IEC	independent Ethics Committee
IRB	Institutional Review Board
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging (scan)
MS	multiple sclerosis
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NMSC	non-melanoma skin cancer
PAS	post-authorization study
PBRER	periodic benefit-risk evaluation report
PPMS	primary progressive multiple sclerosis
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
SEER	Surveillance, Epidemiology, and End Results (Program)
SMQ	Standardized MedDRA Queries
SPMS	secondary progressive multiple sclerosis
SoC	standard of care
STIAMP	suspected transmission of infectious agent by medicinal product
ULN	upper limit of normal
U.S.	United States

3. RESPONSIBLE PARTIES

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4. ABSTRACT

TITLE:	**AN OBSERVATIONAL STUDY OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS TO DETERMINE THE INCIDENCE AND MORTALITY RATES OF BREAST CANCER AND ALL MALIGNANCIES (VERISMO STUDY)**
PROTOCOL NUMBER:	BA39731
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 the U.S. Food and Drug Administration (FDA) approval in March 2017 for the treatment of relapsing forms of multiple sclerosis (RMS), or primary progressive multiple sclerosis (PPMS) (OCREVUS™ U.S. prescribing information 2017).

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 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 imbalance was driven by 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 the risk of malignancy, due to the low number of events and the limited follow-up, therefore, the risk of malignancies, including breast cancer, remains potential

In response to the U.S. FDA post-marketing requirement (3194-2), this prospective longitudinal observational study will further characterize the potential risk of breast cancer, all malignancies, and the long-term safety regarding SAEs over a minimal 5-year follow-up period among patients with MS newly exposed to ocrelizumab under routine clinical care.

Research Question and Objectives

To assess and characterize the incidence and mortality rates of breast cancer, all malignancies, and the long-term safety regarding SAEs among patients with MS newly exposed to ocrelizumab under routine clinical care.

Objectives

The primary objective for this study is as follows:

- To determine the incidence rate of breast cancer and all malignancies following the first ocrelizumab treatment among patients with MS

The secondary objectives for this study are as follows:

- To determine the mortality rate of breast cancer and all malignancies following the first ocrelizumab treatment among patients with MS
- To compare the observed incidence and mortality rates of breast cancer and all malignancies between ocrelizumab-exposed MS patients and patients newly treated with approved MS disease modifying therapies (DMTs) other than ocrelizumab as well as general populations

- To determine the event rate of all SAEs in the ocrelizumab-treated patients with MS

Study Design

This is a prospective, non-interventional, longitudinal, observational study of MS patients who have newly initiated treatment with ocrelizumab. Approximately 1,000 patients from the United States and 3,000 patients from Germany who have initiated treatment with ocrelizumab according to the local label, no more than 30 days prior to study entry, will be followed for a minimum of 5 years following their first exposure to ocrelizumab or until death, whichever comes first. A cohort of 2,360 MS patients from the United States and Germany who are newly treated with approved MS DMTs (per local label) other than ocrelizumab will be enrolled as an internal comparator.

Comparisons will be made with internal and external comparator MS populations who are treated with approved MS DMTs other than ocrelizumab, and with general population malignancy incidence and mortality rates.

Description of Study

Patients will be followed for a minimum of 5 years, or until death (whichever comes first) following the initiation of ocrelizumab or approved MS DMTs other than ocrelizumab (internal comparator only). All treatments will be provided per standard of care (SoC). There are no mandated study encounters, and data from any encounter with the neurologist during follow-up will be entered by clinicians (anticipated to occur approximately every 3-6 months). Follow-up is planned regardless of whether patients discontinue treatment with their current MS DMT (including ocrelizumab) or develop a malignancy or a non-melanoma skin cancer (NMSC).

Population

Patients must meet the following criteria for study entry:

- Signed informed consent
- Have a diagnosis of MS
- Aged 18 years or older
- Newly treated with ocrelizumab (within 30 days of study entry) according to the local label irrespective of the reason for starting ocrelizumab (ocrelizumab cohort)

OR

- Newly treated with an approved MS DMT other than ocrelizumab (within 30 days of study entry) according to the local label irrespective of the reason for starting a new MS DMT (internal comparator cohort)

Patients who meet the following criteria will be excluded from study entry:

- Patients who have any prior exposure to rituximab
- Active participation in other clinical trials for MS
- Patients who have received ocrelizumab more than 30 days prior to study entry date

Variables

The following variables will be collected during the study, as part of the local routine clinical practice, besides documentation of informed consent:

Baseline (Study entry):

- Documentation of informed consent
- Patient demographic information
- Medical history and comorbidities
- Height, and weight
- Laboratory parameters, if available (e.g., blood cell count, liver enzymes, renal status, immunoglobulins)
- Current MS DMT administration information (e.g., start date, dose, dosing frequency)

- Any malignancy risk factor information available (including previous malignancies and precancerous lesions)
- MS disease status and treatment history
  - Including number of relapses within the past 12 months, 2 years, and 3 years and/or magnetic resonance imaging (MRI) (scan) activity history in the last 12 months, EDSS score
- Any other medications from 3 months prior to enrollment
- Pregnancy status, if applicable

Follow-up after study entry (anticipated approximately every 3-6 months):

- Weight
- Laboratory parameters, if available (e.g., blood cell count, liver enzymes, renal status, immunoglobulins)
- Current MS DMT administration information (e.g., dates of administration [stop and re-start dates, if applicable], dose, dosing frequency, reason for discontinuation)
- Concomitant medications
- MS disease status since last encounter
- Cancer screening examinations
- Pregnancy status, if applicable
- SAEs/AEs of malignancies, including but not limited to MedDRA Standardized MedDRA Queries (SMQ) of malignant or unspecified tumors
- Malignancy information, if applicable
- SAEs (other than malignancies) and NMSCs
- AEs of special interest (AESIs), which are events falling under Hy's Law and events of suspected transmission of infectious agent by medicinal product (STIAMP)
- Death information, if applicable (e.g., date of death, primary and underlying causes of death)

At time of withdrawal from the study, if applicable:

- Weight
- Laboratory parameters, if available (e.g., blood cell count, liver enzymes, renal status, immunoglobulins)
- Current MS DMT administration information (e.g., dates of administration [stop and re-start dates], dose, dosing frequency, reason for discontinuation)
- Concomitant medications
- MS disease status since last encounter
- SAEs/AEs of malignancies, including but not limited to MedDRA SMQ of malignant or unspecified tumors
- Cancer screening examinations
- Malignancy information
- SAEs (other than malignancies) and NMSCs
- AESIs (i.e., events falling under Hy's Law and events of STIAMP only)
- Death information (e.g., date of death, primary and underlying causes of death)
- Pregnancy status
- Reason for study withdrawal

Data Sources

In this prospective study, data from each patient will be recorded in the electronic data capture (EDC) tools by the investigator (neurologist), during routine clinical practice encounters. The patient medical records detailing the malignancy diagnosis, such as tumor grade, method of diagnostic confirmation and histopathologic testing will be provided, upon identification of a malignancy event, by the patient's treating oncologist/pathologist.

Study Size

The study population comprises 6,360 patients with MS of which a cohort of 4,000 ocrelizumab-exposed patients (approximately 1,000 patients from the United States and 3,000 patients from Germany) will be enrolled in the study to satisfy the primary objective; and 2,360 patients from the United States (n=860) and Germany (n=1,500) who are exposed to an approved MS DMT other than ocrelizumab will form the internal comparator cohort for secondary objective analyses. Patients will be followed for a minimum of 5 years or until death, whichever comes first.

At least 70% of the ocrelizumab-exposed population will be females (i.e., 2,800 out of the 4,000 patients). The sample size and study duration should provide sufficient precision around the incidence rates in order to address the primary study objective. With this sample size and study duration, up to 103 cases of all malignancies (with an incidence rate of 604.2 per 100,000 patient-years [95% CI, 556.0-652.4]) and up to 27 cases of breast cancers (with an incidence rate of 224.7 per 100,000 patient-years [95% CI, 195.3-254.1]) are expected among ocrelizumab-exposed patients based on the background rate from Surveillance, Epidemiology, and End Results (SEER).

Data Analysis

The analysis population for all analyses will include patients who meet all eligibility criteria, and consent to the study. The incidence rate of breast cancer and all malignancies among patients exposed to ocrelizumab will be calculated as the total number of first (i.e., incident) events divided by the total patient-years at risk. Total patient-years at risk will be calculated from the first dose of ocrelizumab until the event, death, loss to follow-up, or the end of the study, whichever occurs first, irrespective of the ocrelizumab exposure duration. Exact Poisson 95% CIs will be calculated.

Incidence rates of malignancies will be presented according to various subgroups, including but not limited to: sex, age, malignancy type, MS type, prior exposure to MS DMT at study entry, and duration and dose of cumulative exposure to ocrelizumab. Similar analyses will be performed to determine the mortality rates of breast cancer and all malignancies.

For all SAEs and AESIs except malignancies, event rates will be based on a time-on-drug approach that uses person-time as exposed from first ocrelizumab dose in the study up to 6 months (26 weeks) after the last administration of ocrelizumab.

The incidence and mortality rates of breast cancer and all malignancies observed in this study will be compared with rates derived from the cohort of patients treated with approved MS DMTs other than ocrelizumab (internal comparator) and external databases, including the international, longitudinal, observational MSBase Registry and the SEER Program.

Similar data analysis procedures as for the internal comparator patients will be performed for comparisons to the ocrelizumab-exposed patients. Comparisons of ocrelizumab-exposed patients to the internal comparator group of patients treated with approved MS DMTs other than ocrelizumab will be accomplished using time to event regression approaches treating the first event as the outcome of interest and allowing for statistical adjustment for confounding factors. For outcomes that can occur repeatedly, Poisson regression models will be used.

Interim Analyses

Interim reports will align with study progress reports according to the regulatory reporting schedule approximately every 6 months.

Milestones

Start Date of Study

The study start date will be the date of the first data collection: the date on which information on the first study patient is recorded in the study database. The planned start of study is Q1 2019. However, the exposure of interest may start up to 30 days earlier, as per inclusion criterion.

End of Study

The end of the study will be the date on which the last data collected from the last patient is recorded in the study database. The study will be completed by November 2029 at the latest.

Length of Study

This study will last approximately 10 years.

5. PROTOCOL AMENDMENTS AND UPDATES

None

6. MILESTONES

Regular study updates will be provided through the periodic benefit-risk evaluation reports [PBRERs] as agreed with health authorities).

Study milestones are given in the following table.

Table 1 Study Milestones

Milestone	Planned Date
Registration of protocol in the E.U. PAS register	Study not registered
Start of data collection	Q1 2019
End of data collection	Nov 2029 (at the latest)
Final report of study results	Nov 2030 (at the latest)
Study progress reports	According to PBRER schedule
Interim reports	Interim reports will align with study progress reports according to the regulatory reporting schedule approximately every 6 months

E.U. = European Union; PBRER = periodic benefit-risk evaluation report;
PAS = post-authorization study

7. RATIONALE AND BACKGROUND

7.1 STUDY RATIONALE

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the 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 (Tullman 2013; MSIF 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% to 15% of all MS cases (Ciotti and Cross 2018; Miller and Leary 2007; Piccinni et al 2018). 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 U.S. Food and Drug Administration (FDA) on 28 March 2017, for the treatment of adult patients with relapsing forms of MS (RMS) or PPMS (OCREVUS™ U.S. prescribing information 2017).

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) (scan) outcomes related to disease progression and reflective of neural tissue loss.

