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:	6.0
AUTHORS:	Dr. [redacted] [redacted] PD Dr. [redacted] [redacted] Roche Pharma AG [redacted] Emil-Barell-Straße 1 79639 Grenzach-Wyhlen
EU PAS REGISTER NUMBER:	EUPAS22951
ACTIVE SUBSTANCE:	L04AA36 (ocrelizumab)
STUDIED MEDICINAL PRODUCTS:	Ocrelizumab (OCREVUS®) Alemtuzumab (Lemtrada®) Cladribine (Mavenclad®) Dimethyl fumarate (Tecfidera®) Fingolimod (Gilenya®) Natalizumab (Tysabri®) Teriflunomide (Aubagio®)
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
04-Jul-2024 05:16:24	Deputy EU QPPV	Tanrikulu, Yusuf (tanrikuy)
04-Jul-2024 08:51:41	Company Signatory	[redacted]

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ACTIVE SUBSTANCE:	L04AA36 (ocrelizumab)
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.
COUNTRY OF STUDY POPULATION:	Germany
MARKETING AUTHORIZATION HOLDER (MAH) OF OCRELIZUMAB:	Roche Registration GmbH (RRG) Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

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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:	6.0
EU PAS REGISTER NUMBER:	EUPAS22951
STUDIED MEDICINAL PRODUCTS:	Ocrelizumab (OCREVUS®) Alemtuzumab (Lemtrada®) Cladribine (Mavenclad®) Dimethyl fumarate (Tecfidera®) Fingolimod (Gilenya®) Natalizumab (Tysabri®) Teriflunomide (Aubagio®)
MARKETING AUTHORIZATION HOLDER (MAH) OF OCRELIZUMAB:	Roche Registration GmbH (RRG) Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

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

Prof. Dr. med. [redacted]

Treating Physician's Name (print)

DocuSigned by:
[redacted]

Treating Physician's Signature

05-Jul-2024

Date

Name des Unterzeichners: Prof. Dr. med. [redacted]
Signiergrund: Ich genehmige dieses Dokument
Signierzeit: 05-Jul-2024 | 12:12:44 AM PDT
B0BBFFA436A84D5A8EB85EE5327CA79B

Please return a copy of this form to the contact provided below. Please retain the signed original for your study files.

AMS Advanced Medical Services GmbH
Am Exerzierplatz 2, 68167 Mannheim
CONFIDENCE-eTMF@ams-europe.com
Fax: 0621 700 95 140

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BRCA	BReast CAncer
CI	Confidence Interval
CDI	Confirmed Disability Improvement
CDP	Confirmed Disability Progression
CGI	Clinical Global Impression
CNS	Central Nervous System
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DGN	Deutsche Gesellschaft für Neurologie (German Society of Neurology)
DMT	Disease Modifying Therapy
DRM	Data Review Meeting
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
Gd	Gadolinium
GGT, gamma-GT	Gamma-glutamyl Transpeptidase
GPP	Good Pharmacoepidemiological Practice
GVP	Good Pharmacovigilance Practices
HR	Heart Rate
HIV	Human Immunodeficiency Virus
ICH	International Conference of Harmonization
IgA/IgG/IgM	Immunoglobulin A / G / M
IR	Injection Reaction

IRR	Infusion Related Reaction
JCV	John Cunningham Virus
LPLV	Last Patient, Last Visit
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSIF	MS International Federation
MSIS-29 v1	Multiple Sclerosis Impact Scale 29 v1
NCI	National Cancer Institute
NIS	Non-interventional study
NMSC	Non-melanoma Skin Cancer
PAS(S)	Post-authorization Safety (Study)
PPMS	Primary Progressive Multiple Sclerosis
PRO	Patient Reported Outcomes
Q	Quarter
QoL	Quality of Life
RBC	Red Blood Cell
RCT	Randomized Clinical Trial
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
RWD	Real-world Data
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
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

Dr. [redacted]
Roche Pharma AG
[redacted]
Emil-Barell-Straße 1
79639 Grenzach-Wyhlen
[redacted]

PD Dr. [redacted]
Roche Pharma AG
[redacted]
Emil-Barell-Straße 1
79639 Grenzach-Wyhlen
[redacted]

Scientific Responsible

Dr. [redacted]
Roche Pharma AG
[redacted]
Emil-Barell-Straße 1
79639 Grenzach-Wyhlen
[redacted]

Coordinating Investigator

Prof. Dr. [redacted]
Universitätsklinikum Carl Gustav Carus
an der Technischen Universität Dresden
Zentrum für klinische Neurowissenschaften
Fetscherstr. 74
01307 Dresden

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:	5.0
DATE OF SYNOPSIS:	February 28 2022
EU PAS REGISTER NUMBER:	EUPAS22951
STUDIED MEDICINAL PRODUCTS:	Ocrelizumab (OCREVUS®) Alemtuzumab (Lemtrada®) Cladribine (Mavenclad®) Dimethyl fumarate (Tecfidera®) Fingolimod (Gilenya®) Natalizumab (Tysabri®) Teriflunomide (Aubagio®)
SCIENTIFIC RESPONSIBLE	Dr. [redacted]
MAIN AUTHORS:	Dr. [redacted] PD Dr. [redacted]
PHASE:	IV, non-interventional study
INDICATION:	Relapsing multiple sclerosis (RMS) Primary progressive multiple sclerosis (PPMS)
MARKETING AUTHORIZATION HOLDER OF OCRELIZUMAB:	Roche Registration GmbH (RRG) Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

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 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 PPMS. The safety profile of ocrelizumab was consistent between the RMS and PPMS studies. The proportions of patients with adverse events (AEs) or SAEswere 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 MS newly exposed to ocrelizumab (ocrelizumab cohort).

A second cohort of patients newly treated during the course of their MS therapy with alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide (other MS DMTs cohort) will be included in the study to enable the presentation of the collected data on ocrelizumab in the context of the safety profiles of other approved disease modifying MS therapies (MS DMTs). To correct for different prerequisites and minimize potential confounding factors resulting from label differences between ocrelizumab and other DMTs, history of relapse and MRI activity as well as the most recent EDSS will be collected.

Collected safety data from ocrelizumab and other studied MS DMTs will be included in the global ocrelizumab PAS-Studies (BA39730 & BA39731). In addition, real world effectiveness data will be collected over a long treatment duration to complement the efficacy data of ocrelizumab obtained in phase III studies.

