NI PASS PROTOCOL (Primary data collection)

TITLE:	**SAFETY AND EFFECTIVENESS OF OCRELIZUMAB UNDER REAL WORLD CONDITIONS: A NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY IN PATIENTS DIAGNOSED WITH RELAPSING OR PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS - CONFIDENCE**
PROTOCOL NUMBER:	ML39632
VERSION NUMBER:	1.0
AUTHOR:	[redacted] Medical Manager [redacted] [redacted] [redacted] Roche Pharma AG Medical Affairs Emil-Barell-Straße 1 79639 Grenzach-Wyhlen
EU PAS REGISTER NUMBER:	To be determined
ACTIVE SUBSTANCE:	L04AA36 (ocrelizumab)
STUDIED MEDICINAL PRODUCT:	Ocrelizumab (OCREVUS®)
PRODUCT REFERENCE NUMBER:	RO4964913
PROCEDURE NUMBER:	EMEA/H/C/004043; IND 100,593 BLA 761053
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The objective of this study is to collect real-world data on the long-term safety and effectiveness of ocrelizumab in MS patients newly exposed to this substance.

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COUNTRY OF STUDY POPULATION:	Germany
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
MAH CONTACT PERSON:	Head, EU/ROW Regulatory Affairs Telephone number : [redacted] Fax number: [redacted]
DATE FINAL:	January 26, 2018

PROTOCOL FINALIZATION SIGNATURE PAGE

TITLE:	**SAFETY AND EFFECTIVENESS OF OCRELIZUMAB UNDER REAL WORLD CONDITIONS: A NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY IN PATIENTS DIAGNOSED WITH RELAPSING OR PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS - CONFIDENCE**
PROTOCOL NUMBER:	ML39632
VERSION NUMBER:	1.0
EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCT:	Ocrelizumab(OCREVUS®)
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
DATE FINAL:	January 26, 2018

This protocol was finalized on the date shown above.

[redacted] Medical Manager [redacted]

01. Feb. 2018
Date

[redacted]
(QPPV or Deputy's Name)

31 Jan 2018
Date

[redacted] Coordinating Investigator

2. FEB 2018
Date

PROTOCOL FINALIZATION SIGNATURE PAGE

TITLE:	**SAFETY AND EFFECTIVENESS OF OCRELIZUMAB UNDER REAL WORLD CONDITIONS: A NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY IN PATIENTS DIAGNOSED WITH RELAPSING OR PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS - CONFIDENCE**
PROTOCOL NUMBER:	ML39632
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STUDIED MEDICINAL PRODUCT:	Ocrelizumab(OCREVUS®)
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
DATE FINAL:	January 26, 2018

This protocol was finalized on the date shown above.

[redacted] Head of Safety Science

2. Feb. 2018
Date

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PROTOCOL ACCEPTANCE FORM

TITLE:	**SAFETY AND EFFECTIVENESS OF OCRELIZUMAB UNDER REAL WORLD CONDITIONS: A NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY IN PATIENTS DIAGNOSED WITH RELAPSING OR PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS - CONFIDENCE**
PROTOCOL NUMBER:	ML39632
VERSION NUMBER:	1.0
EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCT:	Ocrelizumab (OCREVUS®)
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

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 the contact provided below. Please retain the signed original for your study files.

[redacted]

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BRCA	BReast CAncer
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CNS	Central Nervous System
CDI	Confirmed Disability Improvement
CDP	Confirmed Disability Progression
CGI	Clinical Global Impression
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DGN	Deutsche Gesellschaft für Neurologie (German Society of Neurology)
DMT	Disease Modifying Therapy
EC	Ethics Committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
FDA	Food and Drug Administration
gamma-GT	Gamma-glutamyl Transpeptidase
GPP	Good Pharmacoepidemiological Practice
HR	Heart Rate
HIV	Human immunodeficiency virus
ICH	International Conference of Harmonization
IgG/IgM	Immunoglobulin G / M
JVC	John Cunningham Virus
LPLV	last patient, last visit
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging

Abbreviation	Definition
MS	Multiple Sclerosis
MSIF	MS International Federation
MSIS-29 v2	Multiple Sclerosis Impact Scale 29 v2
NCI	National Cancer Institute
NIS	Non-interventional study
NMSC	Non-melanoma Skin Cancer
PAS(S)	Post-authorization Safety (Study)
PFS	Progression Free Survival
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
PRO	Patients Reported Outcomes
Q	Quarter
QoL	Quality of Life
QPPV	Qualified Person for Pharmacovigilance
RBC	red blood cell
RCT	Randomized Clinical Trial
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-remitting Multiple Sclerosis
RTL	Responsible Team Lead
RWD	Real-world Data
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modality Test
SDV	Source data verification
SMQ	Standardized MedDRA Queries
SoC	Standard of Care
SOC	System Organ Class
SPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
STIAMP	Suspected Transmission of Infection by a Medicinal Product
TSQM1.4	Treatment Satisfaction Questionnaire for Medication 1.4
WPAI:MS	Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis

2. RESPONSIBLE PARTIES

Protocol Development Responsible

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Medical Affairs
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79639 Grenzach-Wyhlen
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3. SYNOPSIS

TITLE:	**SAFETY AND EFFECTIVENESS OF OCRELIZUMAB UNDER REAL WORLD CONDITIONS: A NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY IN PATIENTS DIAGNOSED WITH RELAPSING OR PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS - CONFIDENCE**
PROTOCOL NUMBER:	ML39632
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	March 03, 2017
EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCT:	Ocrelizumab (OCREVUS®)
SCIENTIFIC RESPONSIBLE	[redacted] Medical Manager [redacted]
MAIN AUTHORS:	[redacted] [redacted]
PHASE:	Non-interventional study
INDICATION:	Relapsing multiple sclerosis (RMS) Primary progressive multiple sclerosis (PPMS)
MARKETING AUTHORIZATION HOLDER:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

Rationale and Background

Ocrelizumab is a recombinant, humanized monoclonal antibody that selectively targets CD20-expressing B cells and showed positive effects in different forms of multiple sclerosis (MS). Two identical, randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093], Hauser et al. 2017) demonstrated superior efficacy outcomes of ocrelizumab versus interferon beta-1a in relapsing forms of multiple sclerosis (RMS). One randomized placebo-controlled study (ORATORIO [Study WA25046], Montalban et al. 2017) demonstrated superior efficacy of ocrelizumab versus placebo in primary progressive multiple sclerosis (PPMS). The safety profile of ocrelizumab was consistent between the RMS and PPMS studies. The proportions of patients with adverse events (AEs) or serious adverse events (SAEs) were similar in the ocrelizumab, interferon beta-1a (OPERA I & II) or placebo groups (ORATORIO), respectively. Infusion-related reactions and mild to moderate infections (predominantly respiratory tract infections) were the most commonly reported AEs. The proportion of

patients experiencing a serious infection was low and similar to interferon beta-1a or placebo, respectively. Consistent with the severity of the underlying type of MS there were more serious infections reported in both arms of the PPMS study than in the RMS studies. Pooled data from OPERA I & II and ORATORIO indicated an imbalance in malignancies in the ocrelizumab treatment group versus pooled interferon beta-1a and placebo. The only cluster that could be identified was for female breast cancer. However, incidences remained within the range of placebo data from clinical trials in MS and epidemiological data, and no firm conclusion concerning the relative risk could be made due to the low number of events and the limited follow-up period.

MS is a chronic disease requiring a lifetime treatment. CONFIDENCE is performed to assess long-term safety data (e.g. on malignancies and serious infections) of ocrelizumab in the real world setting and further characterize the safety profile in patients with multiple sclerosis newly exposed to ocrelizumab. Collected safety data will be included in the global PAS-Studies (BA39730 & BA39731). In addition, real world effectiveness data will be collected to complement the efficacy data collected in phase III studies over a long treatment duration.

Research Question and Objectives

Long-term use of highly effective therapies for the treatment of MS has been associated with the occurrence of serious side effects. So far the safety and efficacy profile of ocrelizumab in MS patients is only described under controlled clinical trial conditions over a mid-term observation period and the present study is designed to collect long-term safety and effectiveness data of ocrelizumab in the real world setting.