This longitudinal observational study is designed to further assess the long-term safety profile of ocrelizumab in the real-world setting. In response to the U.S. FDA post-marketing requirement (3194-2), this study will further characterize the potential risk of breast cancer, all malignancies, and the long-term safety regarding serious adverse events (SAEs) over at least a 5-year follow-up period among patients with MS newly exposed to ocrelizumab under routine clinical care.

7.2 STUDY BACKGROUND

Ocrelizumab has demonstrated a favorable safety profile in RMS and PPMS patients (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events (AEs) was similar in ocrelizumab patients compared with interferon β-1a (both 83.3%) or placebo 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 RMS trials compared to interferon β-1a-treated patients (1.3% vs. 2.9%), and similar in PPMS trials (6.2% [ocrelizumab] and 5.9% [placebo]).

Eight deaths occurred in ocrelizumab trials (RMS trials: 2 interferon β-1a patients [suicide and mechanical ileus] and 1 ocrelizumab patient [suicide]; PPMS trial: 1 placebo patient [road traffic accident] and 4 ocrelizumab patients [pulmonary embolism, pneumonia, pancreatic carcinoma, and pneumonia aspiration]) (Hauser et al. 2017; Montalban et al. 2017). Although the proportion of patients experiencing 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]), further safety assessment is needed to characterize SAEs.

In controlled studies, the pooled overall incidence of a first malignancy 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). No patients died due to breast cancer, and 1 PPMS patient who was treated with ocrelizumab died due to pancreatic carcinoma (Hauser et al. 2017; Montalban et al. 2017).

In the Phase II trial, two malignancies were reported in RRMS patients treated with ocrelizumab; none in patients receiving placebo (Kappos et al. 2011; Genentech, Inc. 2017). In RMS trials (OPERA I and II), malignancies 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), malignancies 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 imbalance was driven by 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 of malignancy due to the low number of events and the limited follow-up period. Therefore, the risk of malignancies, including breast cancer, remains potential.

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

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

To determine and characterize the incidence and mortality rates of breast cancer, all malignancies, and the long-term safety regarding SAEs among patients with MS who are newly exposed to ocrelizumab under routine clinical care.

8.2 OBJECTIVES

The primary objective for this study is as follows:

- To determine the incidence rate of breast cancer and all malignancies following the first ocrelizumab treatment among patients with MS

The secondary objectives for this study are as follows:

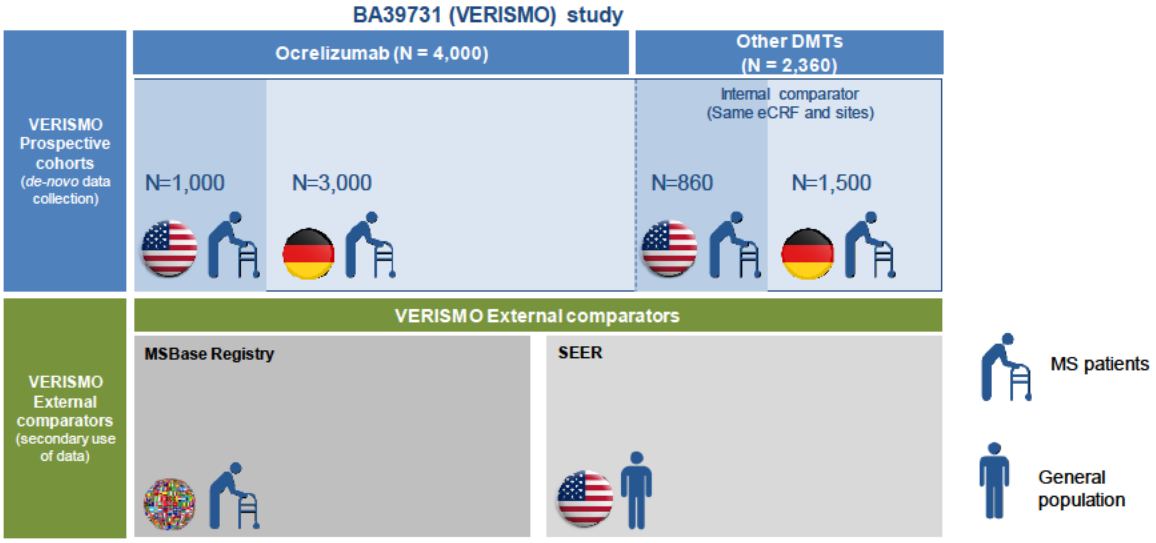
- To determine the mortality rate of breast cancer and all malignancies following the first ocrelizumab treatment among patients with MS
- To compare the observed incidence and mortality rates of breast cancer and all malignancies between ocrelizumab-exposed MS patients and patients newly treated with approved MS disease modifying therapies (DMTs) other than ocrelizumab as well as general populations
- To determine the event rate of all SAEs in the ocrelizumab-treated patients with MS

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a prospective, non-interventional, longitudinal, observational study of MS patients who have newly initiated treatment with ocrelizumab. Approximately 1,000 patients from the United States and 3,000 patients from Germany who have initiated treatment with ocrelizumab no more than 30 days prior to study entry, will be followed for a minimum of 5 years following their first exposure to ocrelizumab or until death, whichever comes first. An internal comparator of 2,360 patients newly treated with approved MS DMTs (per local label) other than ocrelizumab (e.g., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide) will also be enrolled from the United States and Germany (Figure 1). Data from Germany will be collected through the Roche Study ML39632 and pooled with data collected in the United States to build the study database for BA39731. The research methods, including data elements and inclusion/exclusion criteria outlined in this protocol also apply to ML39632, unless otherwise stated in this protocol.

Figure 1 BA39731 (VERISMO) Study Population Cohorts and Comparator Populations



DMT = disease modifying therapy; eCRF = electronic case report form; MS = multiple sclerosis; SEER = Surveillance, Epidemiology, and End Results (Program)

Follow-up is planned regardless of whether patients discontinue their current MS DMT (including ocrelizumab) or have a malignancy diagnosis. Data on incidence and mortality of breast cancers, all malignancies and other SAEs will be recorded to meet the primary and secondary study objectives. Comparisons will be made with internal and external comparator populations who are treated with approved MS DMTs other than ocrelizumab, and with general population malignancy incidence and mortality rates.

Dosing and treatment duration of ocrelizumab or other approved MS DMTs as a part of this non-interventional study are at the discretion of the physician in accordance with labeling and local clinical practice. This study will be conducted at least 90 centers in the United States and 250 centers in Germany. In addition to increasing the likelihood of meeting the target recruitment rates, these two populations have shown comparable incidence and mortality rates for the malignancies and breast cancers (Ferlay et al. 2013; Appendix 1). Additional countries and centers may be added or substituted if the ones stated above are underperforming.

9.1.1 Recruitment and Retention Efforts

Study enrollment will be monitored closely for U.S. and German sites and will include a mitigation plan if recruitment goals are lagging. Steps to help meet enrollment targets include but are not limited to: adding additional study sites, increasing the scope of patient recruitment materials, and performing "booster monitoring visits" with non-enrolling or under-enrolling sites. Enrollment reports will be generated on a regular basis and shared with sites to inform target goals and implement any new strategies based on results.

Retention efforts to minimize loss to follow-up and missing data will include, but are not limited to:

- Judicious design of electronic case report forms (eCRFs) to minimize length and enhance ease of use
- Comprehensive site staff training emphasizing the importance of data collection through the end of follow-up, even if the patient discontinues ocrelizumab or another MS DMT
- Ensuring staff provide a welcoming environment (e.g., friendly and trustworthy) to study participants
- Engaging healthcare providers (HCPs) with a good track record for both enrollment and retention of patients
- Creation of an investigator portal with study resources, recruitment tracker information, and patient recruitment resources
- Promote HCP engagement through regular registry updates including best practice guidance and scientific exchanges
- Educating patients about the importance of continued participation
- Updating contact information at each patient encounter
    - Collecting contact information for the patient's primary care physician, next of kin, or secondary contacts (if consent is given and information is available), where local regulations allow, to be contacted if patient is non-responsive
- Close monitoring of data collection throughout the study
- Collect informed consent for continuous patient follow-up, even after leaving the initially associated study site

9.2 SETTING

9.2.1 Study Population

Patients with MS from the post-marketing

setting who have initiated treatment with ocrelizumab or an approved MS DMT other than ocrelizumab no more than 30 days prior to study entry will participate in this study.

Patients must meet the following criteria for study entry:

- Signed informed consent
- Have a diagnosis of MS
- Aged 18 years or older
- Newly treated with ocrelizumab (within 30 days of study entry) according to the local label irrespective of the reason for starting ocrelizumab (ocrelizumab cohort)

OR

- Newly treated with an approved MS DMT other than ocrelizumab (within 30 days of study entry) according to the local label irrespective of the reason for starting a new MS DMT (internal comparator cohort)

Patients who meet the following criteria will be excluded from study entry:

- Patients who have any prior exposure to rituximab
- Active participation in other clinical trials for MS
- Patients who have received ocrelizumab more than 30 days prior to study entry date

Enrollment of patients will be conducted to ensure at least 70% of the population is female in order to adequately power breast cancer event rates (see Section 9.6); and to ensure that the internal comparator meet the same eligibility criteria as the ocrelizumab-exposed cohort. Sites will be required to maintain a patient screening log of eligible patients reviewed for participation at their treatment centers. This log will document how patients were included or excluded from the study in order to assess the representativeness of the study population.

9.2.2 Prior and Concomitant Medication and Treatment

Prior and concomitant medications and treatments at the beginning of the study or introduced during the study will be collected as following:

- All previous treatments and therapies for MS, including anti-neoplastic agents (if any) with their duration (start/stop dates) and dose, if available
- All other prior and concomitant immunomodulatory and immunosuppressive treatments including their duration (start/stop dates) and dose, if available
- Other previous and ongoing medications: from 3 months prior to study entry only (except premedications given per local label prior to administration of ocrelizumab or other approved MS DMTs [e.g., methylprednisolone, antihistamines, non-steroidal anti-inflammatory drugs])

9.3 STUDY DATA COLLECTION

Scheduled assessments for the study are presented in Table 2 below. All data elements will be collected prospectively from information routinely recorded in the medical records, extracted by the investigator (neurologist) for the purposes of the study. Per the non-interventional study setting, no mandatory encounters are required. The data collection schedule will map routine care and occur at any patient encounter with the neurologist (anticipated to occur approximately every 3-6 months), following inclusion and baseline encounter until the study completion or study withdrawal.