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. 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 of ocrelizumab, with special focus on the occurrence and characterization of uncommon AEs in patients with MS newly exposed to ocrelizumab

The key secondary 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 selected MS disease modifying therapies (DMTs) other than ocrelizumab (i.e., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide)

Additional 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 AEs [excluding pregnancies] and lack of therapeutic effectiveness) in patients with MS newly exposed to ocrelizumab and criteria (identification/evaluation of reasons) for not reaching treatment success

- to estimate long-term effectiveness of other selected MS DMTs, i.e. treatment success (no clinical disease activity measured by relapse and disease progression and no treatment discontinuation due to AEs [excluding pregnancies] and lack of therapeutic effectiveness) in patients with MS newly exposed to alemtuzumab, cladribine, dimethyl fumarate, fingolimod; natalizumab, or teriflunomide and criteria (identification/evaluation of reasons) for not reaching treatment success

- to estimate the incidence of serious infections and malignancies as well as malignancy related mortality rate 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 alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide

Study Design

CONFIDENCE is a prospective, multicenter, non-interventional, long-term study collecting primary data in RMS and PPMS patients newly treated during their course of MS therapy with ocrelizumab, or other selected MS DMTs (i.e., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide), in routine clinical practice. To provide robust evidence on the safety and effectiveness profile of ocrelizumab, data from approximately 3000 MS patients treated with ocrelizumab and 767 MS patients treated with other selected MS DMTs from approximately 185 neurological centers and practices in Germany are planned to be included. Approximately 70% of each study cohort will be females. According to routine practice and as recommended by the German Society of Neurology data will be collected according to SoC and most recent data are expected to be documented every 6 months in the main study p

eriod up to 10 years, once the initial dose of ocrelizumab, or other selected MS DMTs, has been administered to the patient.

Description of Study

CONFIDENCE recruitment has started in April 2018 and will be closed in March 2022 (total recruitment time of 48 months). The study aims to recruit approximately 3000 MS patients treated with ocrelizumab and 767 MS patients treated with other selected MS DMTs. This 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 their current MS treatment or develop any malignancy.

Studied Medicinal Products

Dosing and treatment duration of ocrelizumab, alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide, collected as parts of this non-interventional study are at the discretion of the physician in accordance with local clinical practice and local labeling.

Population

The decision of the treating physician to prescribe ocrelizumab or other selected MS DMTs 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 for the first time during the course of their MS therapy with ocrelizumab (up to 30 days prior to or 60 days after study enrollment) according to the local label irrespective of the reason for starting ocrelizumab (ocrelizumab cohort)

OR

newly treated for the first time during the course of their MS therapy with a selected MS DMT other than ocrelizumab (i.e., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide, up to 30 days prior to or 60 days after study enrollment) according to the local label irrespective of the reason for starting a new MS DMT

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

- participation in other interventional studies investigating DMTs for MS
- patients who have received ocrelizumab or their new MS therapy with a selected MS DMT other than ocrelizumab more than 30 days prior to study entry date
- patients who have been previously treated with rituximab or any other anti-CD20 therapy for MS

Variables and Outcome Measures

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 of 0.1% to 1% [1 to 10 out of 1000 patients] or less) and death with primary and underlying causes in patients with MS newly exposed to ocrelizumab

Secondary Outcome Measures

The key secondary outcome measure for this study is as follows:

- incidence and type of uncommon AEs (i.e. AEs with an incidence of 0.2% to 1% [1 to 5 out of 500 patients] or less) and death with primary and underlying causes in patients with MS newly exposed to selected MS DMTs other than ocrelizumab

Additional 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 discontinuation of current treatment due to AEs [excluding pregnancies] and lack of therapeutic effectiveness) and proportion of patients not reaching treatment success and the proportion of underlying reasons
    - annualized relapse rate since start of treatment
    - proportion of patients with relapses since start of treatment
    - mean number of relapses per patients within the last 1, 2 and 3 year before start of treatment
    - change in EDSS from baseline
    - proportion of patients with CDP
    - time to onset of CDP
    - time to onset of CDI
    - PRO: treatment satisfaction (TSQM)), cognitive function (SDMT), and health related QoL (MSIS-29))
- other safety endpoints:
    - incidence of all AEs
    - incidence of serious infections
    - incidence of malignancies
    - incidence of mortality due to malignancies

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- number of Gd enhancing T1 lesions as detected by MRI
- number of T2 lesions as detected by MRI
- global impression on the disease course as reported by physician and patient using an adapted CGI scale (collected until protocol V_6.0 due to reduce the documentation burden):

  - severity score change from baseline
  - improvement score by descriptive statistics (mean, standard deviation)
- change from baseline in pharmacoeconomic outcomes as measured by '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 effectiveness of the current MS treatment. According to the guideline on GVP Annex I the completion of such questionnaires may be performed as normal clinical practice. Therefore, usage of PRO is considered non-interventional in this study.In case of malignancies available information on cancer (e.g., diagnosis date, tumor type and location, grade, stage, cancer treatment, hormone receptor status) will be collected and reported by the neurologist in the eCRF. For additional information the treating oncologist/pathologist will be contacted (see 8.3.4.).

In addition, data linkage with national and regional cancer registries will be explored to ensure identifying all malignancy cases in the study population.

Overall, 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 AEs in MS patients receiving treatment with ocrelizumab from study start over a maximum time period of 10 years. The sample size is thus planned to allow for the detection of AEs with an incidence 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, the aimed study sample size is 3000 ocrelizumab patients. This will result in a precision of the estimate of AEs with an incidence rate of 0.1% (1 out of 1000 patients) of 0.27%. This precision is based on a pre-defined two-sided alpha level of 5%. In addition, the precision will not exceed 0.76% if AEs are observed in up to 1% of the patients. Even for a sample size of 2800 ocrelizumab patients (conservatively estimated for the recruitment end) the precision will not exceed 3.74% for a worst case scenario of an incidence rate of 50.0%, which is deemed acceptable.

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.

A cohort of 767 patients newly treated for the first time during the course of their MS therapy with a selected MS DMT other than ocrelizumab will result in a precision of the estimate of AEs with an incidence rate of 0.2% (1 out of 500 patients) of 0.91%. The precision will not exceed 1.6% if AEs are observed in up to 1% of the patients.

Patient recruitment and observation will take place at approximately 185 centers.

Data Analysis

Detailed information will be given in the SAP.