Objectives

The primary objective for this study is as follows:

- to assess the long-term safety, with special focus on the occurrence and characterization of uncommon AEs in patients with MS newly exposed to ocrelizumab

The secondary objectives for this study are as follows:

- to estimate long-term effectiveness of ocrelizumab, i.e. treatment success (no clinical disease activity measured by relapse and disease progression and no treatment discontinuation due to adverse events [excluding pregnancies] and lack of effectiveness) in patients with MS newly exposed to ocrelizumab

- to estimate the incidence of serious infections and malignancies as well as malignancy related mortality rate in patients with MS newly exposed to ocrelizumab

Study Design

CONFIDENCE is a prospective, multicenter, non-interventional, long-term study collecting primary data in RMS and PPMS patients newly treated with ocrelizumab in routine clinical practice. To provide robust evidence on the safety and effectiveness

profile of ocrelizumab, data from 3000 MS patients from approx. 250 neurological centers and practices in Germany are planned to be included. At least 60% of the study population will be females. According to routine practice and as recommended by the German Society of Neurology (DGN Guideline 2015), visits are expected to be documented every 6 months in the main study period up to 10 years, once the initial dose of ocrelizumab has been administered to the patient.

Description of Study

The present study comprises an initial recruitment period of 30 months – which is anticipated to start in the first quarter 2018 – and will be followed by an observation period of at least 7.5 and up to 10 years maximum. Follow-up for the whole period is planned for all study participants, regardless of whether patients discontinue treatment with ocrelizumab or develop any malignancy.

Studied Medicinal Product

Ocrelizumab is a clear to slightly opalescent, colorless to pale brown solution. It is provided as concentrate in vials containing 300 mg in 10 mL, i.e. 30mg/mL, which is diluted with a 0.9% sodium chloride solution to a final drug concentration of 1.2 mg/mL for intravenous infusion. 30 to 60 minutes prior to each ocrelizumab infusion 100 mg intravenous methylprednisolone or equivalent and an antihistamine must be administered to reduce the frequency and severity of infusion-related reactions.

The initial 600 mg dose is administered as two separate intravenous infusions of 300 mg in 250 mL at a rate of 30 mL/hour; followed 2 weeks later by a second 300 mg infusion. The rate can be increased in 30 mL/hour increments every 30 minutes to a maximum of 180 mL/hour. Each of the initial infusions should be given over approximately 2.5 hours.

Subsequent doses of ocrelizumab thereafter are administered as a single 600 mg in 500 mL intravenous infusion every 6 months. The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose at a rate of 40 mL/hour for 30 minutes, which can be increased in 40 mL/hour increments every 30 minutes to a maximum of 200 mL/hour. Each of the subsequent infusions should be given over approximately 3.5 hours.

Patients should be monitored during the infusion and for at least one hour after the completion of the infusion. A minimum interval of 5 months should be maintained between each dose of ocrelizumab.

Population

The decision of the treating physician to prescribe ocrelizumab must have been made for the patients beforehand and independent of participation 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 prior to enrollment) according to the local label

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

- active participation in other interventional and non-interventional studies investigating disease modifying therapies (DMTs) for MS

Variables

Only variables obtained according to routine clinical practice and follow objectives can and should be documented in this study.

Primary Safety Outcome Measures

The primary outcome measure for this study is as follows:

- incidence and type of uncommon AEs (i.e. AEs with an incidence rate of at least 0.1% [1 out of 1000 patients] at least once) and death with primary and underlying causes in patients with MS newly exposed to ocrelizumab

Secondary Outcome Measures

The secondary objectives for this study are as follows:

- long-term effectiveness
    - treatment success (proportion of patients with no clinical disease activity measured by relapse and disease progression and no treatment discontinuation due to adverse events [excluding pregnancies] and lack of effectiveness)
    - proportions of patients with relapses
    - proportions of patients with confirmed disability progression (CDP)
    - time to onset of CDP
    - time to onset of confirmed disability improvement (CDI)
    - Patient reported Outcomes: treatment satisfaction
- other safety endpoints:
    - incidence of all adverse events

- incidence of serious infections
- incidence of malignancies
- mortality rate due to malignancies

Exploratory Outcome Measure

The exploratory outcome measures for this study are as follows:

- change from baseline in magnetic resonance imaging (MRI) lesions
- change from baseline in global impression on the disease course as reported by physician and patient using the 'Clinical Global Impression (CGI)' scale
- change from baseline in pharmacoeconomic outcomes as measured by 'Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis (WPAI:MS)'

Data Sources

Demographic and clinical data of participants are obtained from interviews or medical examinations and are collected by the treating neurologist. During regular routine visits additional questionnaires on patient-reported outcomes are completed by participants to substantiate the data collected on safety and efficacy of ocrelizumab collected during this study. The completion of such questionnaires is not routine practice but is allowed according to local regulations (published by a joint notification of the two German higher federal authorities), if the content of the questionnaires is in scope of the routine practice. In case of malignancy the treating physician or oncologist will be asked to complete a malignancy questionnaire.

The degree of detail and completeness of data collected during this study depends on local clinical practice. Relevant data from patient notes and charts should be entered in the case report form as soon as they become available.

Study Size

The primary objective of this study is to investigate the occurrence of uncommon adverse events in MS patients receiving treatment with ocrelizumab over a maximum time period of 10 years. The sample size is thus planned to allow for the detection of adverse events with an incidence rate of at least 0.1% (1 out of 1000 patients) at least once with a probability of 95%. Applying the Poisson distribution model for uncommon events, this results in a total sample size of approximately 3000 patients. Taking into account that ocrelizumab is currently the only approved disease modifying medication for PPMS and the resulting unmet need in this population approximately 700-1000 are expected to be PPMS patients. Patient recruitment and observation will take place at approximately 250 centers.

Data Analysis

Detailed information will be given in the statistical analysis plan (SAP).

The safety analyses will be done for the safety analysis population, the effectiveness analyses will be done for the Full Analysis Set. All other analyses will be done for all enrolled patients.

Statistical analysis will be mainly based on descriptive methods. To check for potential channeling effects various time spans of patients enrolled will be analyzed.

Generally, all safety analyses will be presented separately for the MS types RMS and PPMS as well as pooled. Analyses of effectiveness will be prepared by MS type only.

The analysis of the primary endpoint will be done on the safety analysis population. Incidence rates of adverse events will be calculated on the basis of system organ class and preferred term of the Medical Dictionary for Regulatory Activities (MedDRA) and presented along with two-sided 95% confidence intervals (Clopper-Pearson). In addition time adjusted analyses will be done based on patient years.

All other data collected including data on effectiveness will be presented using descriptive statistics (mean, standard deviation, median, range and interquartile range, time to event) or absolute and relative frequencies depending on the type of variable.

Other Analyses

Subgroup Analyses

- Subgroup analyses for the primary and secondary endpoints will be performed according to SAP and will comprise:
    - EDSS at baseline
    - By pre-treatment
    - Age
    - Gender (male vs. female)

Interim Analyses

Annual interim analyses are planned starting when 1-year data of at least 500 patients are available.

Interim analysis reports will include all analyses planned for all endpoints. In absence of hypothesis testing, α levels will not be adjusted for multiplicity.

Milestones

Start Date of Study:

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database. The planned

start date is first quarter 2018. 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 from which the last data collected from the last subject is recorded in the study database. The planned end of study date is estimated for the second quarter 2028, depending on the date of last patient last visit.

Length of Study

This study will last 10 years.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by Roche or designee.

Protocol amendments will be submitted to the Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: none.

5. MILESTONES

Study milestones are given in the following table.

Milestone	Planned Date
Registration of protocol in the EU PAS register	Q1 2018
Start of data collection	Q1 2018
End of data collection	Q2 2028
Annual Interim reports starting when 1-year data of at least 500 patients are available	expected Q4 2019
Final report of study results	Q2 2029
Registration of the results in the EU PAS register	Q4 2029

EU: European Union; PAS: post-authorization study; Q: quarter

6. RATIONALE AND BACKGROUND

6.1 STUDY RATIONALE

Multiple sclerosis (MS) is a chronic, inflammatory and demyelinating disease of the central nervous system (CNS) that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, the prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 respectively) (MSIF 2013). MS is commonly diagnosed between 20 to 40 years of age (Tullman 2013). Overall, women are affected approximately twice as often as men, except in individuals with the primary progressive form of the disease, where there is no gender prevalence difference (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 irreversible worsening neurologic disability either with or without occasional superimposed relapses (relapsing or non-relapsing secondary progressive MS [SPMS]). Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression (Tullman 2013).