Table 2 Data Collection Overview (as per Standard of Care)

Data Collection [a]	Baseline (Study Entry) [b]	Data Collection (Approximately Every ~3-6 Months)	Data Collected at Study Completion/ Study Withdrawal Encounter
Informed consent [c]	X		
Inclusion/exclusion criteria	X		
Patient demographics	X		
Medical history and comorbidities	X		
Malignancy risk factor information (including previous malignancies and precancerous lesions) [d]	X		
Height and weight	X	X [e]	X [e]
Prior and concomitant medications [f]	X	X	X
Current MS DMT administration information [g]	X	X	X
MS disease history [h]	X		
MS treatment history [i]	X		
MS disease status [j]	X	X	X
Cancer screening examinations [k]		X	X
Laboratory test results	X	X	X
Pregnancy status [l]	X	X	X [m]
SAEs/AEs of breast cancer, all malignancies [n]		X	X [m]
SAEs (other than malignancies), NMSCs, and AESIs [o]		X	X [m]
Death information		X [m]	X [m]
Reason for withdrawal			X [m, p]

AE = adverse event; AESI = adverse event of special interest; DMT = disease modifying therapy; EDC = electronic data capture; EDSS = Expanded Disability Status Scale; MedDRA = Medical Dictionary for Regulatory Activities; MRI = magnetic resonance imaging (scan); MS = multiple sclerosis; NMSC = non-melanoma skin cancer; SAE = serious adverse event; SMQ = Standardized MedDRA Queries; STIAMP = suspected transmission of infectious agent by medicinal product

[a] Available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice

[b] Up to 30 days after the first ocrelizumab infusion or start of another approved MS DMT

[c] Written informed consent must be obtained before any data collection (per local regulations or ethics committee requirements)

[d] Including tobacco use history, alcohol use history, family disease history (e.g., genetic testing such as BRCA1 and 2), personal history of malignancy, or other risk factors including reproductive history (women only)

[e] Only weight will be collected during follow-up time points.

[f] Up to 3 months prior to study entry

[g] Dates of administration (start, stop, and restart dates), dose, dosing frequency, reason for discontinuation (if applicable)

[h] Including MS date of diagnosis, type of MS, duration of MS, MS disease symptom history, number of relapses within the past 12 months, 2 years, and 3 years, EDSS (or proxy) change over the last 12 months (if available) and MRI results (if available). The reporter of malignancy information (e.g., neurologist, oncologist/pathologist) will be included, along with their relevant contact information, if available. Collection of this information will be outside of the EDC at the site-level, only.

[i] Prior use and duration of therapies for MS and prior use and duration of immunomodulatory, immunosuppressive, and anti-neoplastic agents (if any)

[j] Including MS relapse during treatment period, MS type changes, date of last administration of ocrelizumab (if applicable), MS DMT changes and rationale, most recent EDSS score since last encounter (if available), MRI activity (history in the last 12 months at baseline) and most recent MRI result since last encounter during follow-up (if available)

[k] Including gynecological consultation, breast check, dermatological check, or other malignancy/cancer screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)

[l] Patient-reported, female patients

[m] If applicable

[n] SAEs/AEs of malignancies, including but not limited to MedDRA SMQ of malignant or unspecified tumors

[o] AESIs are events falling under Hy's Law and events of STIAMP only. Study protocol ML39632 will collect all AEs, but for the purpose of this study only malignancies, SAEs, NMSCs, and AESIs will be analyzed

[p] Including the number of attempts to contact patient, method of contact, and reasons for early termination (e.g., death, withdrawal of consent, loss to follow-up) (if applicable)

9.4 VARIABLES

9.4.1 Exposure Variables

This is an observational study of real-world new users of ocrelizumab for MS. Patients are considered as exposed to ocrelizumab for the malignancy incidence and mortality rate estimates if they received at least one dose of ocrelizumab ("ever-exposed"). MS patients in the comparator groups who are newly treated with an approved MS DMT other than ocrelizumab (with no prior ocrelizumab exposure) will be compared with ocrelizumab-exposed MS patients. The "ever-exposed" definition also applies to the comparison groups. Patients with MS who switch or discontinue treatment regimens during the course of follow-up will continue to be followed with the date of switching recorded. For all malignancy endpoints, the total patient-years at risk will be calculated from the first dose of ocrelizumab (or first new MS DMT start [MS comparator group]) until the event, death, loss to follow-up, or the end of the study, whichever occurs first, irrespective of the drug exposure duration.

Periods of exposure will be described in the statistical analysis plan (SAP). The cumulative dose of ocrelizumab exposure will be calculated as the sum of all doses of ocrelizumab received from the first dose until death, loss to follow-up, or the end of the study, whichever occurs first. Comparison groups of patients newly exposed to another approved MS DMT will be defined similarly.

For the estimation of incidence and mortality rates of all SAEs and adverse events of special interest (AESIs) (except for malignancies), exposure will be based on a time-on-drug approach that uses person-time as exposed from first ocrelizumab dose in the study up to 6 months (26 weeks) after the last administration of ocrelizumab. The risk window of exposure will be varied in sensitivity analyses to assess the robustness of findings, including but not limited to 72 weeks after last administration of ocrelizumab and up until the date of switch to another MS DMT. Should ocrelizumab be stopped and restarted in the same patient, time exposed will be summed together with the same pre-defined time windows following each start and stop as described above.

Any further exposure classifications, stratifications, or restrictions will be detailed in the SAP.

9.4.2 Outcome Variables

9.4.2.1 Breast Cancer

A breast cancer diagnosis will be defined as the first occurrence of breast cancer after exposure. A cancer diagnosis will prompt two reporting channels. Available information on cancer (e.g., diagnosis date, tumor type and location, grade, stage, cancer treatment, hormone receptor status) will be collected for this study and reported by the neurologist. The neurologist, or the contract research organization (CRO) on his/her behalf, will request the patient medical records detailing the malignancy diagnosis, such as tumor grade, method of diagnostic confirmation and histopathologic testing, upon identification of a malignancy event, from the patient's treating oncologist.

Two qualified independent oncologists and/or pathologists will be used throughout the study for formal adjudication of malignancy diagnoses cases. In the event there is discordance between the two oncologists/pathologists, a third oncologist/pathologist will independently review the reports for final case determination. Patients will be made aware in the informed consent form (ICF) that if they develop a malignancy, diagnostic information will be requested from the treating oncologist and reviewed for the formal adjudication of their malignancy diagnosis. Adjudicator roles and responsibilities will be outlined in a separate Charter document.

For mortality rate calculations, all deaths where breast cancer is noted as a primary or underlying cause will be included in the analyses. In comparative analyses, breast cancer-related outcomes will be defined similarly for patients exposed to approved MS DMTs other than ocrelizumab.

9.4.2.2 All Malignancies

Any malignancy will be defined as the first occurrence of a cancer diagnosis during study follow-up. A malignancy diagnosis will prompt two reporting channels. Available information on malignancy (e.g., diagnosis date, tumor type and location, grade, stage, malignancy treatment, hormone receptor status) will be collected for this study and reported by the neurologist.

The neurologist, or the CRO on his/her behalf, will request the patient medical records detailing the malignancy diagnosis, such as tumor grade, method of diagnostic confirmation and histopathologic testing, upon identification of a malignancy event, from the patient's treating oncologist/pathologist.

Two qualified independent oncologists and/or pathologists will be used throughout the study for formal adjudication of malignancy diagnoses cases. In the event there is discordance between the two oncologists/pathologists, a third oncologist/pathologist will independently review the reports for final case determination. Adjudicator roles and responsibilities will be outlined in an external Charter document.

For mortality rate calculations, all deaths where malignancy is noted as a primary or underlying cause will be included in the analyses. In comparative analyses, outcomes related to all malignancies will be defined similarly (inclusive of the adjudication process) for patients exposed to approved MS DMTs other than ocrelizumab.

9.4.2.3 Serious Adverse Events and Non-Melanoma Skin Cancers

All SAEs, other than a malignancy (above in Section 9.4.2.2), and non-melanoma skin cancers (NMSCs), will be collected throughout follow-up. A patient can have more than one SAE and/or NMSC during follow-up. Comorbidities newly diagnosed during follow-up will be recorded as SAEs according to the definition in Sections 11.1.1.1 and 11.1.1.2.

9.4.2.4 Adverse Events of Special Interest

AESIs (i.e., events falling under Hy's Law and events of suspected transmission of infectious agent by medicinal product [STIAMP] only) will be collected throughout follow-up and at the time of withdrawal from the study, if applicable.

9.4.3 Information Collected at Baseline (Study Entry), Follow-Up, and Withdrawal from the Study

See Table 2 for the data collection overview (as per standard of care [SoC]) during the treatment period. A detailed listing of data elements is provided in Appendix 2.

9.4.3.1 Baseline (Study Entry)

- Documentation of informed consent
- Patient demographic information
- Medical history and comorbidities
- Height and weight

- Laboratory parameters, if available (e.g., blood cell count, liver enzymes, renal status, immunoglobulins, and CD4+, CD8+, CD19+ cell count)
- Current MS DMT administration information (e.g., start date, dose, dosing frequency)
- Malignancy risk factor information
    - Tobacco use history
    - Alcohol use history
    - Family disease history, including genetic testing, if available
    - Personal history of malignancy or precancerous lesions
    - Other risk factors (e.g., obesity, metabolic syndrome, radiation exposure, hormone replacement therapy exposure, reproductive history, immunosuppression, infection known to be associated with an increased risk of malignancy, etc.)
- MS disease status and treatment history
    - Date of MS symptoms onset and date of MS diagnosis
    - Type of MS
    - Number of relapses within the past 12 months, 2 years, and 3 years
    - MRI activity history in the last 12 months
    - Change in EDSS over the last 12 months, if available
    - All previous treatments and therapies for MS, including their duration (start/stop dates) and dose (if available)
    - All other prior and concomitant immunomodulatory, immunosuppressive treatments, and anti-neoplastic agents including their duration (start/stop dates) and dose (if available)
    - MS status at initiation with current MS DMT, including most recent Expanded Disability Status Scale (EDSS) score, if available
- Any other medications from 3 months prior to study entry
- Pregnancy status, if applicable

9.4.3.2 Follow-Up after Study Entry (Anticipated Approximately Every 3-6 Months)

- Weight
- Laboratory parameters, if available (e.g., blood cell count, liver enzymes, renal status, immunoglobulins, and CD4+, CD8+, CD19+ cell count)
- Current MS DMT administration information (e.g., dates of administration [stop and re-start dates, if applicable], dose, dosing frequency, reason for discontinuation)
- Concomitant medications
- MS disease status since last encounter
    - MS relapse during the treatment period (start/end dates)

    - Most recent EDSS score, if available
    - Most recent MRI results, if available
    - MS DMT changes and rationale
- Cancer screening examinations, if applicable
    - Gynecological consultation
    - Breast check
    - Dermatological check
    - Malignancy/cancer screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)
- Pregnancy status, if applicable
- SAEs/AEs of malignancies, including but not limited to MedDRA Standardized MedDRA Queries (SMQ) of malignant or unspecified tumors
- Malignancy information, if applicable:
    - Cancer type
    - Diagnosis date
    - Location of primary tumor
    - Tumor grade
    - Stage at diagnosis
    - Hormone receptor status
    - Action taken with ocrelizumab therapy or other DMTs at the point of diagnosis
    - Cancer status updates including remission/relapse and updated treatment status
- SAEs (other than malignancies) and NMSCs
- AESIs
    - Events falling under Hy's Law and events of STIAMP only
- Death information, if applicable
    - Primary and underlying causes of death, including autopsy results
    - Date of death

9.4.3.3 At Time of Withdrawal from the Study, if Applicable

- Weight
- Laboratory parameters, if available (e.g., blood cell count, liver enzymes, renal status, immunoglobulins, and CD4+, CD8+, CD19+ cell count))
- Current MS DMT administration information (e.g., dates of administration [stop and re-start dates], dose, dosing frequency, reason for discontinuation)

- Concomitant medications
- MS disease status since last encounter
    - Most recent EDSS score
    - Most recent MRI results
    - MS DMT changes and rationale
- SAEs/AEs of malignancies, including but not limited to MedDRA SMQ of malignant or unspecified tumors
- Cancer screening examinations
    - Gynecological consultation
    - Breast check
    - Dermatological check
    - Malignancy/cancer screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)
- Malignancy information:
    - Cancer type
    - Diagnosis date
    - Location of primary tumor
    - Tumor grade
    - Stage at diagnosis
    - Hormone receptor status
    - Action taken with ocrelizumab therapy or other DMTs at the point of diagnosis
    - Cancer status update including remission/relapse and updated treatment status
- SAEs (other than malignancies) and NMSCs
- AESIs
    - Events falling under Hy's Law and events of STIAMP only
- Death information
    - Primary and underlying causes of death, including autopsy results
    - Date of death
- Pregnancy status
- Reason for study withdrawal

9.5 DATA SOURCES

9.5.1 Collection of Data on the Electronic Case Report Form

Patients' data will be recorded on eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient medical files should be entered on the eCRF as soon as they become available after the encounter.