Data of patients switching their treatment during the course of the study will be examined by analyzing effectiveness and safety variables for the following subsets:

- Set 1: Patients, who received during the whole course of the study ocrelizumab plus those patients having been switched from ocrelizumab to DMT until the treatment switch from ocrelizumab to DMT
- Set 2: Patients, who received during the whole course of the study DMT plus those patients having been switched from DMT to ocrelizumab until the treatment switch from DMT to ocrelizumab
- Set 3: Patients, starting with ocrelizumab treatment after their switch from DMT
- Set 4: Patients, starting with DMT treatment after their switch from ocrelizumab

Due to the long observation time of CONFIDENCE it is anticipated that there will be time frames where a patient does not fit into Set 1-4. For example, if a patient starts with ocrelizumab, switches to a selected other DMT and switches to ocrelizumab afterwards. The handling and analyses of these patients' data will be discussed in the DRMs.

Set 1 and Set 4 will be compared descriptively.

Patients switching to Ocrelizumab s.c.will be analyzed according to SAP.

Detailed information about handling of patients switching to other DMTs, not specified in this protocol, is given in the SAP.

The safety analyses will be done for the safety analysis population (defined in 8.7.1). The effectiveness analyses will be done for the Full Analysis Set (defined in 8.7.1). All other analyses will be done for all enrolled patients.

All analyses are regarded exploratory and will be done separately for the sets described above. All analyses will be performed for Set 1 to Set 4.

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

The analysis of the primary endpoint will be done on the safety analysis population. Incidence rates of AEs will be calculated on the basis of SOC and preferred term of the MedDRA and presented along with two-sided 95% CIs (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.

Generally, all safety analyses will be presented by MS treatment at enrolment, i.e. ocrelizumab cohort or pooled other selected MS DMTs cohort, and separately for the MS types RMS and PPMS as well as MS types pooled. In addition, for all safety endpoints time adjusted analyses will be done based on patient years. Analyses of effectiveness will be prepared by MS type for both cohorts.

If the sample sizes allow, further statistical analyses of the other DMT cohort may be performed by DMT in addition.

Other Analyses

The number/percentage of patients with a change in MS/RMS type at any time during the study will be summarized and the time to change in years will be calculated. The number/percentage of patients with relapses any time and per visit during study will be calculated. Methods of survival analysis (Kaplan-Meier summary and corresponding Kaplan-Meier plot) will be done. A logistic regression model will evaluate how far the probability for treatment success is influenced by the EDSS baseline score, age (continuous), gender, the categories based on patient informed consent date, MS type. Treatment exposure, the total dose per patient, and the number of patients still under treatment at each visit will be summarized as numeric variables. Additionally, the number of administrations per patient and the time between doses will be analyzed for all patients treated with ocrelizumab.

Subgroup Analyses

Subgroup analyses for all outcome measures will be performed according to SAP and will comprise:

- EDSS at baseline (0-3.5 / ≥4 for RMS, 0-5.5 / >5.5–6.5 / ≥7 for PPMS)
- By pre-treatment
- Age (≤55 / >55 years for RMS, ≤40 / 41-55 / >55 years for PPMS)
- Gender (male vs. female vs. undifferentiated)

Interim Analyses

Annual interim analyses are planned starting when 1-year data of at least 500 patients treated with ocrelizumab are available (ocrelizumab cohort). Analysis of the second cohort will be included when at least baseline data of 500 patients treated with other DMTs are available.

Interim analysis will include selected analyses and will be delivered in tables, listings and figures. The selection of analyses will be documented in the DRM minutes. No adjustment for multiplicity will be done.

The final analysis is planned after final database lock and will include all analyses planned for all endpoints and will be delivered in tables, listings and figures.

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 study started in April 2018. However, the exposure of interest might have started 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 will be 7.5 years after last patient enrollment and is estimated for the third Q 2029, depending on the date of last patient last visit.

Length of Study

This study will last approximately 11 years.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by Roche or designee.

Protocol amendments will be submitted to the ECand 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: see table below.

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
Protocol V2.0	January 2019	Sections 3, 4, 8 and 9	Inclusion of an additional cohort of patients newly treated with a selected MS DMT other than ocrelizumab. Detailing of data items to be collected and included in the analyses; Clarification of the validation workflow of malignancies diagnosis by the oncologist.	Feedback from the US FDA to the protocol for study BA39731
Protocol V3.0	September 2020	Title Page	MAH Contact Person updated to Dr. [redacted]	Change in Personnel.
		3. Synopsis - Secondary Objectives, 7.2 Objectives	Criteria for not reaching treatment success added to secondary objectives	
		3. Synopsis – Secondary outcome measures, 8.2.2 Secondary outcome measures, 10.1.2.2 Procedures for Recording Adverse Events	Correction of AE incidence rates Addition of proportion of patients not reaching treatment success and the proportion of underlying reasons Lack of effectiveness reworded with more detail to “lack of therapeutic effectiveness” Measurement of mean number of relapses now including one and two years prior to treatment start	

		3. Synopsis – Exploratory outcome measures, 8.2.3 Exploratory outcome measures	Correction regarding T1 and T2 lesions detected by MRI	
		3. Synopsis – Data Analysis, 8.6 Data Analysis	In addition, for all safety endpoints time adjusted analyses will be done based on patient years	
		3. Synopsis – Other Analysis, 8.6.3 Other Analyses	Clarification of analysis regarding treatment groups.	
		3. Synopsis – Subgroup analysis	All outcome measures will be performed for subgroup analyses Gender now including "undifferentiated"	
		3. Synopsis – Interim Analyses, 8.6.4 Interim/Final Analysis and Timing of Analyses	No report will be generated. Outputs will be delivered in the form of tables, listings and figures.	
		3. Synopsis – Study Design, Study Size, 8.1 Study Design, 8.1.1 Overview of Study Design, 8.1.3 Sites, 8.4 Study Size	Number of participating sites reduced from 250 to 185	
		3. Synopsis – Population, 8.1.4 Study Population	Exclusion criteria definition described in more detail – also patients excluded that have been treated previously with rituximab or any other anti-CD20 therapy for MS	To avoid a possible interference in analyzing the effects of ocrelizumab, at baseline patients newly or previously treated with drugs having a comparable mode of action are excluded from the study.
		3. Synopsis – Description of Study, End of Study, Length of Study, 5.	Recruitment period extended from 30 to 44 months End of study updated according to prolongated	Patient recruitment reduced