Primary progressive MS (PPMS) is a less common form of MS, accounting for approximately 10% of all cases (approximately 40,000 individuals in the United States). 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).

To date, MS cannot be cured and requires a lifelong therapy. Disease modifying therapies (DMTs) have been shown to reduce the number of relapses, to slow progression of disease and thus delay disability in RRMS (DGN Guideline 2015). In contrast, PPMS does not respond to standard DMT treatment. For information on the condition under observation please refer to the most recent version of the SPC.

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 all measurable parameter of clinical and subclinical disease activity, including relapses, disability progression, in addition to an impact on magnetic resonance imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss.

The objective of this study is to collect real-world data on the long-term safety and effectiveness of ocrelizumab in MS patients newly exposed to this substance.

For information on ocrelizumab please refer to the most recent version of the SPC.

6.2 STUDY BACKGROUND

OCREVUS® (ocrelizumab) was approved by the United States (US) Food and Drug Administration (FDA) on March 28, 2017, as first medication for the treatment of adult patients with relapsing forms of MS (RMS) as well as PPMS (Genentech Inc., 2017). In

clinical studies ocrelizumab has demonstrated a favorable benefit/risk profile in RMS and PPMS patients (Hauser et al. 2017; Montalban et al. 2017).

The 96-week, phase 3 OPERA I & II trials reached all relevant clinical endpoints and ocrelizumab demonstrated consistent efficacy in the overall population of RMS patients. Compared with the active comparator, interferon beta-1a, ocrelizumab was associated with a significantly lower annualized relapse rate, a significantly reduced percentage of patients with disability progression confirmed at 12 and 24 weeks (both in the pre-specified pooled analysis and in each of the two phase 3 trials separately) and with an increased percentage of patients with disability improvement confirmed at 12 weeks. These findings were supported by a significantly greater suppression of brain lesions (Hauser et al. 2017).

In patients with PPMS, the phase 3 ORATORIO study demonstrated superior efficacy of ocrelizumab versus placebo with respect to the risk of confirmed disability progression at 12 and 24 weeks, ambulation speed as assessed by the timed 25-foot walk, change in the total volume of brain lesions on T2-weighted images, and change in brain volume (Montalban et al., 2017).

Overall, ocrelizumab demonstrated a favorable safety profile in RMS and PPMS patients 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]).

In the pivotal ocrelizumab trials eight deaths occurred (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). The proportion of patients experiencing a serious adverse event (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]), In controlled studies, the pooled overall incidence of a first neoplasm among patients with MS who were treated with ocrelizumab (Phase II study, OPERA I & 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).

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

While the pivotal studies OPERA I & II and ORATORIO established the safety and efficacy of ocrelizumab, data are needed to confirm the safety and efficacy of ocrelizumab over a long treatment duration and, importantly, in a clinical practice setting.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

Long-term use of highly effective therapies for the treatment of MS has been associated with the occurrence of serious side effects. So, a highly effective drug with a favorable safety profile is still needed to further improve overall patient outcomes. The safety and efficacy profile of ocrelizumab in MS patients is so far only described under study conditions in a highly selected patient population. The present study is designed to confirm safety and effectiveness of ocrelizumab in the real world setting over a long period of time, i.e. in a diverse patient population without additional inclusion and exclusion criteria besides the requirements of the local label.

7.2 OBJECTIVES

The primary objective for this study is as follows:

- to assess the long-term safety, with special focus on the occurrence and characterization of uncommon AEs in patients with MS newly exposed to ocrelizumab

The secondary objectives for this study are as follows:

- to estimate long-term effectiveness of ocrelizumab, i.e. treatment success (no clinical disease activity measured by relapse and disease progression and no treatment discontinuation due to adverse events [excluding pregnancies] and lack of effectiveness) in patients with MS newly exposed to ocrelizumab
- to estimate the incidence of serious infections and malignancies, as well as malignancy related mortality rate in patients with MS newly exposed to ocrelizumab

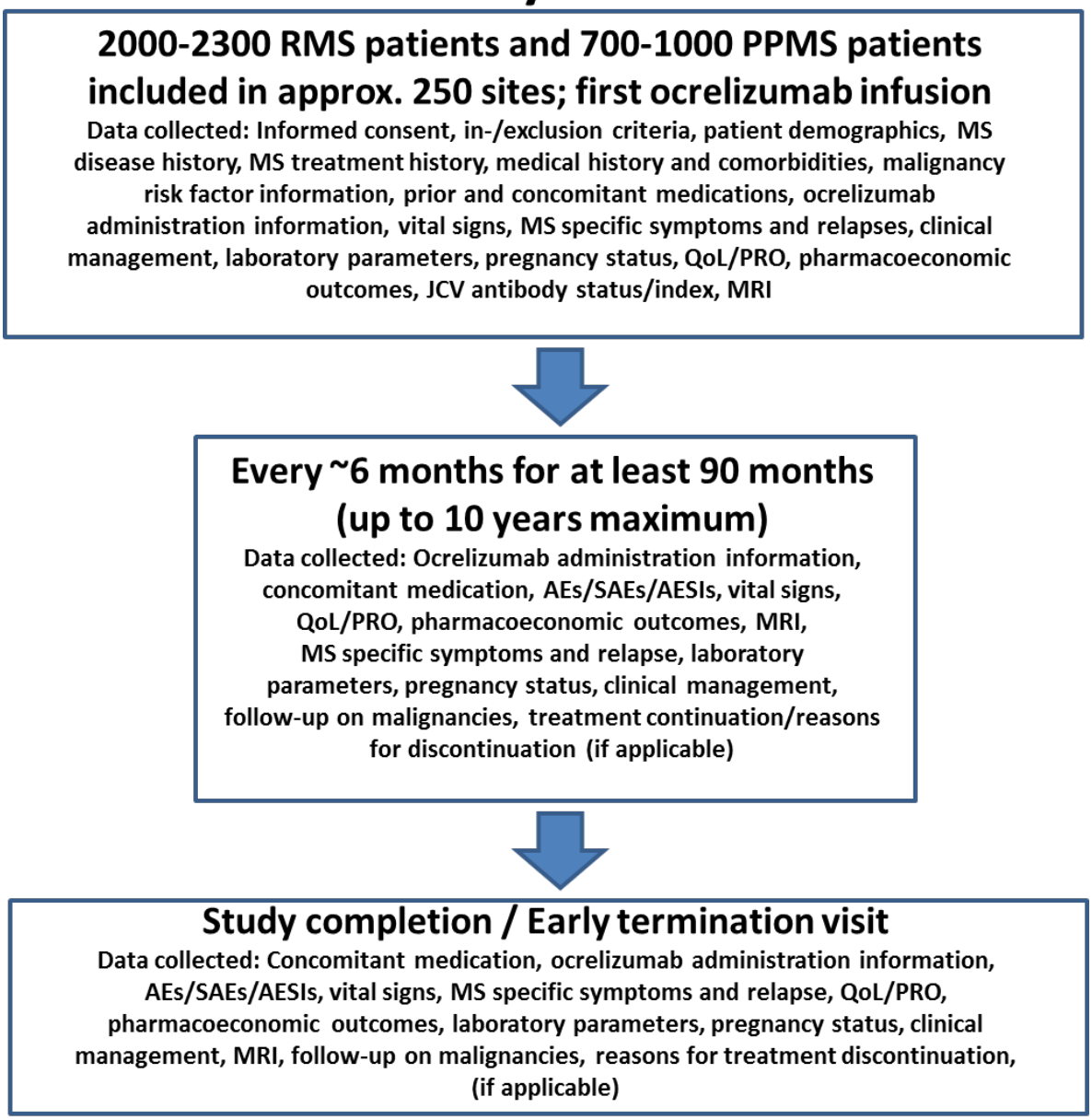
8. RESEARCH METHODS

8.1 STUDY DESIGN

CONFIDENCE is a prospective, multicenter, non-interventional, long-term study collecting primary data in RMS and PPMS patients newly treated with ocrelizumab in routine clinical practice. To provide robust evidence on the safety and effectiveness profile of ocrelizumab in real-world conditions, data from 3000 MS patients from approximately 250 neurological centers and practices in Germany are planned to be included. At least 60% of the study population will be females. According to routine practice and as recommended by the German Society of Neurology (DGN Guideline 2015), visits are expected to be documented every 6 months in the main study period up to 10 years, after the initial infusions have been administered to the patient.