9.5.2 Data Collected During the Study

During therapy with ocrelizumab or with an approved MS DMT other than ocrelizumab, laboratory assessments are expected to be routinely performed in accordance with current guidelines and local SoC. In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessments after treatment. Thus, there are no mandatory encounters in the context of this non-interventional study. Patients with a malignancy diagnosis will continue to be followed until the end of the study or death, whichever occurs first.

When performed during the study, available results from the range of assessments described above will be documented on the eCRF as soon as possible after the encounter occurs. Most data will be documented approximately every 3 to 6 months. The proposed assessments and suggested timings for assessments in the protocol/observational plan are not mandatory. It is up to the treating physician to perform and document the assessments as performed in the real clinical setting.

Patients will remain in the study for a minimum of 5 years, or until death, lost to follow-up or until they withdraw their consent from the study, whichever comes first, irrespective of whether they continue or discontinue their MS DMT. If a patient withdraws from the study, study completion encounter assessments should be performed.

See Table 2 for the data collection overview (as per SoC) during the treatment period. A detailed listing of data elements is provided in Appendix 2.

9.5.3 Data Collected at Study Completion

For patients who complete the study, the study completion encounter should be documented. See Table 2 for the data collection overview including the data collected at study completion.

9.5.4 Comparator Populations

The findings from this study will be compared with comparison groups, including MS-specific and general populations. Comparison groups were chosen to reflect the source populations from which the study population will arise, with prioritization of U.S. and German data sources. More specifically, the Surveillance, Epidemiology, and End Results (SEER) Program was selected because it provides accurate information on malignancy incidence and mortality rates and calculates standardized rates. MSBase and the internal comparator group of patients newly exposed to an approved MS DMT

other than ocrelizumab were selected for comparator data, because both contain MS-specific populations, have patient-level information, and collect detailed clinical and risk factor information that allow for calculations of adjusted incidence and mortality rates. Patients from the internal comparator population will be enrolled from the same clinical sites as the U.S. and German patients and data collection (procedures and variables) will be identical. If additional, relevant non-MS or MS publications or data sources become available during the study, they may also be used as comparator groups. See Appendix 3 for a summary of covariates available from comparator data sources.

Comparator populations include the following:

Internal Comparator: Patients newly exposed to approved MS DMTs other than ocrelizumab

Patients with MS initiating a new approved MS DMT per local label (other than ocrelizumab) irrespective of the reason for starting a new therapy will serve as an internal comparator population. Data from German internal comparator patients will be collected from the prospective, longitudinal, observational study ML39632 and pooled with data collected from the U.S. internal comparator collected as part of this protocol.

Malignancy and mortality outcomes will be collected and reported using the same approach as described in Section 9.4.2. Patients who have received ocrelizumab more than 30 days prior to study entry, or patients who have current or past exposure to rituximab, will be excluded.

External Comparator: Surveillance, Epidemiology, and End Results Program (United States)

The SEER Program of the National Cancer Institute (NCI) is an authoritative source of information on malignancy incidence and survival in the United States (https://seer.cancer.gov/about/overview.html). SEER collects and publishes malignancy incidence and survival data from population-based malignancy registries covering approximately 28% of the U.S. population. The SEER Program registries routinely collect data on patient demographics, primary tumor sites, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. The mortality data reported by SEER are provided by the National Center for Health Statistics (NCHS). All death certificates (>99%) filed in the 50 states and the District of Columbia are processed by the NCHS, where mortality medical coders and nosologists are responsible for coding the underlying cause of death from death certificates filed in the states (SEER 2017).

External Comparator: MSBase (International)

MSBase (www.msbase.org) is a longitudinal, observational registry that collects treatment and outcome information from routine clinical practice for MS patients.

MSBase was started in 2004, 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 MS patients (MSBase 2017; Butzkueven et al. 2006).

MSBase collects data from 33 countries worldwide, summing up to over 52,000 patient records so far (MSBase 2017). Patient data are collected at regular (at least annual) assessments of each patient. Data is encoded using MedDRA. Although no source data verification (SDV) is conducted, automated validation steps are performed. Additionally, a data quality score covariate is provided in the database to ensure data quality, stemming from four metrics: completeness, syntactic accuracy, consistency and believability (Kalincik et al. 2017).

In 2012, a safety module was implemented in the MSBase interface in Australia, in order to collect safety outcomes (including breast cancer and all malignances) related to MS treatments (Haartsen et al. 2015). In 2017, MSBase introduced a global, prospective, longitudinal, observational safety sub-study that collects information on SAEs, including breast cancer and all malignancies. For malignancies, the diagnosis date, primary tumor type and grade, location of primary tumor, stage, treatment, and histopathologic or genetic testing results are all collected. Due to the extensive patient-level clinical information collected in MSBase and in this observational cohort, incidence and mortality rates will be compared using appropriate adjustment methods (see Section 9.8). Covariates such as demographics, smoking, MS disease and treatment history, and significant medical conditions are captured in this database (see Appendix 3).

9.6 STUDY SIZE

Primary objective: incidence rate of breast cancer and all malignancies following ocrelizumab treatment

A sample size of 6,360 patients with MS of which a cohort of 4,000 ocrelizumab-exposed patients (approximately 1,000 patients from the United States and 3,000 patients from Germany exposed to ocrelizumab) will participate in the study to satisfy the primary objective; and 2,360 patients from the United States (n=860) and Germany (n=1,500) who are exposed to an approved MS DMT other than ocrelizumab will form the internal comparator cohort for secondary objective analyses. Patients will be followed for a minimum of 5 years or until death, whichever comes first. The sample will be monitored during recruitment to ensure that at least 70% of the study sample is female (see Section 9.2.1), which will ensure the study is sufficiently powered to detect expected breast cancer event rates. Follow-up is planned regardless of whether patients discontinue treatment with ocrelizumab or another MS DMTs during this period. The sample size was chosen to ensure a reasonable likelihood of observing meaningful, feasible numbers of malignancy and breast cancer incident cases, and to calculate informative CIs.

Table 3 summarizes the hypothetical numbers of female breast cancer and all malignancy events, with corresponding incidence rates and 95% CIs, assuming a target study size of 4,000 MS patients exposed to ocrelizumab and a dropout rate of 15%. Breast cancer calculations were restricted to women, assuming that their percentage share of the total study population is at least 70% (i.e., 2,800 out of 4,000 ocrelizumab-exposed patients) (Ziemssen et al. 2018). The sample size and study duration should provide sufficient precision around the incidence rates in order to address the primary study objective. With this sample size and study duration, up to 103 cases of all malignancies (with an incidence rate of 604.2 per 100,000 patient-years [95% CI, 556.0-652.4]) and up to 27 cases of breast cancers (with an incidence rate of 224.7 per 100,000 patient-years [95% CI, 195.3-254.1]) are expected among ocrelizumab-exposed patients given the background rate from SEER.

Table 3 Event Rates for Female Breast Cancer and All Malignancies and Confidence Intervals under Different Scenarios

Observed breast cancer events, females only (n) [a] [b]	Incidence rate (per 100,000 patient-years)	95% CI of the incidence rate
10	84	(40, 155)
20	168	(103, 260)
30	252	(170, 360)
40	336	(240, 458)
50	420	(312, 554)
All malignancy events except NMSC, males and females (n) [b] [c]	Incidence rate (per 100,000 patient-years)	95% CI of the incidence rate
60	353	(269, 454)
80	471	(373, 586)
100	588	(479, 715)
120	706	(585, 844)
140	824	(693, 972)

CI = confidence interval; NMSC = non-melanoma skin cancer; SEER = Surveillance, Epidemiology, and End Results (Program)

[a] Number of observed cases (in 2800 female patients with 11900 patient-years of follow-up assuming 15% attrition).

[b] SEER 2016. Rates are age-standardized to the 2000 U.S. Standard Population (Census P25-1130) aged 20 years or older. NMSCs are not recorded in the SEER Program.

[c] Number of observed malignancies (in 4,000 patients with 17,000 patient-years of follow-up assuming 15% attrition).

Secondary objective: mortality rate of breast cancer and all malignancies following ocrelizumab treatment

Similarly, Table 4 shows mortality rates and 95% CIs for varying counts of breast cancer and all malignancy deaths. The CIs were calculated based on the assumption of Poisson

distributed incidence rates, which provide sufficient precision around the incidence rates for this study.

Table 4 Mortality Rates for Female Breast Cancer and All Malignancies and Confidence Intervals under Different Scenarios

Observed breast cancer deaths, females only (n) [a b]	Mortality rate (per 100,000 patient-years)	95% CI [c]
1	8.4	(0.2, 46.8)
2	16.8	(2.0, 60.7)
3	25.2	(5.2, 73.7)
10	84.0	(40.3, 154.5)
15	126.1	(70.5, 207.9)
All observed malignancy deaths, males and females (n) [b c]	Mortality rate (per 100,000 patient-years)	95% CI
20	118	(72, 182)
40	235	(168, 320)
60	353	(269, 454)
80	471	(373, 586)
100	588	(479, 715)

CI = confidence interval; NMSC = non-melanoma skin cancer; SEER = Surveillance, Epidemiology, and End Results (Program)

[a] Number of observed cases (in 2,800 female patients with 11,900 patient-years of follow-up assuming 15% attrition).

[b] Howlader et al. 2017. Rates are age-standardized to the 2000 U.S. Standard Population (Census P25-1130) aged 20 years or older. NMSCs are not recorded in the SEER Program.

[c] Number of observed malignancies (in 4,000 patients with 17,000 patient-years of follow-up assuming 15% attrition).

Secondary objective: comparative analyses of malignancy incidence and mortality rates

Comparison with external data source

Data from SEER (see Section 9.5.4) served as a reference for the power calculations. With a dropout rate of 15% and a target power of 80%, for all malignancy incidence and mortality rates, minimum rate ratios of 1.30 and 1.61 are detectable with statistical significance of 2.5% in a population size of 4,000 ocrelizumab-exposed patients, respectively (Table 5). In a female population of 2,800 ocrelizumab-exposed patients, the minimum rate ratio for breast cancer incidence which can be detected with statistical significance of 2.5% is 1.62 (Table 5). Due to the low number of expected breast cancer deaths throughout the study period, the study is not powered to detect a meaningful difference in breast cancer mortality rate compared to the background mortality rates of breast cancer (Howlader et al. 2017). The breast cancer mortality rate will be summarized descriptively, and 95% CIs will be calculated.