		Milestones, 8.1 Study Design	recruitment time to Q2 2029 Addition of actual dates for First Patient In (Start of Data collection) and First Analysis of Study Data including date of treatment visit of 500th patient	
		8.3.2 Data Collected during the Observation Period	Baseline Characteristic “Race” excluded	
		Table 1	Naming of Baseline Visit updated Footnote m: updated to current data collection in eCRF	
		8.6.1 Safety Analyses	Baseline Characteristics and demographics updated including current and previous DMTs, ethnicity and employment status	
		8.7.3 Retention of Records	Record retention requirements updated	
		9.3 Informed Consent	Updated wording regarding Patient informed consent	
		9.5 Confidentiality	Description of any foreseen further uses of personal data or biological material (if permitted)	
		10.3 Reporting of product complaints without adverse events	Clarification on reporting product complaints	
		Appendix 3.3.10	Renaming to Lack of therapeutic effectiveness	
		Appendix 3.3.11	Introduction of definition for lack of efficacy (drug ineffective)	
		Appendix 4-8	Insertion of the printed versions of the questionnaires	
Protocol V4.0	September 2021	Title Page	MAH Contact Person deleted	Due to change in personnel, contact

				person not named in person
		3. Synopsis – Study Design; 8.1 Study Design; 8.1.1 Overview of Study Design	Reduction of patient numbers enrolled for the internal comparator group (other DMT) from 1500 to 767	To reflect changes in routine clinical care and more recently available rates of cancer incidence and cancer mortality rates, age distribution of patients with MS and routine clinical practice during the period of the study
		3. Synopsis – Description of Study; 8.1 Study Design	Enrollment period aimed to recruit 3000 ocrevus and 767 other DMT patients – estimated at approximately 47 months	
		3. Synopsis – Study size; 8.4 Study Size		Correction of AE incidence rates due to reduction of enrolled patients in the internal comparator group
		3. Synopsis – Data analysis; 8.6 Data Analysis	Special considerations forpatients, who switched between treatment with ocrelizumab or a DMT in both directions more than one time	Due to the long observation time of CONFIDENCE it is anticipated that there will be patients with more than one treatment switch between ocrelizumab and a selected other DMT in both directions.
		8.6.1 Safety Analysis	Clarification of data lock and freeze process	
		3. Synopsis – Subgroup analysis; 8.6.3 Other Analysis	RMS subgroups changed from <40 / ≥40 years to ≤55 / >55 years	Alignment with age groups described in OPERA I and II pivotal trials
		3. Synopsis – Interim Analysis; 8.6.4 Interim/Final Analysis and Timing of Analyses	Distinction between interim and final analysis. Interim Analysis will allow a selection of planned analysis, which will be specified in the DRM Minutes. Final Analysis will include all analysis planned in the protocol.	

		Appendix 3.3.1	Infusion related reactions further specified by naming infusion of an other selected DMT	
Protocol V5.0	February 2022	3. Synopsis – Description of Study; 8.1 Study Design	First Patient In: April 2018, Last patient in: March 2022	
		3. Synopsis – Study Design; 8.1 Study Design; 8.1.1 Overview of Study Design	"Approximately" added as the aim of the study is to recruit 3000 MS patients treated with Ocrevus, but recruitment will be limited to March 2022.	Changed definition for the end of the recruitment (date instead of number of patients)
		3. Synopsis – Study Design; 8.1 Study Design	Change of wording for distribution female/male "at least" was changed to "approximately" 70% female patients	
		3. Synopsis – Data Sources; 8.3 Data Sources		The joint notification of the two German higher federal authorities is not valid anymore since 31.01.2022 so use of PROs is now referred to Good Pharmacovigilance Practice (GVP) Annex I.
		3. Synopsis – Study Size; 8.4 Study Size (incl. Table 3)	Study size calculations and precision to primary endpoint evaluated for 3000 and 2800 Ocrevus patients	Due to limitation of recruitment period.
		8.5.2 Electronic Case Report Forms	eCRF data can be requested by the physician to be archived with the study records.	
		8.7.3 Retention of Records	Clarification on archiving of eCRF data: only if applicable	
		Titel page	Author updated to Dr. [redacted]	Personell change
Protocol V6.0	June 2024	3. Synopsis	Updated scientific responsible and main authors to Dr. [redacted] Switch patients to Ocrevus s.c. will be	Personell change Introduction of Ocrevus s.c. Reduce burden of documentation for

			analyzed according to SAP Deletion of CGI	patient and physicians
		8.2.3 Exploratory Outcome Measures	Deletion of CGI	Reduce burden of documentation for patient and physicians
		8.3.4 Safety Data Collection	Inclusion and definition of injection reactions	Introduction of Ocrevus s.c.
		9.1.3 Lost to follow up	The handling of data from patients whose missed data collection periods is longer than 20 months will be described in the SAP.	possibility created to continue documenting for patients whose missed data collection periods is langer than 20 months
		10.1.1.1	Inclusion and definition of injection reactions	Introduction of Ocrevus s.c.
		Apendix 4	Deleted	Reduce burden of documentation for patients and physicians

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	03.04.2018
End of data collection	Q3 2029
Annual Interim reports starting when 1year data of at least 500 patients treated with ocrelizumab are available	01.04.2020 (treatment date of 500th patient: 06.09.2019)
Final report of study results	Q3 2030
Registration of the results in the EU PAS register	Q4 2030

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

6. RATIONALE AND BACKGROUND

6.1 STUDY RATIONALE

MS is a chronic, inflammatory and demyelinating disease of the CNS that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, the prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 respectively) (MSIF 2013). MS is commonly diagnosed between 20 to 40 years of age (Tullman 2013). Overall, women are affected approximately twice as often as men, except in individuals with the primary progressive form of the disease, where there is no gender 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 (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. 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 RMS. 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 MRI outcomes related to disease progression and reflective of neural tissue loss.

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

6.2 STUDY BACKGROUND

OCREVUS® (ocrelizumab) was approved by the United States (US) 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). The EMA approved ocrelizumab for the treatment of active RMS and early PPMS on January 08, 2018.

In 2024 ocrelizumab was approved by the EMA as a 920mg subcutaneous formulation, based on the phase Ib study OCARINA I and the phase III non-inferiority study OCARINA II.

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 prespecified 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 new 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 CDP 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 AEs (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 reported more herpes virus-associated infections (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%) than patients who received interferon β-1a or placebo. In RMS trials the overall percentage of patients reporting a serious infection was lower in ocrelizumab-treated patients compared to interferon β-1a-treated patients (1.3% vs. 2.9%), In PPMS trials the distribution of serious infections was similar (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 SAE 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 malignancy among MS patients 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.

Collected safety data will be included in the global ocrelizumab PAS-Studies (BA39730 & BA39731). In addition, real world effectiveness data will be collected to complement the efficacy data of ocrelizumab collected in phase III studies over a long treatment duration.