CONFIDENCE comprises an initial recruitment period of 30 months – which is anticipated to start in the first quarter 2018 – and will be followed by an observation period. Depending on the time point of study inclusion (i.e. start of ocrelizumab) each patient will be observed for a total duration of at least 7.5 and up to 10 years maximum, or until death / withdrawal of consent / loss to follow-up. Follow-up during the whole period is planned for all study participants, regardless of whether patients discontinue treatment with ocrelizumab or have a malignancy diagnosis. Data from CONFIDENCE will also be included in two global PAS studies (BA39730 & BA39731).

Study Flow



Start Date of Study:

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database.

End of Study:

The end of the study will be the date from which the last data collected from the last subject is recorded in the study database. A data collection overview is provided in Table 1 in section 8.4.2.

8.1.1 Recruitment and Retention Efforts

Study enrollment will be monitored closely and 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 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 electronic case report form (eCRF) design 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
- Engaging healthcare providers (HCPs) with a good track record for both enrollment and retention of patients
- Promote HCP engagement through regular registry updates including best practice guidance and scientific exchanges
- Updating contact information at each patient encounter
- Close monitoring of data collection throughout the study
- Collect informed consent for continuous patient follow-up, even after leaving the initially associated study site

8.1.2 Rationale for Study Design

Data collected from clinical studies with ocrelizumab provide a sound body of evidence on its efficacy and safety in the treatment of RMS and PPMS. Although randomized controlled trials (RCTs) are the 'gold standard' for generating evidence of these data, enrolment criteria, short observation periods, and low patient numbers limit relevance to standard clinical practice.

Data on the utilization and the treatment outcomes of ocrelizumab under clinical practice conditions in a large, unselected patient population still need to be elicited to obtain an overview not only on the incidence of expected AEs but also of uncommon and unexpected AEs. Therefore, only a study performed in a real life setting can help fill this knowledge gap between clinical trials and clinical practice.

8.2 SETTING

8.2.1 Centers

This study will be conducted at approximately 250 centers specialized in MS covering all regions of Germany.

8.2.2 Study Population

This study will enroll patients with MS from the post-marketing setting who have initiated treatment with ocrelizumab no more than 30 days prior to baseline visit. The decision of the treating physician to prescribe ocrelizumab must have been made for the patients beforehand and independent of participation 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 prior to enrollment) according to the local label

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

- active participation in other interventional and non-interventional studies investigating DMTs for MS

Patients receiving treatment for MS with Ocrelizumab (OCREVUS®) according to standard of care and in line with the current summary of product characteristics (SPC) / local labeling and who have no contraindication to ocrelizumab therapy as per the local label are eligible for observation in this study if written informed consent is provided.

Enrollment of patients will be conducted to ensure 60% of the study population is female in order to adequately power breast cancer event rates in the global PAS studies (BA39730 & BA39731). 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.

8.2.3 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 their duration (start/stop dates)
- All other prior and concomitant immunomodulatory and immunosuppressive treatments including their duration (start/stop dates)
- Other previous and ongoing medications: from 3 months prior to enrollment only

8.2.4 Dosage, Administration, and Compliance

Dosing and treatment duration of ocrelizumab collected as parts of this non-interventional study are at the discretion of the physician in accordance with local clinical practice and local labeling.

8.3 VARIABLES

8.3.1 Primary Safety Outcome Measures

The primary outcome measure for this study is as follows:

- incidence and type of uncommon AEs (i.e. AEs with an incidence rate of at least 0.1% [1 out of 1000 patients] at least once) and death with primary and underlying causes in patients with MS newly exposed to ocrelizumab

8.3.2 Secondary Outcome Measures

The secondary outcome measures for this study are as follows:

- long-term effectiveness
    - treatment success (proportion of patients with no clinical disease activity measured by relapse and disease progression and no treatment discontinuation due to adverse events [excluding pregnancies] and lack of effectiveness)
    - proportion of patients with relapses
    - proportion of patients with confirmed disability progression (CDP)
    - time to onset of CDP
    - time to onset of confirmed disability improvement (CDI)
    - Patient reported Outcomes: treatment satisfaction
- other safety endpoints:
    - incidence of all adverse events
    - incidence of serious infections
    - incidence of malignancies
    - mortality rate due to malignancies

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- change from baseline in magnetic resonance imaging (MRI) lesions
- change from baseline in global impression on the disease course as reported by physician and patient using the ‘Clinical Global Impression (CGI)’ scale

- change from baseline in pharmacoeconomic outcomes as measured by 'Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis (WPAI:MS)'

8.4 DATA SOURCES

8.4.1 Collection of Data on the electronic CRF (eCRF)

Patients' data will be recorded on electronic case report forms (eCRFs). The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the eCRF as soon as they become available.

8.4.2 Data Collected during the Observation Period

During therapy with ocrelizumab, laboratory assessments are expected to be routinely performed in accordance with current guidelines and local standard of care. In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessments after treatment. When performed during the observational period, available results from the range of assessments described below will be documented on the eCRF. Most data will be documented at baseline and approximately every six months according to standard of care. 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.

All AEs occurring during the observational period will be reported. In addition, laboratory parameters (blood cell count, immunoglobulins, liver enzymes, and renal status), vital signs and weight will be recorded as available at baseline and every six months.

Effectiveness of treatment will be assessed via MS specific symptoms, relapses, and Expanded Disability Status Scale (EDSS) at baseline and approximately every six months and via MRI if available. Patient reported outcomes (PRO) regarding quality of life (QoL) and pharmacoeconomic outcomes will be collected at baseline and every six months or less frequently via questionnaires. Although the completion of such questionnaires is not routine practice it is allowed according to local regulations.

The following data will be collected during the study, as part of the local routine clinical practice:

Baseline (Study enrollment):

- Documentation of written informed consent
- Patient demographic information,
- Weight and height
- Medical history and comorbidities (including significant medical and surgical history, previous malignancies and precancerous lesions)
- Vital signs (blood pressure [BP], heart rate [HR], body temperature)

- Ocrelizumab administration information (e.g., start date, dose, dosing frequency)
- Any malignancy risk factor information available:
    - Tobacco use history
    - Alcohol use history
    - Family disease history, including genetic testing (e.g. BRCA1 and 2), if available
    - Personal history of malignancy
    - 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 and treatment history
    - Date of MS symptoms onset and date of MS diagnosis
    - Type of MS
    - MS relapse history
    - All previous treatments and therapies for MS, including their duration (start/stop dates)
    - All other prior and concomitant immunomodulatory and immunosuppressive treatments including their duration (start/stop dates)
    - MS status at initiation with ocrelizumab, including most recent Expanded Disability Status Scale (EDSS) score, if available
- Any other prior and concomitant medications from 3 months prior to enrollment
- Pregnancy status, if applicable (patient-reported, female patients)
- Laboratory parameters, if available:
    - Blood cell count (red blood cell count [RBC], hemoglobin, hematocrit, absolute and differential white blood cell count [WBC], absolute neutrophil count [ANC], quantitative platelet count)
    - Immnunoglobuline levels (IgG, IgM, IgA)
    - Liver enzymes (alanine transaminase [ALT], aspartate transaminase [AST], gamma-glutamyl transpeptidase [gamma-GT])
    - Renal status (creatinine, blood urea nitrogen [BUN], urinalysis)
    - Clinical chemistry (alkaline phosphatase, amylase, total bilirubin, urea, uric acid, random glucose, potassium, sodium)
    - Flow cytometry (B-cell depletion and recovery [CD19+] and T-cell counts [CD3+, CD4+, CD8+])
    - Viral serology and detection (Hepatitis B, Hepatitis C, HIV)
- QoL / PRO:

  - Clinical Global Impression (CGI)
  - Treatment Satisfaction Questionnaire for Medication (TSQM1.4)
  - Multiple Sclerosis Impact Scale (MSIS-29 v2)
  - Symbol Digit Modality Test (SDMT)
- Clinical management questions:
  - Gynecological consultation
  - Breast check
  - Dermatological check
- Malignancy/cancer detection tests (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)
- Pharmacoeconomic outcomes:
  - Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis (WPAI:MS)
- JCV antibody status / index
- Most recent MRI results, if available