Table 5 Detectable Rate Ratios for All Malignancies, All Malignancy Deaths, and Female Breast Cancer

	Crude background incidence/mortality rate per 100,000 patient-years	Background incidence/mortality rate per 100,000 patient-years standardized to the U.S. general population [a]	Background incidence/mortality rate per 100,000 patient-years standardized to the MS patient population [b]	Rate ratio detectable with a power of 80% based on background rate standardized to MS patient population [c]
All malignancies [d]	689.5	698.5	604.2	1.30
All malignancy deaths [e]	NA	232.0	161.1	1.61
Breast cancer (female) [d]	228.4	219.5	224.7	1.62

MS = multiple sclerosis; NMSC = non-melanoma skin cancer; SEER = Surveillance, Epidemiology, and End Results (Program)

[a] Rates are age-standardized to the 2000 U.S. Standard Population (Census P25-1130) aged 20 years or older. NMSCs are not recorded in the SEER Program.

[b] Rates are age-standardized to the MS patient population in MSBase (MSBase Data and Findings: Patient Demographics 2017).

[c] Assuming a sample size of 4,000 ocrelizumab-exposed patients, a female percentage share of 70%, a dropout rate of 15%, a follow-up time of 5 years, and a one-sided type-I error of 0.025.

[d] SEER 2016.

[e] Howlader et al. 2017

Comparison with internal comparator

Table 6 displays the statistical power for the internal comparison with MS patients treated with MS DMTs other than ocrelizumab (2,360 patients, assuming 70% of whom will be females [Ziemssen et al. 2018]). From a detectable effect size calculation using a log-rank test to compare the time to first malignancy and applying the same assumptions as in Table 5, the minimum detectable hazard ratio (HR) with 80% power will be 1.46 for the rate of all malignancies and 2.00 for the rate of female breast cancer.

Table 6 Power Calculation for the Internal Comparison between 4,000 Ocrelizumab-Exposed Patients and 2,360 MS Patients Treated with Approved MS DMTs Other than Ocrelizumab

	HR detectable with 80% power [a]
All malignancies	1.46
All malignancy deaths	1.99
Breast cancer (female)	2.00

DMT = disease modifying therapy; HR = hazard ratio; MS = multiple sclerosis; SEER = Surveillance, Epidemiology, and End Results (Program)

[a] Null hypothesis assumes constant hazard rate and the same incidence rate as observed in SEER age-standardized to the MS patient population in MSBase, a female percentage share of 70%, an enrollment time of 2 years, a follow-up time of 5 years, a dropout rate of 15% over 5 years, and a one-sided type-I error of 0.025.

9.7 DATA MANAGEMENT

9.7.1 Data Quality Assurance

CROs will be responsible for the data management for this study, including quality checking of the data. Data will be collected via two separate electronic data capture (EDC) systems (one in Germany, one in the United States). Sites will be responsible for data entry into the EDC systems. In the event of discrepant data, the CROs will request data clarification from the sites, which the sites will resolve electronically in the EDC systems.

Each CRO will produce a Data Quality Review Plan that describes the quality checking to be performed on the data. Data Collection and data quality review will be aligned between the CROs to ensure adequate alignment of data elements.

Roche will perform oversight of the data management of this study, including approval of the CRO-respective data management plans and specifications.

eCRFs and correction documentation will be maintained in the EDC systems' audit trails. Systems' backups for data stored at the CROs, and records retention for the study data will be consistent with the CRO standard procedures. The CROs will comply with Roche's procedures regarding archiving and record management.

9.7.2 Electronic Case Report Forms

eCRFs are to be completed using approved EDC systems. Sites will receive training and will have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the CROs and should be handled in accordance with instructions from the CROs.

All eCRFs should be completed by designated trained site staff. eCRFs should be reviewed and electronically signed and dated by the physician or a designee.

At the end of the study, the physician will receive the data related to patients from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

9.7.3 Source Data Documentation

Site Operations Representative may conduct SDV as defined in the Study Monitoring Plan to confirm that critical protocol data (i.e., source data) entered in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche,

photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Study Monitoring Plan. The Study Monitoring Plan defines which kind of source data – if available from clinical routine – can be used for documentation into the eCRF. No additional source data creation beyond routine is allowed.

Source documents that are required to verify the validity and completeness of data entered in the eCRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 9.9.4.

To facilitate SDV, the physicians and institutions must provide Roche or one of Roche's representatives with direct access to applicable source documents and reports for study-related monitoring, Roche audits, and Institutional Review Board (IRB)/independent Ethics Committee (IEC) review. The participating sites must also allow inspection by applicable health authorities.

9.8 DATA ANALYSIS

The study population will include all patients who meet eligibility criteria, consent to participate in the study, and are treated with at least one dose of ocrelizumab or are treated with an approved MS DMT other than ocrelizumab (internal comparator). Demographic and baseline characteristics (e.g., age, sex, type and duration of prior MS DMTs) will be summarized by descriptive summary statistics for continuous variables and frequency distribution for categorical variables.

Exposure to ocrelizumab or approved MS DMTs other than ocrelizumab will be summarized as the number and percentage of patients who stayed on the same MS DMT until the end of the study, patients who discontinued the use of their MS DMT including the reason for discontinuation, treatment duration, the number of infusions received, and the total cumulative dose (mg). The denominator for percentages will be the number of patients in that treatment group.

Similar data analysis procedures as for the internal comparator patients will be performed for comparisons to the ocrelizumab-exposed patients.

Primary Objective Analysis

The incidence rate of breast cancer and all malignancies in patients exposed to ocrelizumab will be calculated as the total number of first (i.e., incident) events divided by the total patient-years at risk. When estimating the incidence rates of any specific malignancies, such as breast cancer, the patient will continue to contribute patient-years

at risk even if there is a different prior malignancy diagnosis. In this case, the incidence rate will be calculated as the total number of first (i.e., incident) events of that particular malignancy divided by the total patient-years at risk for that particular malignancy. Total patient-years at risk will be calculated from the first dose of ocrelizumab until the event, death, loss to follow-up, or the end of the study, whichever occurs first, irrespective of the ocrelizumab exposure duration. Exact Poisson 95% CIs will be calculated.

Secondary objective analyses on mortality rates of breast cancer and malignancy, and rates of all SAEs and AESIs

The mortality rate of breast cancer and all malignancies in patients exposed to ocrelizumab will be calculated as the number of malignancy deaths recorded, divided by the total patient-years at risk, and the corresponding 95% CIs will be calculated. Total patient-years at risk will be calculated from the first dose of ocrelizumab until the event, death, loss to follow-up, or the end of the study, whichever occurs first, irrespective of the ocrelizumab exposure duration (ever-exposed model).

For all SAEs and AESIs (except malignancies), event rates will be based on a time-on-drug approach that uses person-time as exposed from first ocrelizumab dose in the study, up to 6 months (26 weeks) after the last administration of ocrelizumab. The risk window will be varied in sensitivity analyses to assess the robustness of findings, including but not limited to 72 weeks after last administration of ocrelizumab and up until the date of switch to another MS DMT. Among patients who stop and restart ocrelizumab, where the gap in between is greater than the risk window, the duration of exposure will be summed as the time periods from each ocrelizumab start date to the end of the risk window. Event rates including all events reported within the qualifying exposure window will be presented. The rates will then be re-presented using first events only (with data censored at the time of first event).

Secondary objective analyses on comparison with internal and external populations

Comparison of incidence and mortality rates will be made between patients exposed to ocrelizumab and patients from the comparators listed in Section 9.5.4.

Different statistical approaches will be used, depending on the availability of aggregated or patient-level data in the comparator populations. For outcomes that can occur repeatedly, Poisson regression models will be used.

As the analysis of the primary objective will apply an ever-exposed model of ocrelizumab exposure, incidence rates are comparable to these data sources that contain patient-level information (including MS DMT exposure) (see Section 9.4). To compare the risk between all ocrelizumab-treated patients from this study with patients from MSBase and the internal comparator, HRs with associated 95% CIs will be estimated. Differences between groups in potential confounders will be minimized through standard

regression-based covariate adjustments, and through appropriate causal inference methods (Hernán and Robins 2017). Potential confounders will include, but not limited to, age, sex, disease duration and prior MS DMT use.

MSBase and the observational, longitudinal internal comparator MS cohort with prospectively collected data will provide access to patient-level data.

SEER provides aggregated level data, such as age- and sex-specific incidence and mortality rates by malignancy type. Incidence and mortality rates from the study population will be compared with SEER data using direct and indirect methods of standardization.

Handling of patients who switch DMTs during the course of the study will be described in detail in the SAP.

Subgroup and Sensitivity Analyses

Subgroup analyses will be presented by sex, age, history of prior malignancy, malignancy type, MS type (RMS, PPMS), disease duration, disease severity (such as the number of relapses, MRI lesions, EDSS score if available) prior exposure to MS DMT at study entry (yes/no, by type, duration and number of previous MS DMTs), active disease (yes/no), and duration and dose of cumulative exposure to ocrelizumab. An additional sensitivity analysis will be performed excluding patients who have ever been exposed to alemtuzumab. Hospitalization to treat an MS relapse will be collected; however, SAE rate estimates will analyze these events separately. Outcome differences by country will be examined by stratification (United States and Germany). Any additional subgroup or sensitivity analyses will be described in the SAP.

Latency between exposure and onset of malignancy or AEs will be handled in the following ways. For the primary analyses, all outcomes observed after exposure will be counted as attributable to ocrelizumab or another MS DMTs. This will produce the most conservative possible assessment of safety and ocrelizumab exposure. In addition, outcome rates will be presented by study year which will allow different assumptions about latency to be examined. A sensitivity analysis will be performed eliminating diagnoses occurring after periods of exposure of less than a year (e.g., 6 months). A survival analysis method will also be considered to provide evidence on the time from initiation of ocrelizumab to events of interest. Results will be presented as lifetables and instantaneous hazard rates that will provide insight into the distribution of time to diagnosis without pre-specifying latency periods.

Full details of the statistical analyses will be described in the SAP.

9.8.1 Interim/Final Analysis and Timing of Analyses

Interim analysis reports will align with study progress reports according to regulatory reporting schedule approximately every 6 months. Interim analysis reports will include crude incidence and mortality rates, and α levels will not be adjusted for multiplicity.

The final analysis will be performed at the completion of the observational study.

9.9 QUALITY CONTROL

9.9.1 Study Documentation

The physician 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, ICFs, and documentation of IRB/IEC and governmental approval. In addition, at the end of the study, the physician will receive the patient data, which include an audit trail containing a complete record of all changes to data.

Roche shall ensure that the dataset 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.

9.9.2 Site Audits and Inspections

Site visits may be conducted by Roche or an authorized representative for audit of study data, patients' medical records, and eCRFs.

The physician will also permit national and local health authorities to inspect facilities and records relevant to this study.

9.9.3 Use of Site Computerized Systems

When clinical observations are entered directly into a participating site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

9.9.4 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs and ICFs, must be retained by the physician for at least 15 years after completion or discontinuation 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 Roche. Written notification should be provided to Roche prior to transferring any records to another party or moving them to another location.

All supporting functional parties will comply with Roche's procedures regarding archiving and record management.

9.10 LIMITATIONS OF THE RESEARCH METHOD

This study aims to evaluate the risk profile of ocrelizumab in patients with MS in a real-world setting, specifically related to breast cancer, malignancies, and long-term safety regarding SAEs.

Potential limitations of the study design and measures proposed to address them include the following:

Enrollment bias: Sites will be expected to maintain screening logs of all patients meeting eligibility criteria, along with reasons for non-enrollment.