The dose selection and non-inferiority of OCR s.c. was evaluated in two studies. The dose finding Ib study OCARINA I aimed to select the appropriate OCR s.c. dose for use in the Phase III OCARINA II trial, based on safety, tolerability and PK data in people with RMS or PPMS. The study results supported the selected dose of 920 mg ocrelizumab s.c. to be evaluated in the Phase 3 OCARINA II study. The phase III study OCARINA II evaluated the PK, PD, safety, immunogenicity and radiological and clinical effects of OCR SC vs OCR IV in people with RMS or PPMS. The study achieved its primary objective of demonstrating non-inferiority of ocrelizumab SC 920 mg to ocrelizumab IV 600 mg with respect to AUCW1–12 while safety and clinical profiles remained comparable between OCR s.c. and i.v.

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 a diverse patient population in the real world setting over a long period of time.

7.2 OBJECTIVES

The primary objective for this study is as follows:

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

The key secondary 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 selected MS disease modifying therapies (DMTs) other than ocrelizumab (i.e., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide)

Additional 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 AEs [excluding pregnancies] and lack of therapeutic effectiveness) in patients with MS newly exposed to ocrelizumab and criteria for not reaching treatment success

- to estimate long-term effectiveness of other selected MS DMTs, i.e. treatment success (no clinical disease activity measured by relapse and disease progression and no treatment discontinuation due to AEs [excluding pregnancies] and lack of therapeutic effectiveness) in patients with MS newly exposed to alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide and criteria for not reaching treatment success

- to estimate the incidence of serious infections and malignancies, as well as malignancy related mortality rate 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 alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide

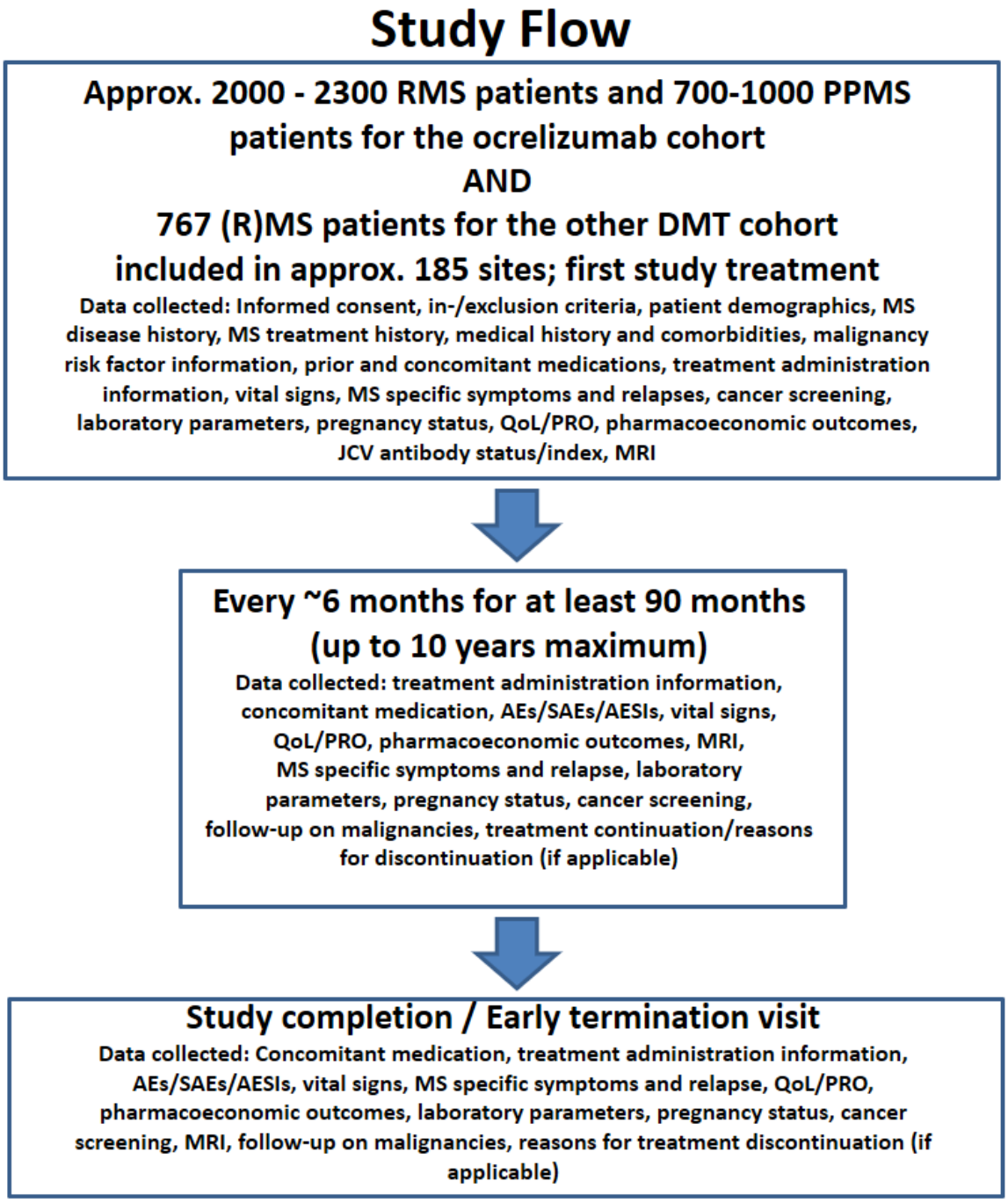
8. RESEARCH METHODS

8.1 STUDY DESIGN

CONFIDENCE is a prospective, multicenter, non-interventional, long-term study collecting primary data in RMS and PPMS patients newly treated during their course of MS therapy with ocrelizumab, or other selected MS DMTs (i.e., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide), in routine clinical practice. To provide robust evidence on the safety and effectiveness profile of ocrelizumab in real-world conditions, data from approximately 3000 MS patients treated with ocrelizumab and 767 MS patients treated with other selected MS DMTs, from approximately 185 neurological centers and practices in Germany are planned to be included. Approximately 70% of each study cohort will be females. This ratio will be ensured through monitoring reports, and by stopping enrollment of men if male quota is reached. According to routine practice and as recommended by the German Society of Neurology, data will be collected according to SoC and most recent data are expected to be documented every 6 months in the main study period up to 10 years, once the initial dose of ocrelizumab, or other selected MS DMTs, has been administered to the patient.

CONFIDENCE recruitment has started in April 2018 and will beclosed in March 2022 (total recruitment time of 48 months). The study aims to recruit approximately 3000 MS patients treated with ocrelizumab and 767 MS patients treated with other selected MS DMTs. Depending on the time point of study inclusion (i.e. start of a new MS DMT treatment) 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 their current MS treatment or have a malignancy diagnosis. Data from CONFIDENCE will be included in two global ocrelizumab PAS studies (BA39730 & BA39731).