Follow-up after study enrollment (anticipated every ~6 months):

- Vital signs (BP, HR, body temperature) and weight
- Laboratory parameters, if available:
  - Blood cell count (RBC, hemoglobin, hematocrit, absolute and differential WBC, ANC, quantitative platelet count)
  - Immunoglobuline levels (IgG, IgM, IgA)
  - Liver enzymes (ALT, AST, gamma-GT
  - Renal status (creatinine, BUN, urinalysis)
  - Clinical chemistry (alkaline phosphatase, amylase, total bilirubin, urea, uric acid, random glucose, potassium, sodium)
  - Flow cytometry (B-cell depletion and recovery [CD19+] and T-cell counts [CD3+, CD4+, CD8+])
- Continuation of therapy or reason for discontinuation, if applicable
- Concomitant medications
- MS specific symptoms and treatment, relapses:
  - MS relapse during the treatment period (start/end dates)
  - Most recent EDSS score since the last encounter, if available
  - Most recent MRI results since the last encounter, if available
  - MS treatment changes and rationale

- Clinical management questions during study:
    - Gynecological consultation
    - Breast check
    - Dermatological check
    - Malignancy/cancer detection tests (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)
- Pregnancy status, if applicable (patient-reported, female patients)
- Safety assessments:
    - all AEs
    - SAEs
    - pregnancies
    - any malignancies, including but not limited to MedDRA Standardized MedDRA Queries (SMQ) of malignant or unspecified tumors, and non-melanoma skin cancers (NMSCs)
- Malignancy information, if applicable (questionnaire regarding in-depth malignancy information will be solicited from the patient's treating physician or oncologist [only collected if a malignancy is identified]), including, but not limited to:
        - Cancer type
        - Diagnosis date
        - Location of primary tumor
        - Tumor grade
        - Stage at diagnosis
        - Action taken with ocrelizumab therapy at the point of diagnosis
    - AEs of special interest (AESIs):
        - 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 3).
        - Suspected transmission of an infectious agent by the study medicine (STIAMP)
    - Death information, if applicable (e.g., date of death, primary and underlying causes of death as entered for the AE)

- Ocrelizumab administration information (e.g., dates of administration [stop and re-start dates, if applicable], dose, dosing frequency)
- QoL / PRO:
        - Clinical Global Impression (CGI)
        - Treatment Satisfaction Questionnaire for Medication (TSQM1.4)

  - Multiple Sclerosis Impact Scale (MSIS-29 v2)
  - Symbol Digit Modality Test (SDMT)
- Pharmacoeconomic outcomes:
  - Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis (WPAI:MS)
- MRI, if available

At time of study completion or withdrawal from the study, if applicable:

- Ocrelizumab administration information (e.g., dates of administration [stop and re-start dates, if applicable], dose, dosing frequency, reason for discontinuation)
- Vital signs (BP, HR, body temperature)
- Laboratory parameters:
  - Blood cell count (RBC, hemoglobin, hematocrit, absolute and differential WBC, ANC, quantitative platelet count)
  - Immunoglobuline levels (IgG, IgM, IgA)
  - Liver enzymes (ALT, AST, gamma-GT)
  - Renal status (creatinine, BUN, unrinalysis)
  - Clinical chemistry (alkaline phosphatase, amylase, total bilirubin, urea, uric acid, random glucose, potassium, sodium)
  - Flow cytometry (B-cell depletion and recovery [CD19+] and T-cell counts [CD3+, CD4+, CD8+])
- Concomitant medications
- MS specific symptoms and treatment, relapses:
  - MS relapse during the treatment period (start/end dates)
  - Most recent EDSS score since the last encounter, if available
  - Most recent MRI results since the last encounter, if available
  - MS treatment changes and rationale
- Clinical management questions during study:
  - Gynecological consultation
  - Breast check
  - Dermatological check
  - Malignancy/cancer detection tests (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)
- Pregnancy status, if applicable (patient-reported, female patients)
- QoL / PRO:
  - Clinical Global Impression (CGI)

    - Treatment Satisfaction Questionnaire for Medication (TSQM1.4)
    - Multiple Sclerosis Impact Scale (MSIS-29 v2)
    - Symbol Digit Modality Test (SDMT)
- Pharmacoeconomic outcomes:
    - Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis (WPAI:MS)
- Safety assessments:
    - all AEs
    - SAEs
    - pregnancies
    - any malignancies, including but not limited to MedDRA SMQ of malignant or unspecified tumors, and NMSCs
    - Malignancy information, if applicable (questionnaire regarding in-depth malignancy information will be solicited from the patient's oncologist [only collected if a malignancy is identified]), including, but not limited to:
        - Cancer type
        - Diagnosis date
        - Location of primary tumor
        - Tumor grade
        - Stage at diagnosis
        - Action taken with ocrelizumab therapy at the point of diagnosis
    - AESIs (i.e., Hy's Law and STIAMP only)
    - Death information, if applicable (e.g., date of death, primary and underlying causes of death as entered for the AE)
- Reason for study withdrawal

Scheduled assessments for the study are presented in Table 1 below.

Table 1 Data Collection Overview (as per Standard of Care)

Data Collection [a]	Baseline [b] (Study Enrollment)	Data Collected every ~6 months	Data Collected at Study Completion/ Early Termination Visit
Informed consent [c]	x		
Inclusion/exclusion criteria	x		
Patient demographics, height and weight	x		
MS disease history [d]	x		
MS treatment history [e]	x		
Medical history and comorbidities [f]	x		
Malignancy risk factor information [g]	x		
JCV antibody status / index	x		
Prior and Concomitant medications [h]	x	x	x
Ocrelizumab administration information [i]	x	x	x
Vital signs	x	x	x
MS specific symptoms and treatment, relapses [j]		x	x
Clinical management [k]	x	x	x
Laboratory parameters [l]	x	x	x
Pregnancy status [m]	x	x	x
QoL / PRO [n]	x	x	x
Pharmacoeconomic outcomes [o]	x	x	x
MRI	x	x	x
All serious and non-serious AEs incl. AESIs and information on reasons for death, if applicable	whenever occur		
Pregnancies [p]	whenever occur during treatment with ocrelizumab and within 6 months after last administration		
Any malignancies (incl. NMSCs) and malignancy-specific questionnaire [q, s]	whenever occur		
Continuation of therapy or Reasons for treatment discontinuation [r, s]		x	x
Premature termination incl. reasons for withdrawal [s]		x	x

AE: adverse event; AESI: adverse event of special interest; MRI: magnetic resonance imaging; MS: multiple sclerosis; NMSC: non-melanoma skin cancer; SAE: serious adverse event; PRO: patient reported outcome; QoL: quality of life; STIAMP: suspected transmission of infection by a 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 prior to first ocrelizumab infusion

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

[d] Including MS date of diagnosis, type of MS, duration of MS, MS disease symptom history, relapse history, EDSS and MRI results (if available)

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

[f] Including significant medical and surgical history, previous malignancies and precancerous lesions

[g] 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

[h] Up to 3 months prior to enrollment

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

[j] Including MS relapse during treatment period, MS type changes, date of last administration of ocrelizumab (if applicable), MS treatment changes and rationale, most recent EDSS score since last encounter (if available), most recent MRI results since last encounter (if available)

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

[l] Blood cell count, immunoglobulins, liver enzymes, renal status, clinical chemistry, flow cytometry, viral serology

[m] Patient-reported, female patients

[n] TSQM1.4, MSIS-29v2, CGI, SDMT. Collected every six months

[o] WPAI:MS. Collected every six months

[p] AESIs are Hy's Law and STIAMP only

[q] Questionnaire regarding in-depth malignancy information will be solicited from the patient's oncologist (only collected if a malignancy is identified)

[r] Including number of attempts to contact patient, method of contact, and reasons for early termination (e.g., death, withdrawal of consent, lost to follow-up)

[s] If applicable

All assessments will be performed per standard of care (SoC). There are no mandated study visits, and data from any encounter with the neurologist during follow-up will be entered by clinicians (anticipated to occur every ~6 months). Follow-up is planned regardless of whether patients discontinue treatment with ocrelizumab. Please see Table 1 in section 8.4.2 for the data collection overview (as per standard of care with exception of questionnaires) during the treatment period.