Channeling bias: There is the likelihood of channeling bias with the use of an internal comparator group that has been exposed to a variety of other MS DMTs with varying label indications. Additionally, MS DMT labeling (inclusive of ocrelizumab) may differ regionally. Evaluations of these differences will be examined at baseline (study entry) to assess channeling bias, including any factors associated with treatment choice, prior MS DMT exposures, any specified reasons for switching from a prior MS DMT to the current therapy (e.g., disease progression), local label indication(s), and MS disease severity. These characteristics will be described and accounted for in multivariate analyses using standard regression-based covariate adjustments or appropriate causal inference methods, as described further in Section 9.8.

Residual confounding between the study population and comparators: Data analysis will examine the distributions of key variables that could cause confounding (e.g., baseline severity of MS disease, sex, age, comorbidities), and will be accounted for in multivariate analyses. However, residual confounding due to unknown and imprecisely measured confounders may still remain. See Appendix 3 for a summary of covariates available from comparator data sources. Methods for adjustment are described further in Section 9.8.

Healthy user bias/depletion of susceptibles: Long-term users of a given medication may be at lower risk of malignancies than new users (i.e., they would have survived to the time of study entry). Since patients will participate in the study at the time of ocrelizumab or other MS DMT treatment initiation, this should eliminate bias associated with the study of prevalent medication users.

Misclassification: All centers/sites will undergo standardized training and utilize standardized documentation for completing eCRFs at study entry and for each follow-up assessment; specifically, on the importance of accurately collecting exposure information as well as outcome variable information. However, the same rigor may not apply to the data collection in the external control cohorts.

Comparison of malignancies between adjudicated events with external comparators: The rate of observed, adjudicated malignancies in the study sample may be different from the external comparators, which are not based on adjudicated results. The malignancy event rates used to power the study will likely be lower than the observed rates in the study sample if the rates used to power the study (e.g., from SEER) are not based on adjudicated results.

Site and HCP fatigue: The required data elements and follow-up time for patients could result in site and/or HCP fatigue resulting from the burden of data collection and reporting effort required over a long period of time. Efforts to retain sites and keep them engaged in the study will be implemented and are described in Section 9.1.1.

Recruitment of patients is dependent on several factors: Uptake of new medications such as ocrelizumab is unpredictable and has the potential to impact the feasibility of meeting the recruitment targets in the United States and Germany. However, continuous monitoring of patient recruitment at the site and country levels 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 initiation of additional sites within participating countries, and/or expansion of the study into additional countries.

10. PROTECTION OF HUMAN SUBJECTS

10.1 PATIENT DISCONTINUATION

Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Patient death
- Patient is lost to follow-up
- Investigator decision
- Sponsor decision

10.1.1 Discontinuation from Treatment with Ocrelizumab or Another Approved Multiple Sclerosis Disease Modifying Therapy

The decision for discontinuation from treatment lies with the treating physician in agreement with the patient's decision and is not regulated by this protocol.

The primary reason for treatment discontinuation should be documented on the appropriate eCRF page.

10.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF page. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

10.1.3 Lost to Follow-up

For patients whose status is unclear because they fail to appear for study encounters without stating an intention to withdraw or if the patient switches clinical practices, the treating physician will attempt to contact the patient in order to assess the patient's interest in continuing study participation. At least three documented follow-up contact attempts should be made before considering the patient to be lost to follow-up. If a patient does not respond, attempts will be made to contact the patient's primary health care physician, next of kin, or secondary contacts (if consent is given and information is available), where local regulations allow, to obtain follow-up information. If contact with a missing patient is re-established, follow-up should continue according to the protocol, and exposure and outcome variable information for the missed periods should be collected to the extent possible.

10.1.4 Study and Site Discontinuation

Roche has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Patient enrollment is unsatisfactory
- Patient safety

Roche will notify the physician if the study is placed on hold, or if Roche decides to discontinue the study.

Roche has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiology Practice (GPP) or any other pertinent local law or guideline

10.2 COMPLIANCE WITH LAWS AND REGULATIONS

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

The study will comply with national and E.U. requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

10.3 INFORMED CONSENT

Roche's sample ICF (and ancillary sample ICFs, such as a Caregiver's ICF, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Roche must review and approve any proposed deviations from Roche's sample ICFs or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before IRB/IEC submission. The final Consent Forms approved by the IRB/IEC must be provided to Roche for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before start of documentation of his or her data in the eCRF. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to first documentation of this patient's data in the eCRF.

By signing the form, the patient confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the responsibility of the physician to obtain written informed consent from each patient participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The physician must also explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the patient is entitled or is presently receiving.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by Site Operations Representative at any time.

For sites in the United States, each ICF may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other

processes outlined above apply, except that IRB review and approval may not be required per study site policies.

10.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

In addition to the requirements for collecting and reporting all SAEs (including malignancies), AESIs (i.e., events falling under Hy's Law and events of STIAMP only), and NMSCs to Roche, physicians must comply with requirements for AE reporting to the local health authority and IRB/IEC.

10.5 CONFIDENTIALITY

Confidentiality standards will be maintained by coding each patient who participates in the study through the assignment of a unique patient identification number. This means that patient names will not be included in datasets transmitted to any location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Roche monitors, representatives, and collaborators, and the IRB/IEC for each study site, as appropriate.

The participating physician commits to complying with all related applicable local laws and regulations.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

11.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products (observational products of interest, as specifically stated in the study objectives). For safety reporting requirements for non-studied medicinal products, see Section 11.2.

Safety assessments for all patients from the United States will consist of monitoring and recording SAEs, AESIs (i.e., events falling under Hy's Law and events of STIAMP only), and NMSCs, performing safety laboratory assessments, measuring vital signs, and conducting other tests that are deemed critical to the safety evaluation of the study as per standard medical practice. Safety assessment of patients from Germany will also consist of monitoring and recording non-serious AEs, but are outside the scope of this study (see Section 9.3, Table 2). Details on the management and collection of AEs in the United States are described in Section 11 of this protocol. Study protocol ML39632 provides further details on the management and reporting of non-serious AEs.

11.1.1.1 Adverse Events

According to the International Conference on Harmonisation, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a ocrelizumab, whether or not considered related to ocrelizumab
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Appendix 5
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline (study entry)
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

11.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to Roche) and Non-Serious Adverse Events of Special Interest

Serious Adverse Events

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)

- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe)
- Requires or prolongs inpatient hospitalization (see Appendix 5.3.10)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician’s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (e.g., rated using the NCI’s Common Terminology Criteria for Adverse Events [CTCAE]); see Appendix 5); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

For AEs, serious and non-serious, the physician’s assessment of severity using the NCI-CTCAE and the relationship to therapy (i.e., related or unrelated), will be recorded (Appendix 5). Severity and seriousness need to be independently assessed for each AE recorded on the eCRF (for detailed instructions, see Appendix 5).

This study is specifically designed to collect detailed information about malignancies and other SAEs. SAEs/AEs of malignancies (including but not limited to MedDRA SMQ of malignant or unspecified tumors), SAEs (other than malignancies), NMSCs, and AESIs (i.e., events falling under Hy’s Law and events of STIAMP only) will be recorded in the eCRF during the study as described in Section 9.3. For all of the following sections, the term SAE will refer to all SAEs including malignancies. NMSCs and AESIs (defined below) will be considered separately from other SAEs.

Non-Serious Adverse Events of Special Interest

AESIs, defined in this protocol, are non-serious AEs that follow the reporting rules of SAEs. There are no ocrelizumab-specific AESIs, but the two described below apply to all Roche products:

- Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Appendix 5)
- Suspected transmission of an infectious agent by the study medicine, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected.

11.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is responsible for ensuring that all SAEs, AESIs, and NMSCs are collected as per protocol (see Section 11.1.1 for definitions), are recorded in the AE section of the eCRF and are reported to Roche in accordance with the instructions provided in this section and in Section 11.1.3.

For each SAE, AESI, and NMSC recorded in the AE section of the eCRF, the physician will make an assessment of seriousness (see Section 11.1.1.2), severity (see Appendix 5), and causality (see Appendix 5).

11.1.2.1 Adverse Event Reporting Period

Physicians will seek information on SAEs, AESIs, and NMSCs during each patient contact. These events are subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel and will be recorded in the patient's medical record and in the AE section of the eCRF.

Once the patient begins participation in the study, SAEs, AESIs, and NMSCs will be actively monitored and collected until the end of his or her participation in the study. After this period, the physician is not required to actively monitor patients for SAEs, AESIs, and NMSCs; but if the treating physician becomes aware of any related AEs to ocrelizumab they should notify the competent authority in the Member State where the reactions occurred or to Roche, but not to both (to avoid duplicate reporting).

11.1.2.2 Procedures for Recording Adverse Events

Physicians should use correct medical terminology/concepts when recording SAEs, AESIs, and NMSCs in the AE section of the eCRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field of the eCRF.

See Appendix 5 for further specific instructions regarding:

- Diagnosis versus signs and symptoms
- AEs occurring secondary to other AEs
- Persistent or recurrent AEs
- Abnormal laboratory values
- Abnormal vital sign values
- Abnormal liver function tests
- Deaths
    - All events with an outcome or consequence of death should be classified as SAEs and reported to Roche immediately. In certain circumstances, however, suspected adverse reactions with a fatal outcome may not be

subject to expedited reporting (see Section 11.3). All deaths that occur during the protocol-specified AE reporting period, regardless of their relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to Roche.

- Preexisting medical conditions
- Hospitalization or prolonged hospitalization
- Overdoses, misuses, abuses, off-label use, occupational exposure, or medication error
- Drug interactions
- Quality defects and falsified medicinal products

11.1.3 Reporting Requirements from Physician to Roche

11.1.3.1 Rationale for Selective Adverse Event Data Collection in the Study

During the course of this study, reporting and collection will be limited to all SAEs, pre-specified AESIs (i.e., events falling under Hy's Law and events of STIAMP only), and cases of NMSC, in agreement with the U.S. FDA (see Section 11.1.1). The investigator will assess the seriousness of the AEs and AESIs based on well-established pre-defined criteria specified in Section 11.1.1.2. Additional guidelines to assessing and reporting of safety events in this study are given in Section 11 and in Appendix 5.

Other non-serious AEs will not be systematically collected for U.S. patients.

However, throughout the course of the study, investigators from the United States shall report suspected adverse drug reactions (ADRs) using the usual post-marketing spontaneous reporting mechanisms as per relevant national reporting systems. The rationale for selective collection of safety events during the course of the study is as follows:

Safety data collection is driven by the objectives of the study which are to determine and characterize the incidence and mortality rates of breast cancer, all malignancies, and the long-term safety regarding SAEs among patients with MS who are newly exposed to ocrelizumab under routine clinical care. Systematic collection of AEs other than defined above would not contribute to the objectives of the study.

Comparative safety analyses may be prone to various type of reporting bias. Previous studies have shown that serious AEs are reported more frequently and systematically over several years following marketing authorization, whereas non-serious AEs are reported less frequently over time (Gavaza et al. 2011; Matsuda et al. 2015; Moulis et al. 2012). Furthermore, reporting bias has been associated with the number of years in the marketing life of a drug and with an increased reporting of AEs for newly marketed products (Gross 1992). Therefore, collection of non-serious AEs for

ocrelizumab would carry a risk of misinterpretation bias in this observational, non-interventional study. Many comparators to ocrelizumab will have been marketed for a number of years at the time of this study. It is expected that AEs or ADRs associated with these MS DMTs would not be reported in a systematic manner, whereas this is more likely for a newly marketed product, such as ocrelizumab. As detailed in Section 7.2, comparative data for all AEs are available from placebo and interferon-controlled clinical trials.