8.1.1 Overview of Study Design



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 study started in April 2018. However, the exposure of interest might have started 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 will be 7.5 years after last patient enrollment and is estimated for the third Q 2029, depending on the date of last patient last visit. A data collection overview is provided in Table 1 in section 8.3.2.

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' at 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.

To avoid bias by site effects, sites will be encouraged to enroll patients into both treatment cohorts. The disposition of patients and distribution to treatment regimes should reflect as far as possible the general patient population of the participating sites to ensure the representativeness of the study population. Retention efforts to minimize loss to follow-up and missing data will include, but are not limited to:

- Judicious eCRFdesign 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 current MS DMT
- Engaging healthcare providers (HCPs) with a good track record for both enrollment and retention of patients
- Promote HCP engagement through regular newsletter regarding study updates including best practice guidance and scientific exchanges
- Informing patients about the rationale of the study and therefore importance of continued participation
- Updating contact information at each patient encounter
- Obtaining informed consent to contact the patient's primary care physician if patient is non-responsive
- Close monitoring of data collection throughout the study
- Collect informed consent for continuous patient follow-up, even after leaving the initially associated study site

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, enrollment 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.

In addition to the patients treated with ocrelizumab (ocrelizumab cohort), a second cohort of patients newly treated during the course of their MS therapy with alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide (other MS DMTs cohort) will be included in the study to enable the presentation of ocrelizumab data in the context of the safety profiles of other selected DMTs. This data collection strategy will also facilitate comparative analyses with larger samples and higher statistical power required by regulatory authorities (Ziemssen et al., 2018).

To correct for different prerequisites and minimize potential confounding factors resulting from label differences between ocrelizumab and other DMTs, history of relapse and MRI activity and most recent EDSS will be collected.

8.1.3 Sites

This study will be conducted at approximately 185 centers specialized in MS covering all regions of Germany.

8.1.4 Study Population

This study will enroll patients with MS from the post-marketing setting who have for the first time initiated treatment with ocrelizumab or another selected MS DMT no more than 30 days prior to or 60 days after study enrollment. The decision of the treating physician to prescribe ocrelizumab or another selected MS DMT 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 for the first time during the course of their MS therapy with ocrelizumab (up to 30 days prior to or 60 days after study enrollment) according to the local label irrespective of the reason for starting ocrelizumab (ocrelizumab cohort)

OR

newly treated for the first time during the course of their MS therapy with an selected MS DMT other than ocrelizumab (i.e., alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, or teriflunomide, up to 30 days prior to or 60 days after study enrollment) according to the local label irrespective of the reason for starting a new MS DMT

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

- participation in other interventional studies investigating DMTs for MS
- patients who have received ocrelizumab or their new MS therapy with a selected MS DMT other than ocrelizumab more than 30 days prior to study entry date
- patients who have been previously treated with rituximab, or any other anti-CD20 therapy for MS

Patients receiving treatment for MS with ocrelizumab (OCREVUS®), alemtuzumab (Lemtrada®), cladribine (Mavenclad®), dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®), natalizumab (Tysabri®), or teriflunomide (Aubagio®) according to SoC and in line with the current SPC / local labeling and who have no contraindications to treatment 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 70% of each cohort is female in order to adequately power breast cancer event rates in the global ocrelizumab PAS studies (BA39730 & BA39731). In addition, the patients enrolled in the cohort of MS DMTs other than ocrelizumab have to meet the same eligibility criteria as the ocrelizumab-exposed cohort. In order to ensure distribution of patients newly treated with DMTs other than ocrelizumab according to local practice and to avoid over-presentation of single DMTs, recruitment of individual treatments shall aim to have a maximum of 500 subjects with a specific new DMT treatment at enrolment.

8.1.5 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 immunomodulatory and immunosuppressive treatments for MS, including their duration (start/stop dates) and main reason for discontinuation, if available
- All other prior immunomodulatory and immunosuppressive treatments not for MS including their duration (start/stop dates) and dose, if available
- All concomitant immunomodulatory and immunosuppressive treatments including their duration (start/stop dates) and dose, if available
- Other previous and ongoing medications: from 3 months prior to enrollment only

8.1.6 Dosage, Administration, and Compliance

Dosing and treatment duration of studied medicinal products collected as parts of this non-interventional study are at the discretion of the physician in accordance with local clinical practice and local labeling. For information on the studied medicinal products please refer to the most recent version of the SPC.

8.2 OUTCOME MEASURES

8.2.1 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 of 0.1% to 1% [1 to 10 out of 1000 patients] or less) and death with primary and underlying causes in patients with MS newly exposed to ocrelizumab.

8.2.2 Secondary Outcome Measures

The key secondary outcome measures for this study are as follows:

- incidence and type of uncommon AEs (i.e. AEs with an incidence of 0.2% to 1% [1 to 5 out of 500 patients] or less) and death with primary and underlying causes in patients with MS newly exposed to selected MS DMTs other than ocrelizumab.

Additional 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 discontinuation of current treatment due to AEs [excluding pregnancies] and lack of therapeutic effectiveness) and proportion of patients not reaching treatment success and the proportion of underlying reasons
    - annualized relapse rate since start of treatment
    - proportion of patients with relapses since start of treatment
    - mean number of relapses per patients within the last 1, 2 and 3 years before start of treatment
    - change in EDSS from baseline
    - proportion of patients with CDP
    - time to onset of CDP
    - time to onset of CDI
    - PRO: treatment satisfaction (TSQM), cognitive function (SDMT), and health related QoL (MSIS-29)
- other safety endpoints:
    - incidence of all AEs
    - incidence of serious infections
    - incidence of malignancies
    - incidence of mortality due to malignancies

8.2.3 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- number of Gd enhancing T1 lesions as detected by MRI
- number of T2 lesions as detected by MRI

- global impression on the disease course as reported by physician and patient using the adapted 'Clinical Global Impression (CGI)' scale (collected until protocol V_6.0 due to reduce the documentation burden):
    - severity score change from baseline
    - improvement score by descriptive statistics (mean, standard deviation)
- change from baseline in pharmacoeconomic outcomes as measured by 'WPAI:MS'

8.3 DATA SOURCES

8.3.1 Collection of Data on the electronic CRF (eCRF)

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

8.3.2 Data Collected during the Observation Period

During therapy with ocrelizumab, and other selected MS DMTs, laboratory assessments are expected to be routinely performed in accordance with the local label, current guidelines, and local SoC. In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessments after treatment. When performed during the observational period, available results from the range of assessments described below will be documented on the eCRF. Most recent data prior to first dose of the relevant treatment at study enrolment should be documented at baseline and approximately every six months. The proposed assessments and suggested timings for assessments in the protocol/observational plan are not mandatory. It is up to the treating physician to perform and document the assessments as performed in the real clinical setting.