8.4.3 Data Collected at Study Completion

All patients treated with at least one dose of ocrelizumab will be observed for the whole period of at least 7.5 and up to 10 years, regardless whether ocrelizumab treatment is discontinued during the course of the study. For patients who complete this observation

period either as scheduled or due to withdrawal, the study completion visit should be documented. Study completion encounter assessments should be completed if possible.

Please see Table 1 in section 8.4.2 for the data collection overview at the study completion visit, if available.

8.4.4 Safety Data Collection

Clinical AEs, serious and non-serious, as well as safety data other than AEs as described in Section 8.3 will be recorded in the eCRF during the observation period. For clinical AEs, serious and non-serious, physician's assessment of severity (according to Common Terminology Criteria for Adverse Events [CTCAE]) and relationship to therapy (i.e., related or unrelated) will be recorded as described in Appendix 3. Every CTCAE Grade 4 has to be reported as an SAE.

A pregnancy has to be reported as an AE within the eCRF.

AEs which are symptoms of the MS and expected during the course of the disease are not to be recorded in the eCRF.

Medical occurrences or symptoms of deterioration that are anticipated as part of MS or which are expected in the patient population studied should be recorded as an AE only if judged by the physician to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study.

Following the above rationale, all events that are captured in scope of the effectiveness objective, will not be considered as Adverse Events for this study:

- Hospitalizations following an MS relapse as long as the reason for hospitalization is to receive standard treatment with i.v. methylprednisolone, is not considered as SAE
- EDSS progression
- MRI activity (new T2 or Gadolinium enhancing lesion in spinal or cerebral MRI)MS signs and symptoms
- Disability
- events originating from patient questionnaires (e.g. fatigue, pain, cognition decline)

As health-related quality of life is a secondary endpoint of this study all MS-related AEs reported within the patient-reported outcome using the Treatment Satisfaction Questionnaire for Medication (TSQM1.4), Multiple Sclerosis Impact Scale (MSIS-29 v2), Clinical Global Impression (CGI), and Symbol Digit Modality Test (SDMT) should not be

documented per default within the eCRF. During site review of the PRO questionnaire data the physician/study personnel should screen for additional potential safety information out of scope of the questionnaires. If the criteria for an adverse event have been met this must be reported using the Adverse Event eCRF, if not already documented.

As the Pharmacoeconomic outcome 'Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis (WPAI:MS)' is an exploratory endpoint of this study all AEs reported within the scope of the questionnaire should not be documented per default within the eCRF, but only if not MS-related AEs have been added by the patient .

Abnormal laboratory parameters i.e. blood cell count (RBC, hemoglobin, hematocrit, WBC, platelets), immunoglobulins, liver enzymes (ALT, AST, gamma-GT), renal status (creatinine, BUN, unrinalysis), clinical chemistry, flow cytometry, viral serology should be only recorded in the eCRF as an AE when the treating physician considers the deviating laboratory parameters as medically significant.

8.5 STUDY SIZE

The primary objective of this study is to investigate the occurrence of uncommon adverse events in multiple sclerosis patients receiving treatment with ocrelizumab over a maximum time period of 10 years. The sample size is thus planned to allow for the detection of adverse events with an incidence rate of at least 0.1% (1 out of 1000 patients) at least once with a probability of 95%. Applying the Poisson distribution model for uncommon events, this results in a total sample size of approximately 3000 patients. Taking into account that ocrelizumab is currently the only approved disease modifying medication for PPMS and the resulting unmet need in this population approximately 700-1000 are expected to be PPMS patients. Patient recruitment and observation will take place at approximately 250 centers.

With the sample size of 3000 patients in this non-interventional study (NIS), following precision of the estimation of incidence rates in terms of 95% confidence intervals (Clopper-Pearson) can be obtained:

Table 2 95% Confidence Intervals for the Primary Safety Outcome Measures Based on 3000 Patients Receiving Ocrelizumab

Number of AE events/observed AE incidence	95% Confidence Interval (Clopper-Pearson) for the incidence rate
3 (0.1%)	[0.02%; 0.29%]
15 (0.5%)	[0.28%; 0.82%]
30 (1.0%)	[0.68%; 1.42%]

8.6 DATA MANAGEMENT

8.6.1 Data Quality Assurance

A CRO will be responsible for data management of this study, including quality checking of the data. All data will be collected via electronic data capture (EDC). Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

A Data Quality Review Plan will be produced that describes the quality check to be performed on the data.

Roche will perform oversight of the data management of this study, including approval of the CRO data management plans (including Data Quality Review Plan) and guidance. Data will be periodically transferred electronically from the CRO to Roche, and the CRO's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at MedicalSyn and records retention for the study data will be consistent with MedicalSyns standard procedures. MedicalSyn will comply with the Roche's procedures regarding archiving and record management.

8.6.2 Electronic Case Report Forms

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

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.

8.6.3 Source Data Documentation

Site Operations Representative will perform ongoing source data verification (SDV) as defined in the Trial 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, PROs, 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 Trial Monitoring Plan. The Trial Monitoring Plan defines which kind of source data – if available from routine clinical practice - 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 8.6.5.

To facilitate SDV, the physicians and institutions must provide Roche direct access to applicable source documents and reports for study-related monitoring, Roche audits, and EC review. The participating sites must also allow inspection by applicable health authorities.

8.7 DATA ANALYSIS

The statistical analysis will be described in a prospective statistical analysis plan. This plan will summarize all analyses in detail. Statistical analysis will be mainly based on descriptive methods. To check for potential channeling effects various time spans of patients enrolled will be analyzed. No hypothesis testing will be performed in this NIS. All analyses are regarded exploratory in nature.

All available data will be included in the analyses and will be summarized as far as possible. In general, there will be no substitution of missing data, i.e. missing data will not be replaced, missing data will be handled as 'missing' in the statistical evaluation ('observed cases analysis'). All data of patients who withdraw (e.g., who discontinued prematurely) will be documented anonymously and discussed, as necessary, in the clinical study report.

Generally, all safety analyses will be presented separately for the MS types RMS and PPMS patients as well as pooled. Analyses of effectiveness will be prepared by MS type only.

8.7.1 Safety Analyses

Analysis population

The core analysis population consists of all enrolled patients with data available.

The following analysis sets of patients will be used in this study:

- Enrolled Set (ES) defined as all patients recorded in the clinical database
- Safety Set (SS) defined as all patients in the ES treated with at least one dose of studied medicinal product
- Full Analysis Set (FAS) defined as all patients of the SS who had at least one documentation after start of the therapy

The safety analyses will be done for the safety analysis population, the effectiveness analyses will be done for the Full Analysis Set. All other analyses will be done for all enrolled patients.

Handling of deviations from the study protocol will be detailed in the SAP or a separate document. It is planned to organize a Data Review Meeting prior to database hard lock and database freeze for interim analyses. This preanalysis review should cover decisions concerning the exclusions of patients or data from the analysis sets.

Patient Disposition

Tables for disposition will be provided for the ES. A flowchart will show the final disposition of all patients in the different analysis sets according to the treatment cohorts together with a summary of the reasons for exclusion.

Baseline Characteristics and demographics

Characterization based on relevant baseline data (age, PPMS history, status at start of PPMS treatment) will be performed by means of descriptive statistics for continuous data or frequency tables for categorical data. Previous and concomitant diseases will be coded and presented according to the MedDRA terminology. Summary tables will be provided for the SS and the FAS.

Analysis of primary endpoint

The analysis of the primary endpoint will be done on the safety analysis population. Incidence rates of adverse events will be calculated on the basis of system organ class and preferred term of the Medical Dictionary for Regulatory Activities (MedDRA) and presented along with two-sided 95% confidence intervals (Clopper-Pearson). In addition time adjusted analyses will be done based on patient years.

The analysis of safety outcomes/variables is based on the incidence and severity (NCI CTCAE grading) of all AEs and SAEs reported.

Events rates per 100 patient years (of treatment exposure) will be determined along with corresponding 95% confidence intervals.

Other safety analyses

Other safety endpoints will be analyzed descriptively in a similar fashion.

Selected lab outcomes/variables will be presented graphically, e.g. boxplots of the median, interquartile range, extreme values and outliers over time or mean and additional corresponding confidence intervals over time, based on standard units (SI units).