In addition, systematic reporting of all AEs throughout the entire study duration, irrespectively on whether patients are treated with ocrelizumab or discontinue treatment, represents a high administrative burden for HCPs. If HCPs are required to systematically collect all AEs, there is concern on how much time is being spent on the endpoints that constitute the outcomes of interest for this study, in an observational setting. Therefore, to ensure appropriate focus of the investigators on collecting detailed information on the primary outcome variables and other pertinent information to fulfill the study objectives, collection of safety events will be restricted to all SAEs, AESIs, and NMSC. The study will apply monitoring mechanisms to support completeness of SAEs reporting.

11.1.3.2 Immediate Reporting Requirements from the Physician to Roche

Certain events require immediate reporting to allow Roche and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The physician must report such events to Roche immediately; under no circumstances should reporting take place more than 24 hours after the physician learns of the event. The following is a list of events that the physician must report to Roche within 24 hours after learning of the event, regardless of relationship to study medicine:

- SAEs
- AESIs (i.e., events falling under Hy's Law and events of STIAMP only)
- Pregnancies

The physician must report new significant follow-up information for these events to Roche immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

For reports of SAEs and AESIs, including follow-up, physicians should record all case details that can be gathered immediately (i.e., within 24 hours) in the AE page of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety by the EDC system.

In the event that the EDC system is temporarily unavailable, refer to Section 11.1.3.3.

Physicians must also comply with local requirements for reporting SAEs to the local health authority and IRB/IEC.

11.1.3.3 If Electronic Data Capture System is Temporarily Unavailable

In the event that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the event) using the fax number or e-mail address provided to physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

11.1.3.4 Reporting Requirements for Pregnancies/Breastfeeding

Pregnancies/Breastfeeding in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study or within 6 months after the last dose of ocrelizumab. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. Pregnancy should not be recorded on the AE section of the eCRF. The physician should discontinue ocrelizumab and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE section of the eCRF.

Suspected adverse reactions that occur in infants following exposure to ocrelizumab from breast milk within 6 months following the last infusion (in the mother) should be reported to Roche Drug Safety.

The Ocrelizumab Pregnancy Registry (Study WA40063) is being conducted independently of this study, and pregnant women who have received ocrelizumab within 6 months prior to their last menstrual period or at any time during pregnancy (regardless of participation in any studies) will be offered participation in the pregnancy registry.

Abortions

Any abortion that occurred in women who received ocrelizumab during pregnancy and/or during the 6 months prior to conception should be classified as an SAE (as Roche considers abortions to be medically significant), recorded in the AE section of the eCRF, and reported to Roche Drug Safety immediately (i.e., no more than 24 hours after learning of the event; see Section 11.1.3.2).

Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to ocrelizumab (mother received ocrelizumab during pregnancy and/or during the 6 months prior to conception) should be classified as an SAE, recorded in the AE section of the eCRF, and reported to Roche Drug Safety immediately (i.e., no more than 24 hours after learning of the event; see Section 11.1.3.2).

11.1.4 Follow-Up of Patients after Adverse Events

11.1.4.1 Physician Follow-Up

The physician should follow each SAE, NMSC, AESI, or pregnancy until the event has resolved to baseline grade or better, until the event is assessed as stable by the physician, until the patient is lost to follow-up, or until the patient withdraws consent. Every effort should be made to follow all SAEs, NMSCs, AESIs, and pregnancies until a final outcome can be reported.

During the study period, resolution of any SAE, NMSC, or AESI (with dates) should be documented in the AE section of the eCRF and in the patient's medical record to facilitate SDV.

All pregnancies reported during the study should be followed until pregnancy outcome.

11.1.4.2 Roche Follow-Up

For all SAEs, AESIs, NMSCs, or pregnancies, Roche or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

11.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED MEDICINAL PRODUCTS

Although AE information is not being actively solicited for non-studied medicinal products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention to Roche, or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed medicinal product, even in the absence of AEs:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products

- Data related to a STIAMP
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol interactions)

When a patient is not exposed to a marketed medicinal product, but the physician/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

11.3 EXPEDITED REPORTING TO HEALTH AUTHORITIES, PHYSICIANS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

Roche will promptly evaluate SAEs and AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to physicians, IRBs, IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAEs and AESIs, Roche will assess the expectedness of these events using the following reference document:

- Local prescribing information for ocrelizumab

Roche will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the physician's assessment of causality and seriousness, with allowance for upgrading by Roche as needed.

12. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of the study, Roche 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. Roche will comply with all requirements for the publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to Roche prior to submission for publication or presentation. This allows Roche to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication

of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

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Appendix 1
Cancer Rates for Germany and the United States

Rates for overall cancer mortality, breast cancer incidence, and breast cancer mortality were similar between the United States and Germany in 2012 (Ferlay et al. 2013).

Table 1. Estimated age-standardized incidence and mortality rates (per 100,000 population) for the United States and Germany [a]

	Male	Female	Both Sexes
United States of America			
All cancers			
Incidence rate	347.0	297.4	318.0
Mortality rate	123.9	91.7	105.8
Breast cancer			
Incidence rate	--	92.9	--
Mortality rate	--	14.9	--
Germany			
All cancers			
Incidence rate	323.7	252.5	283.8
Mortality rate	122.1	83.4	100.8
Breast cancer			
Incidence rate	--	91.6	--
Mortality rate	--	15.5	--

[a] Ferlay et al. 2013

Appendix 2
Collection of Data Elements

Variables

The tables below further characterize corresponding data elements of variables that will be collected during the study as part of local routine clinical practice, as available. All data elements outlined in this protocol are also included in ML39632. Variables and variable specifications are subject to change.

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Date of Encounter/Study Entry	Date	
Eligibility	Informed consent collected from the patient	Date and version of informed consent Protocol version
	Diagnosed with MS	Y/N
	Documentation that the patient was newly exposed to ocrelizumab or other approved MS DMT at any point starting from 30 days prior to study entry encounter	Y/N
	Documentation that the patient was NEVER exposed to rituximab at any point prior to study entry	Y/N
	18 years of age or older at the time of first ocrelizumab or current MS DMT	Y/N
	Not currently an active participant in a clinical trial [a]	Y/N
Demographics	Age	Year of birth
	Sex	Male/Female
Physical Characteristics and	Height	Units of cm or inches and feet

Variable Category	Data Elements	Additional Information
Baseline Labs	Weight	Units of lbs. or kg
	BMI	Calculated using height and weight
	Laboratory parameters (date and value)	Blood cell count, liver enzymes, renal status, immunoglobulins, and $CD4^+$, $CD8^+$, $CD19^+$ cell count
Current Pregnancy	Patient is currently pregnant	Y/N
Lifestyle Risk Factors	Cigarette and tobacco use	Current, former, never; If current or former, regular or occasional use?
	Alcohol consumption	Drinks/week; history of alcohol use
	Illicit drug use	Y/N
Malignancy Risk Factors	Prior malignancy	Y/N, if yes, malignancy type, grade, primary site, hormone receptor status (if applicable), date of diagnosis, date of surgery or procedures associated with malignancy, treatment(s) and duration of therapy Multiple entries allowed
	Precancerous lesions	Y/N, if yes, lesion site(s), date of diagnosis Multiple entries allowed
	Genetic cancer risk factor testing	Date, result; e.g., BRCA-1, BRCA-2
	Other risk factors	e.g., obesity, metabolic syndrome, radiation exposure, hormone replacement therapy exposure, reproductive history, immunosuppression, infections known to be associated with an increased risk of malignancy
Family Malignancy History	Relationship to patient	Multiple entries allowed
	Malignancy type	
Medical History		
Surgical History	Past surgical procedures and date(s)	Multiple entries allowed
Medical Conditions (other than MS)	Condition	Multiple entries allowed; e.g., diabetes, high blood pressure,
	Diagnosis	

Variable Category	Data Elements	Additional Information
	Start date(s)	
	End date(s)	
	Disease duration (calculated field)	
MS Disease Status at the Time of Enrollment	Date of first MS symptom	
	Diagnosis date	
	MS relapse history	Y/N; If yes, total number of relapses experienced within the past 12 months, 2 years, and 3 years
	Type of MS	
	Most recent EDSS	
	MRI results	Pertaining to MS; within the past 12 months
Prior MS DMT	Drug name	Multiple entries allowed
	Start date(s)	
	End date(s)	
	Dose	
	Reason for stopping treatment	
Current MS DMT	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Prior and Current Medications (all medications used 3 months prior to study entry)	Name of medication	Multiple entries allowed; be sure to include all prior and concomitant immunomodulatory immunosuppressive treatments
	Indication	
	Start date(s)	

Variable Category	Data Elements	Additional Information
	End date(s)	
	Dose	

BMI = body mass index; DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; HCP = healthcare provider; MRI = magnetic resonance imaging (scan); MS = multiple sclerosis; Y/N = Yes/No

[a] A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control), to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes (NIH 2014)

Table 2. Follow-up Encounters

Variable Category	Data Elements	Additional Information
Date of Contact	Date	
Physical Characteristics and Labs	Weight	
	Laboratory parameters (date and value)	Blood cell count, liver enzymes, renal status, immunoglobulins, and $CD4^+$, $CD8^+$, $CD19^+$ cell count
Current Pregnancy	Patient is currently pregnant	Y/N
MS Disease Status since Last Encounter	Number of relapses	Or date of relapses, whichever is available
	Recent EDSS score (if available)	
	Recent MRI results	
Current MS DMT	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Concomitant Medications	Medication name	Multiple entries allowed; Includes other MS treatments, if applicable
	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
Cancer Screening Examinations	Gynecological consultation	Date, reason for visit, result(s) if clinically abnormal (as AEs)
	Breast check	Date, reason for visit, result(s) if clinically abnormal (as AEs)
	Dermatological check	Date, reason for visit, result(s) if clinically abnormal (as AEs)
	Malignancy/cancer screening tests and procedures (e.g., mammography, Pap test,	Date, reason for visit, test, result(s) if clinically abnormal (as AEs)

Variable Category	Data Elements	Additional Information
	colonoscopy, laboratory malignancy markers)	
Malignancy information, if applicable [a]	Cancer type	
	Diagnosis date	
	Location of primary tumor	
	Tumor grade	
	Stage at diagnosis	
	Hormone receptor status	
	Treatment received	Surgery, chemotherapy, radiation therapy, other
	Action taken with ocrelizumab/other MS DMT at the point of diagnosis	
	Cancer status update, as applicable	Remission/relapse, updated cancer treatment information
AESIs/SAEs (other than malignancy)	Event	Includes all SAEs other than malignancy, NMSC and AESIs of Hy's Law or STIAMP
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to ocrelizumab	
	Outcome	
	Action taken	
Death, if applicable	Date, primary and underlying cause	

AE = adverse event; AESI = adverse event of special interest; DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging (scan); MS = multiple sclerosis; NMSC = non-melanoma skin cancer; SAE = serious adverse event; STIAMP = suspected transmission of infectious agent by medicinal product; Y/N = Yes/No

[a] The contact details of the reporter of malignancy information (e.g., oncologist/pathologist) will be collected outside of the EDC system at site-level, only.