8.7.2 Effectiveness Analyses

Effectiveness analyses will be conducted on the Full Analysis Set.

Descriptive analyses of the secondary endpoints will be performed. Secondary variables will be summarized. For continuous data, the mean, standard deviation (SD), median, range (min, max) and interquartile range (Q1, Q3) will be presented. Categorical data will be displayed by absolute and relative frequencies (percentages).

Secondary time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distributions and the median time-to-event. The time to endpoint will be defined as an interval between the date of enrolment (date of first visit) and date of first occurrence of the event. For patients who are event free, the censoring time will be calculated as a time interval between date of enrolment and the patient`s final contact with available data concerning the event. The estimates and graphical presentation will be performed via Kaplan-Meier approach.

Further analyses will be performed to investigate the validity of results in this non-interventional study, e.g. time-dependent confounding, informative censoring, informative treatment changes/discontinuations, heterogeneity of results, and how to handle missing data. These will be described in the SAP.

Corresponding 95% confidence intervals will be provided, where appropriate.

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

8.7.3 Other analyses

Subgroup Analyses

- Subgroup analyses for the primary and secondary endpoints will be performed according to SAP and will comprise:
    - EDSS at baseline
    - By pre-treatment
    - Age
    - Gender (male vs. female)

Sensitivity analyses

In order to investigate the relationship between potential prognostic or risk factors and the main outcome, various exploratory analyses are imaginable. Further details will be given in the SAP.

8.7.4 Interim/Final Analysis and Timing of Analyses

Annual interim analyses are planned starting when 1-year data of at least 500 patients are available. The final analysis is planned after final database lock.

Interim analysis reports will include all analyses planned for all endpoints. In absence of hypothesis testing, α levels will not be adjusted for multiplicity.

8.8 QUALITY CONTROL

8.8.1 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, Informed Consent Forms, and documentation of EC and governmental approval/notification. 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.

8.8.2 Site Audits and Inspections

Site visits will 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.

8.8.3 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs and Informed Consent Forms, 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 procedures regarding archiving and record management.

8.8.4 Administrative Structure

Lead Scientific Responsible of this non-interventional study is Prof. Dr. Tjalf Ziemssen, University Clinic Dresden.

The study is conducted by the CRO *AMS* Advanced Medical Services GmbH.

8.9 LIMITATIONS OF THE RESEARCH METHOD

This study aims to evaluate the safety profile of ocrelizumab in patients with MS in a real-world setting.

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: Factors associated with treatment choice and also with any of the study outcomes of interest will be measured at baseline (study enrollment), and will be accounted for in multivariate analyses using standard regression-based covariate adjustments or appropriate causal inference methods, as described further in Section 8.7..

Residual confounding between the study population and comparators: Data analysis will examine the univariate distributions of key variables that could cause confounding (e.g., gender, age, comorbidities), and will be accounted for in multivariate analyses.

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 enrollment). Since patients will be enrolled at the time of ocrelizumab 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 of eCRFs at enrollment 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.

Recruitment of patients 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 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 potentially initiation of additional sites within participating countries, and/or expansion of the study into additional countries.

8.10 OTHER ASPECTS

None

9. PROTECTION OF HUMAN SUBJECTS

9.1 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 discontinuation of treatment with the ocrelizumab or withdrawal from the study may include, but are not limited to, the following:

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

9.1.1 Discontinuation from Treatment with Ocrelizumab

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. All patients regardless whether continuing or withdrawn from treatment with ocrelizumab will be followed-up by an observation period of at least 7.5 and up to 10 years maximum from study start.

The early termination visit should be completed for patients who discontinue study participation due to e.g. withdrawal of consent or death. The primary reason for treatment discontinuation should be documented on the appropriate eCRF page.

9.1.2 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.

9.1.3 Lost to Follow-up

For patients whose status is unclear because they fail to appear for study encounters without stating an intention to withdraw, the treating physician will contact the patient in order to assess the patient's interest in continuing study participation. 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.

In case of patients changing their treating physician they should continue the study at another participating study site if possible. For patients who change the treating physician to a non-participating site an attempt should be made to diminish the impact of patients being lost from the study when they switch clinical practices. A dedicated neurologist will try to contact the participants directly to collect safety data. This information will be added to the eCRFs. Continued patient consent will be required for this further follow-up.

9.1.4 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 Pharmacoepidemiological Practices (GPP) or any other pertinent local law or guideline

9.2 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 European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

9.3 INFORMED CONSENT

Roche’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, 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 Informed Consent Forms or any alternate Consent Forms proposed by the site (collectively, the “Consent Forms”) before EC submission. The final Consent Forms

approved by the EC must be provided to Roche for health authority submission purposes according to local requirements.

The Consent Forms 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), to be contacted in case of contact discontinuation to the study site, 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 Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms 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.

9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

In addition to the requirements for collecting and reporting all AEs, adverse events of special interest (AESI), and SAEs to Roche, physicians must comply with requirements for AE reporting to the local health authority and EC.

9.5 CONFIDENTIALITY

Roche maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any Roche location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (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 EC for each study site, as appropriate.

By signing the protocol, the participating physician commits to complying with all related applicable local laws and regulations, as well as any applicable EU regulations, such as the EU Data Privacy Act.

9.6 FINANCIAL DISCLOSURE

Physicians will provide Roche with sufficient, accurate financial information in accordance with local regulations to allow Roche to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Physicians are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient last visit [LPLV]).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

10.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

10.1.1 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 10.2.

Safety assessments will consist of monitoring and recording SAEs and non-serious AEs (including AESIs), 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.

10.1.1.1 Adverse Events

According to the International Conference of Harmonization (ICH), 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 medicinal product, whether or not considered related to the medicinal product

- 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 3
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to Roche) and Non-serious Adverse Events of Special Interest (AESI) and Other Non-serious Adverse Events

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 were more severe.)
- Requires or prolongs inpatient hospitalization (see Appendix 3.3.11)
- 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)
- All CTCAE Grade 4 are considered to be an SAE

The terms ’severe’ and ’serious’ are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Appendix 3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF (for detailed instructions, see Appendix 3).

Non-Serious Adverse Events of Special Interest

AEs of special interest for this study include the following:

- 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 3).

- 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.

Exemption of Specific Adverse Events from Collection

AEs which are symptoms of the MS and expected during the course of the disease are not to be recorded in the eCRF.

Medical occurrences or symptoms of deterioration that are anticipated as part of MS or which are expected in the patient population studied should be recorded as an AE only if judged by the physician to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study.

Following the above rationale, all events that are captured in scope of the effectiveness objective, will not be considered as Adverse Events for this study:

- Hospitalizations following an MS relapse as long as the reason for hospitalization is to receive standard treatment with i.v. methylprednisolone, is not considered as SAE
- EDSS progression
- MRI activity (new T2 or Gadolinium enhancing lesion in spinal or cerebral MRI)
- MS signs and symptoms
- Disability
- events originating from patient questionnaires (e.g. fatigue, pain, cognition decline)

As health-related quality of life is a secondary endpoint of this study all AEs reported within the patient-reported outcome using the Treatment Satisfaction Questionnaire for Medication (TSQM1.4), Multiple Sclerosis Impact Scale (MSIS-29 v2), Clinical Global Impression (CGI), and Symbol Digit Modality Test (SDMT) should not be documented per default within the eCRF. During site review of the PRO questionnaire data the physician/study personnel should screen for additional potential safety information out of scope of the questionnaires. If the criteria for an adverse event have been met this must be reported using the Adverse Event eCRF, if not already documented.

As the Pharmacoeconomic outcome 'Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis (WPAI:MS)' is an exploratory endpoint of this study all AEs reported within the scope of the questionnaire should not be documented per default within the eCRF, but only if not MS-related AEs have been added by the patient.

Deviating laboratory parameters for example: Blood cell count, RBC, hemoglobin, hematocrit, WBC, platelets, immunoglobulins, liver enzymes (ALT, AST, gamma-GT), renal status (creatinine, BUN, unrinalysis), clinical chemistry, flow cytometry, viral serology should only be recorded in the eCRF as an AE when the treating physician considers the deviating laboratory parameters as medical significant.

10.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is responsible for ensuring that all AEs collected as per protocol (see Section 10.1.1.1 for definition) are recorded in the AE section of the eCRF and reported to Roche in accordance with instructions provided in this section and in Section 10.1.3.

For each AE recorded in the AE section of the eCRF, the physician will make an assessment of seriousness (see Section 10.1.1.2), severity (see Appendix 3), and causality (see Appendix 3).

10.1.2.1 Adverse Event Reporting Period

Physicians will seek information on AEs at each patient contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and in the AE section of the eCRF.

Once the patient is enrolled in the study, AEs will be collected until the end of his or her observation period. After this period, the physician is not required to actively monitor patients for AEs but if the treating physician becomes aware of any related AEs to any medicinal product they should be notified to the competent authority in the Member State where the reactions occurred or to the marketing authorization holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

10.1.2.2 Procedures for Recording Adverse Events

Physicians should use correct medical terminology/concepts when recording AEs 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 3 for further specific instruction regarding:

- Infusion-Related Reactions
- Diagnosis versus signs and symptoms

- Adverse Events occurring secondary to other Adverse Events
- Persistent or recurrent Adverse Events
- 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 serious adverse events (SAEs) and reported to Roche immediately. In certain circumstances, however, suspected adverse reactions with fatal outcome may not be subject to expedited reporting. All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to Roche
- Pre-existing Medical Conditions
- Lack of Therapeutic Efficacy
- Hospitalization or Prolonged Hospitalization
- Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error
- Drug Interactions
- Quality Defects and Falsified Medicinal Products

10.1.3 Reporting Requirements from Physician to Roche

10.1.3.1 Immediate Reporting Requirements from 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
- 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 non-serious AEs of special interest, 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, please refer to Section 10.1.3.3.

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

10.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs, including follow-up reports, physicians must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety or the relevant marketing authorization holder (for non-Roche studied products) no more than 24 hours after learning of the to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

10.1.3.3 If EDC System is Temporarily Unavailable or not Used

In the event that the EDC system is temporarily unavailable, a completed paper reporting form should be faxed to the CRO immediately (i.e., no more than 24 hours after learning of the event) or within 30 days for non-serious AEs if not AEs of special interest, using the fax number provided to physicians.

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

10.1.3.4 Reporting Requirements for Pregnancies

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 six months after the last dose of medicine. 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 the CRO. Pregnancy should also be recorded as an AE on the eCRF. In addition, all pregnancies and their outcome should be reported in the Ocrelizumab Pregnancy Registry (Study WA40063), which is being conducted [in Germany and the US]. 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. 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 also be reported on the AE section of the eCRF.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche Drug Safety.

Abortions

Any abortion 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 immediately (i.e., no more than 24 hours after learning of the event; see Section 10.1.3.1).

Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to the medicine, should be classified as an SAE, recorded in the AE section of the eCRF, and reported to Roche immediately (i.e., no more than 24 hours after learning of the event; see Section 10.1.3.1).

10.1.3.5 Reporting Requirements for Adverse Events originating from Patient Reported Outcomes

As health-related quality of life is a secondary endpoint of this study all AEs reported within the patient-reported outcome using the Treatment Satisfaction Questionnaire for Medication (TSQM1.4), Multiple Sclerosis Impact Scale (MSIS-29 v2), Clinical Global Impression (CGI), and Symbol Digit Modality Test (SDMT) should not be documented per default within the eCRF. During site review of the PRO questionnaire data the physician/study personnel should screen for additional potential safety information out of scope of the questionnaires. If the criteria for an adverse event have been met this must be reported using the Adverse Event eCRF, if not already documented.

As the Pharmacoeconomic outcome 'Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis (WPAI:MS)' is an exploratory endpoint of this study all AEs reported within the scope of the questionnaire should not be documented per default within the eCRF, but only if not MS-related AEs have been added by the patient.

10.1.4 Follow-Up of Patients after Adverse Events

10.1.4.1 Physician Follow-Up

The physician should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the physician, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to studied medicinal product until a final outcome can be reported.

During the study period, resolution of AEs (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.

10.1.4.2 Roche Follow-Up

For all AEs, 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.

10.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED MEDICINAL PRODUCTS

Although adverse event 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 the marketing authorization holder of the suspected medicinal product, 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 adverse events (Special Situation Events):

- 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 suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

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. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a 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 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.

A publication plan will be prepared prior to data analysis.

12. REFERENCES

Coles AJ, Alastair D, Compston S et al. Alentuzumab vs. Interferon beta-1a in early multiple sclerosis. The CAMMS223 Trial Investigators. N Eng J Med 2008;359:1786-801

DGN Leitlinie zur Diagnose und Therapie der MS (DGN Guidelines for MS diagnosis and treatment). 21.08.2015

Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009 May;132(Pt 5):1175-89

Frischer JM, Weigand SD, Guo Y, et al. Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque. Ann Neurol. 2015 Nov;78(5):710-21

Genentech Inc. Ocrevus prescribing information. March 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761053lbl.pdf

Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017 Jan 19;376(3): 221-234

Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology 2014 Jul 15;83(3):278–286

Mehr SR and Zimmerman MP. Reviewing the unmet needs of patients with multiple sclerosis. Am Health Drug Benefits 2015;8(6):426-431

Miller DH and Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol 2007;6:903-12

Montalban, X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017 Jan 19;376(3):209-220

MSIF - Multiple Sclerosis International Federation: Atlas of MS 2013

OCREVUS™ SPC 3/2017

Tullman MJ: Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. Am J Manag Care. 2013 Feb;19(2 Suppl):S15-20

Ziemssen T, Stefano ND, Sormani MP, et al. Optimizing therapy early in multiple sclerosis: an evidence-based view. Mult Scler Relat Disord 2015;4:460–9

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

- List of contact details of responsible parties

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

Please see Table 1 **in section 8.**4.2**.**

Appendix 3
Methods for Assessing and Recording Adverse Events

3.1 Assessment of Severity of Adverse Events

3.2 Assessment of Causality of Adverse Events

3.3 Procedures for recording Adverse Events

Appendix 3.1 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. The table below will be used for assessing severity for AEs 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]

Note: Based on the NCI CTCAE (v4.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[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 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.1.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.1.

Appendix 3.2 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 AE is considered to be related to the study medicine, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study medicine
- Course of the event, considering especially the effects of dose reduction, discontinuation of study medicine, or reintroduction of study medicine (when applicable)
- Known association of the event with the study medicine or with similar treatments
- Known association of the event with the disease under study
- 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 each of the medicinal product.

Appendix 3.3 Procedures for recording Adverse Events

Appendix 3.3.1 Infusion-Related Reactions

AEs that occur during or within 24 hours after studied medicinal product administration should be captured as individual signs and symptoms in the AE section of the eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

Appendix 3.3.2 Diagnosis versus Signs and Symptoms

For AEs, other than infusion-related reactions (see Section 3.3.1) 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 AEs 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 3.3.3 Adverse Events Occurring Secondary to Other Events

In general, AEs 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 AE 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 AEs should be recorded separately in the AE section of the eCRF if it is unclear as to whether the events are associated.

Appendix 3.3.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. 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 AE 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 10.1.3.1 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 AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately in the AE section of the eCRF.

Appendix 3.3.5 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 recorded in the AE section of the eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the AE section of the eCRF, 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, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 3.3.4 for details on recording persistent AEs).

Appendix 3.3.6 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 recorded in the AE section of the eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 3.3.4 for details on recording persistent AEs).

Appendix 3.3.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 ´ the ULN) in combination with either an elevated total bilirubin (> 2 ´ 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 ´ ULN in combination with total bilirubin > 2 ´ the ULN
- Treatment-emergent ALT or AST > 3 ´ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the AE section of the eCRF (see Appendix 3.3.5)

and reported to Roche immediately (i.e., no more than 24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 10.1.3.1).

Appendix 3.3.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.1.2.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to Roche (see Section 10.1.3.1).

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 the 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 3.3.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit 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. 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 3.3.10 Lack of Therapeutic Efficacy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on relapses and EDSS criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

Appendix 3.3.11 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 10.1.1.2), except as outlined below.

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 3.3.12 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 as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).

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 3.3.13 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 as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).

Appendix 3.3.14 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 as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to Roche immediately (i.e., no more than 24 hours after learning of the event, see Section Section 10.1.3.1)

Appendix 3.3.15 Safety data other than Adverse Events

Safety data other than AEs (see section 8.3 Variables) should be recorded in an appropriate section of the eCRF and reviewed on an ongoing basis.