Table 3. End of Study or Early Termination/Withdrawal Encounter

Variable Category	Data Elements	Additional Information
Date of Contact	Date	
Physical Characteristics and Labs	Weight	
	Laboratory parameters (date and value)	Blood cell count, liver enzymes, renal status, immunoglobulins, and $CD4^+$, $CD8^+$, $CD19^+$ cell count
Current Pregnancy, if applicable	Patient is currently pregnant	Y/N
MS Disease Status since Last Encounter	Number of relapses	And date of relapses, whichever is available
	Recent EDSS score (if available)	
	Recent MRI results	
Current MS DMT	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Concomitant Medications	Medication name	Multiple entries allowed; Includes other MS treatments, if applicable
	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
Cancer Screening Examinations, if applicable	Gynecological consultation	Date, reason for visit, result(s)
	Breast check	Date, reason for visit, result(s)

Variable Category	Data Elements	Additional Information
	Dermatological check	Date, reason for visit, result(s)
	Malignancy/cancer screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)	Date, reason for visit, result(s) if clinically abnormal (as AEs)
Malignancy Information, if applicable [a]	Cancer type	
	Diagnosis date	
	Location of primary tumor	
	Tumor grade	
	Stage at diagnosis	
	Hormone receptor status	
	Treatment received	Surgery, chemotherapy, radiation therapy, other
	Action taken with ocrelizumab/other MS DMT at the point of diagnosis	
	Cancer status update, as applicable	Remission/relapse, updated cancer treatment information
AESIs/SAEs (other than malignancy)	Event	Includes all SAEs other than malignancy, NMSC and AESIs of Hy's Law or STIAMP
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to ocrelizumab/other MS DMT	
	Outcome	
	Action taken	
Death, if applicable	Date, primary and underlying cause	

Variable Category	Data Elements	Additional Information
Reason for Early Termination/Withdrawal, if applicable		

AE = adverse event; AESI = adverse event of special interest; DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging (scan); MS = multiple sclerosis; NMSC = non-melanoma skin cancer; SAE = serious adverse event; STIAMP = suspected transmission of infectious agent by medicinal product

[a] The contact details of the reporter of malignancy information (e.g., neurologist, oncologist/pathologist) will be collected outside of the EDC system at site-level, only.

Appendix 3
Covariates across Data Sources

Table 1. Listing of Key Covariates that Overlap between BA39371 and Other Data Sources

Covariate List	Data Source			
	BA39731 (ocrelizumab cohort)	BA39731 (internal comparator)	MSBase	SEER
Exposures				
Smoking/tobacco	X	X	X	
MS treatment history including dose and duration	X	X	X	
Concomitant medications	X	X		
Outcomes				
Events of malignancy, including breast cancer	X	X	X	X [a]
Malignancy information (including type, location, grade, stage, hormone receptor status, treatment)	X	X	X [b]	
NMSCs	X	X	X	X [a]
SAEs	X	X	X	
Mortality, including reported primary and underlying cause	X	X	X	X [a,c]
Covariates				
Age, sex	X	X	X	X [a]
Weight, height, BMI	X	X	X	
Laboratory measures	X	X	X	
Malignancy history (including precancerous lesions)	X	X		
MS disease history (EDSS, MRI results, relapses)	X	X	X	
Surgical and medical history	X	X	X [d]	
Significant medical conditions other than MS (e.g., obesity, metabolic syndrome, radiation exposure, hormone replacement therapy, reproductive history, immunosuppression, infections known to be associated with an increased risk of malignancy)	X	X	X [d]	
Any malignancy risk factor information (including genetic testing, family history of malignancy)	X	X		
Cancer screening examinations (malignancy detection or screening tests)	X	X		

BMI = body mass index; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging (scan); MS: multiple sclerosis; NMSC = non-melanoma skin cancer; SAE: serious adverse event; SEER: Surveillance, Epidemiology and End Results (Program)

[a] Aggregated data only; no patient-level data available

[b] Hormone receptor status is not collected by MSBase

[c] Cancer deaths only obtained from the National Center for Health Statistics

[d] Not systematically collected

Appendix 4
ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
AN OBSERVATIONAL STUDY OF OCRELIZUMAB-TREATED PATIENTS WITH MULTIPLE SCLEROSIS TO DETERMINE THE INCIDENCE AND MORTALITY RATES OF BREAST CANCER AND ALL MALIGNANCIES (VERISMO STUDY)

Study reference number:
BA39731

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 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

1.1.5. Protocol will be registered in the EU PAS register after protocol approval by the FDA.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

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, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1

[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 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.1, 8
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.1, 9.8
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?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.1
	4.2.2 Age and sex?	☒	☐	☐	9.2.1
	4.2.3 Country of origin?	☒	☐	☐	9.1
	4.2.4 Disease/indication?	☒	☐	☐	9.1, 9.2.2
	4.2.5 Duration of follow-up?	☒	☐	☐	9.1
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)	☒	☐	☐	9.1, 9.4.1
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 classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.1, 9.4.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.8

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?	☒	☐	☐	8.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.4.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3, 9.4.2
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.8
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☒	☐	☐	9.10
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.10
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.10
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect 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)	☒	☐	☐	9.8

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?	☒	☐	☐	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)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates? (e.g. 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? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4.3.2, 9.4.3.3
	9.3.3 Covariates?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.8
10.2 Are descriptive analyses included?	☒	☐	☐	9.8
10.3 Are stratified analyses included?	☒	☐	☐	9.8
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.8
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.6

Comments:

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)	☒	☐	☐	9.7.1, 9.9
11.2 Are methods of quality assurance described?	☒	☐	☐	9.7.1, 9.9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

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?	☒	☐	☐	9.10
12.1.2 Information bias?	☒	☐	☐	9.10
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)	☒	☐	☐	7.2, 9.10
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1, 9.2, 9.5, 9.10

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.4
13.3 Have data protection requirements been described?	☒	☐	☐	10.5

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: 23 September 2018

Signature: [redacted]

Appendix 5
Methods for Assessing and Recording Adverse Events

Appendix 5.1 Assessment of Severity of Adverse Events

The adverse event (AE) severity grading scale for the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (v5.0) will be used for assessing serious adverse event (SAE), AE of special interest (AESI) (i.e., events falling under Hy's Law and events of suspected transmission of infectious agent by medicinal product [STIAMP] only), and non-melanoma skin cancer (NMSC) severity. The table below will be used for assessing severity for SAEs, AESIs, and NMSCs that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to AE [d]

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; SAE = serious adverse event

Note: Based on the NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 11.1.3 for reporting instructions), per the definition of SAE in Section 11.1.1.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 11.1.3 for reporting instructions), per the definition of SAE in Section 11.1.1.2.

Appendix 5.2 Assessment of Causality of Adverse Events

Physicians should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an SAE, AESI, or NMSC is considered to be related to ocrelizumab, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of ocrelizumab
- Course of the event, considering especially the effects of dose reduction, discontinuation of ocrelizumab, or reintroduction of ocrelizumab (when applicable)
- Known association of the event with ocrelizumab or with similar treatments
- Known association of the event with the disease under study (all malignancies)
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for ocrelizumab.

Appendix 5.3 Procedures for Recording Adverse Events

Appendix 5.3.1 Infusion-Related Reactions

Serious adverse events that occur during or within 24 hours after ocrelizumab administration and are judged to be related to ocrelizumab infusion should be captured as an overall diagnosis (e.g., “infusion-related reaction” or “anaphylactic reaction”) in the SAE section of the electronic case report form (eCRF) including description of signs and symptoms in the SAE description field. If possible, avoid ambiguous terms such as "systemic reaction." If a patient experiences both serious local infusion site and serious systemic reactions to the same dose, each reaction should be recorded separately in the SAE section of the eCRF, with signs and symptoms recorded in the SAE description.

Medical judgment should be used to distinguish between infusion-related reaction, hypersensitivity, anaphylactic reaction, anaphylactic shock and anaphylactoid reaction.

Appendix 5.3.2 Diagnosis versus Signs and Symptoms

For SAEs, AESIs, and NMSCs, other than infusion-related reactions (see Appendix 5.3.1) a diagnosis (if known) should be recorded in the AE section of the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the AE section of the eCRF. If a diagnosis is subsequently established, all previously reported SAEs,

non-serious AESIs, and NMSCs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Appendix 5.3.3 Adverse Events Occurring Secondary to Other Events

In general, SAEs or AESIs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary SAE or AESI that is separated in time from the initiating event should be recorded as an independent event in the AE section of the eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All SAEs and AESIs should be recorded separately in the AE section of the eCRF if it is unclear as to whether the events are associated.

Appendix 5.3.4 Persistent or Recurrent Adverse Events

A persistent SAE, AESI, or NMSC is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once in the AE section of the eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent SAE, AESI, or NMSC becomes more severe, the most extreme severity should also be recorded in the AE section of the eCRF. If the event becomes serious, it should be reported to Roche immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 11.1.3.2 for reporting instructions). The AE section of the eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent SAE, AESI, or NMSC is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an SAE, AESI, or NMSC should be recorded separately in the AE section of the eCRF.

Appendix 5.3.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be forwarded to Roche according to standard pharmacovigilance practices.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be reported to Roche, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, a neutrophil count of less than 1,500 neutrophils per microliter of blood should be recorded as "neutropenia".

Observations of the same clinically significant laboratory abnormality from encounter to encounter should be forwarded to Roche according to standard pharmacovigilance practices. If the associated AE fulfills the seriousness criteria, the SAE should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 11.1.3.2).

Appendix 5.3.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be forwarded to Roche according to standard pharmacovigilance practices.

Observations of the same clinically significant vital sign abnormality from encounter to encounter should be forwarded to Roche according to standard pharmacovigilance practices. If the associated AE fulfills the seriousness criteria, the SAE should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 11.1.3.2).

Appendix 5.3.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ the ULN) in combination with either an elevated total bilirubin ($> 2 \times$ the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, physicians must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$the ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be forwarded to Roche according to standard pharmacovigilance practices. If the associated AE fulfills the seriousness criteria, the SAE should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 11.1.3.2).

Appendix 5.3.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 11.1.2.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to Roche (see Section 11.1.3.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept on the AE section of the eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of

reporting, **"unexplained death"** should be recorded on the AE section of the eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Appendix 5.3.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening encounter for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions in the eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study.

If the associated AE fulfills the seriousness criteria, the SAE should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 11.1.3.2). When recording such events in the AE section of the eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Appendix 5.3.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 11.1.1.2), except as outlined below. Hospitalization to treat an MS relapse will be collected; however, SAE rate estimates will analyze these events separately.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not suffered an AE.

Appendix 5.3.11 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the eCRF. Any overdose, misuse, abuse, off-label use, occupational exposure or medication error

(including intercepted or potential) reports must be forwarded to Roche with or without an AE.

Reports with or without an AE should be forwarded to Roche according to standard pharmacovigilance practices. If the associated AE fulfills the seriousness criteria, the SAE should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 11.1.3.2).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

Appendix 5.3.12 Quality Defects and Falsified Medicinal Products

Reports of suspected or confirmed falsified medicinal product or quality defect of a medicinal product, with or without an associated AE, should be forwarded to Roche according to standard pharmacovigilance practices. If the associated AE fulfills the seriousness criteria, the SAE should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 11.1.3.2).

Appendix 5.3.13 Drug Interactions

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol interactions should be forwarded to Roche according to standard pharmacovigilance practices. If the associated AE fulfills the seriousness criteria, the SAE should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 11.1.3.2).

Appendix 5.3.14 Safety Data other than Adverse Events

Safety data other than AEs (see Section 9.3) should be recorded in an appropriate section of the eCRF and reviewed on an ongoing basis.