All AEs occurring during the observational period will be reported. In addition, laboratory parameters (e.g. 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 EDSS at baseline and approximately every six months and via MRI if available. PROs regarding QoL, cognitive function, treatment satisfaction and pharmacoeconomic outcomes will be collected at baseline and every six months via questionnaires. According to the guideline on GVP Annex I the completion of such questionnaires may be performed as normal clinical practice.

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

Study enrollment:

- Documentation of written informed consent
- Inclusion and exclusion criteria
- Patient demographic information

Baseline:

- Ethnicity, employment status, weight, and height
- Medical history and comorbidities (including significant medical and surgical history)
- Vital signs (BP, HR, body temperature)
- Current MS treatment administration information:
    - ocrelizumab (date of administration, dose)
    - other selected MS DMTs (start date, dose)
- Any malignancy risk factor information available:
    - Tobacco use history
    - Drug use history
    - Alcohol consumption history
    - Genetic factors (e.g. BRCA1 and 2)
    - Obesity
    - Metabolic syndrome
    - Radiation exposure
    - Hormone replacement therapy exposure
    - Infection known to be associated with an increased risk of malignancy
    - Personal history of malignancy including precancerous lesions
    - Family history of malignancy
    - Other risk factors (e.g., reproductive history)
- MS disease and treatment history
    - Date of MS symptoms onset and symptoms at onset
    - Date of MS diagnosis and symptoms at diagnosis
    - Type of MS at diagnosis
    - MS relapse history (number of relapses within the past 12 months, 2 years and 3 years prior to study entry date / baseline)
    - All previous treatments and therapies for MS, including their duration (start/stop dates) and main reason for discontinuation, if available
    - MS status at initiation with ocrelizumab or other selected MS DMT, including most recent EDSS score, if available
    - Most recent MRI activity history results, if available (in the 3 years prior to study entry date)
- All other prior and concomitant immunomodulatory and immunosuppressive treatments including their duration (start/stop dates)
- Any other prior and concomitant medications from 3 months prior to enrollment
- Pregnancy status, if applicable (patient-reported, female and undifferentiated patients)
- Laboratory parameters, if available:

  - Blood cell count (RBC, hemoglobin, leukocytes, platelet count, absolute neutrophil count [ANC], lymphocytes)
  - Immunoglobulin levels (IgG, IgM, IgA)
  - Liver enzymes (ALT, AST, ALP, GGT)
  - Renal status (serum creatinine, urinalysis)
  - Clinical chemistry (amylase, total bilirubin)
  - Flow cytometry (B-cell depletion and recovery [CD19+] and T-cell counts [CD4+, CD8+])
  - Viral serology and detection (JCV status/index, HIV, hepatitis B virus, hepatitis C virus)
- QoL / PRO / cognitive function:
  - Adapted CGI
  - TSQM1.4
  - Multiple Sclerosis Impact Scale (MSIS-29 v1)
  - SDMT
- Cancer screening; malignancy/cancer detection and screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers):
  - Gynecological consultation
  - Breast check
  - Dermatological check
  - Colon cancer check
  - Prostate cancer check
- Pharmacoeconomic outcomes:
  - WPAI:MS

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, leukocytes, ANC, lymphocytes, platelet count)
  - Immunoglobulin levels (IgG, IgM, IgA)
  - Liver enzymes (ALT, AST, ALP, GGT)
  - Renal status (serum creatinine, urinalysis)
  - Clinical chemistry (amylase, total bilirubin)
  - Flow cytometry (B-cell depletion and recovery [CD19+] and T-cell counts [CD4+, CD8+])
- Continuation of DMT therapy or reason for discontinuation/change, if applicable
- Concomitant medications
- MS disease status and treatment:

- MS specific symptoms
- 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
- MS type change

- Cancer screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers) during study:
    - Gynecological consultation
    - Breast check
    - Dermatological check
    - Colon cancer check
    - Prostate cancer check
    - Malignancy/cancer detection and screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)
- Pregnancy status, if applicable (patient-reported, female and undifferentiated patients)
    - Safety assessments:
    - all AEs
    - SAEs
    - pregnancies
    - any malignancies, including but not limited to MedDRA SMQ of malignant or unspecified tumors
    - NMSCs
- Malignancy information, if applicable (additional in-depth malignancy information and additional clinical information will be solicited from the patient's treating physician or oncologist/pathologist [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
    - Histology, histological subtype
    - Hormone receptor status, if applicable
    - Duration of current MS therapy at the point of diagnosis
    - Action taken with current MS therapy at the point of diagnosis
    - Cancer status updates including remission/relapse, as applicable
    - 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 3.3.2).
    - 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)
- Current MS treatment administration information
    - ocrelizumab cohort: dose and date of administration
    - other DMT cohort: start date, stop date (if applicable)
- QoL / PRO / cognitive function
    - TSQM1.4
    - Multiple Sclerosis Impact Scale (MSIS-29 v1)
    - SDMT
- Pharmacoeconomic outcomes:
    - WPAI:MS

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

- Current MS treatment 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) and weight
- Laboratory parameters:
    - Blood cell count (RBC, hemoglobin, leukocytes, ANC, lymphocytes, platelet count)
    - Immunoglobulin levels (IgG, IgM, IgA)
    - Liver enzymes (ALT, AST, ALP, GGT)
    - Renal status (serum creatinine, urinalysis)
    - Clinical chemistry (amylase, total bilirubin)
    - Flow cytometry (B-cell depletion and recovery [CD19+] and T-cell counts [CD4+, CD8+])
- Concomitant medications
- MS disease status and treatment, relapses:
    - MS specific symptoms
    - 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
    - MS type change
- Cancer screening; malignancy/cancer detection and screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers) during study:

    - Gynecological consultation
    - Breast check
    - Dermatological check
    - Colon cancer check
    - Prostate cancer check
    - Malignancy/cancer detection and screening tests and procedures (e.g., mammography, Pap test, colonoscopy, laboratory malignancy markers)
- Pregnancy status, if applicable (patient-reported, female and undifferentiated patients)
- QoL / PRO / cognitive function
    - Treatment Satisfaction Questionnaire for Medication (TSQM1.4)
    - Multiple Sclerosis Impact Scale (MSIS-29 v1)
    - SDMT
- Pharmacoeconomic outcomes:
    - WPAI:MS
- Safety assessments:
    - all AEs
    - SAEs
    - pregnancies
    - any malignancies, including but not limited to MedDRA SMQ of malignant or unspecified tumors,
    - NMSCs
    - Malignancy information, if applicable (additional clinical details regarding in-depth malignancy information will be solicited from the patient's oncologist/pathologist [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
        - Histology, histological subtype
        - Hormone receptor status, if applicable
        - Duration of current MS therapy at the point of diagnosis
        - Action taken with current MS therapy at the point of diagnosis
        - Cancer status update including remission/relapse, as applicable

      In addition, data linkage with national and regional cancer registries will be explored to ensure identifying all malignancy cases in the study population.
    - 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
- Date of last contact

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

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

Data Collection [a]	Study Enrollment (Screening)	Baseline (prior to treatment) [b]	Data Collection (Approximately Every ~6 Months)	Data Collected at Study Completion/ Study Withdrawal Encounter
Patient demographics	X			
Informed consent [c]	X			
In-/exclusion criteria	X			
Vital signs and measurements [d]		X	X	X
Pregnancy status[e]		X	X	X[f]
Pregnancies		whenever occur to be documented as AE and on pregnancy report form		
Laboratory test results [g]		X	X	X
JCV antibody status / index		X		
MS disease history [h]		X		
MS treatment history [i]		X		
Medical history and comorbidities		X		
Clinically significant medical and surgical history (including previous malignancies and precancerous lesions)		X		
Malignancy risk factor information [j]		X		
Cancer screening [k]		X	X	X
MS symptoms [l]		X	X	X

Current MS DMT administration information [m]		X	X	X
QoL / PRO /cognitive function[n]		X	X	X
Pharmacoeconomic outcomes [o]		X	X	X
Premature termination incl. reasons for study withdrawal [p,f]				X[p,f]
Continuation of therapy or Reasons for treatment discontinuation[f]			X	X
Prior and concomitant medications [q]		X	X	X
Any malignancies [r ,f, s]		whenever occur		
All serious and non-serious AEs incl. AESIs, NMSCs and information on reasons for death [s,f]		whenever occur		
Death information[f]			X[f]	X[f]

AE = adverse event; AESI = adverse event of special interest; CGI = Clinical Global Impression; DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; JCV = John Cunningham Virus; MedDRA = Medical Dictionary for Regulatory Activities; MRI = magnetic resonance imaging (scan); MS = multiple sclerosis; MSIS = Multiple Sclerosis Impact Scale; NMSC = non-melanoma skin cancer; PRO = Patient Reported Outcomes; QoL = Quality of Life; SAE = serious adverse event; SDMT = Symbol Digit Modality Test; TSMQ = Standardized MedDRA Queries Treatment Satisfaction Questionnaire for Medication; STIAMP = suspected transmission of infectious agent by medicinal product; WPAI = Work Productivity and Activity Impairment Questionnaire

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

[b] Prior to the first ocrelizumab infusion or prior to start of another selected MS DMT

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

[d] Height and weight, BP, HR, and temperature

[e] Patient-reported, female and undifferentiated patients

[f] If applicable

[g] Blood cell count, immunoglobulins, liver enzymes, renal status, clinical chemistry, flow cytometry. Viral serology (only at baseline)

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

[i] Prior use and duration of therapies for MS

[j] Including tobacco use history, alcohol use history, family disease history, genetic testing such as BRCA1 and 2, personal history of malignancy, or other risk factors including reproductive history (women and undifferentiated only) and prior use and duration of immunomodulatory, immunosuppressive, and anti-neoplastic agents other than for MS (if any)

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

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

[m] Dates of administration for ocrelizumab, start and stop date for other DMTs, dose (300 or 600mg for i.v., 920mg for s.c.) for ocrelizumab, no dose documentation for other DMTs, reason for discontinuation (if applicable)

[n] TSQM 1.4, MSIS-29 v1, SDMT. Collected every six months

[o] WPAI:MS. Collected every six months

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

[q] Up to 3 months prior to study entry

[r] Medical records regarding in-depth malignancy information will be solicited from the patient's oncologist or pathologist (only collected if a malignancy is identified)

[s] AESIs are events falling under Hy's Law and events of STIAMP only.

All assessments will be performed per 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 their current MS treatment. Please see Table 1 in section 8.3.2 for the data collection overview (as per SoC with exception of questionnaires) during the treatment period.

8.3.3 Data Collected at Study Completion

All patients enrolled in the study will be observed for the whole period of at least 7.5 and up to 10 years, regardless whether their current MS 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 8.3.2 for the data collection overview at the study completion visit, if available.

8.3.4 Safety Data Collection

Clinical AEs, serious and non-serious, NMSCs, as well as safety data other than AEs as described in Section 8.3 will be recorded in the eCRF during the observation period starting from first administration of ocrelizumab or other selected MS DMT. For clinical AEs, serious and non-serious, physician's assessment of severity (according to Common Terminology Criteria for AEs [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.

Any malignancy will be defined as the first occurrence of a cancer diagnosis during study follow-up. A cancer diagnosis will prompt two reporting channels. Available information on cancer (e.g., diagnosis date, tumor type and location, grade, stage, cancer treatment, hormone receptor status) will be collected for this study and reported by the neurologist in the eCRF. The local safety unit of Roche will request additional clinical information, detailing the malignancy diagnosis, such as tumor grade, method of diagnostic confirmation and histopathologic testing, upon identification of a malignancy event, from the patient's treating oncologist/pathologist.

As part of the validation of the malignancy diagnoses required for the study BA39731, two qualified independent oncologists or pathologists will be used throughout the study for formal adjudication of malignancy diagnoses. In the event there is discordance between the two oncologists/pathologists, a third oncologist/pathologist will independently review the reports for final case determination. Adjudicator roles and responsibilities will be outlined in an external Charter document.

In the event there is discordance of malignancy diagnosis of the treating medical team and the two independent oncologists, the neurologist will be asked to inform the treating medical team.

In addition, data linkage with national and regional cancer registries will be explored to ensure identifying all malignancy cases in the study population.

For mortality rate calculations, all deaths where malignancy is noted as a primary or underlying cause will be included in the analyses.

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

Symptoms of the MS which are expected during the course of the disease are not to be reported as AEs but only recorded in the eCRF section MS symptoms.

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 Gd enhancing lesion in spinal or cerebral MRI)
- MS signs and symptoms
- Disability caused by MS
- Events originating from patient questionnaires (e.g. fatigue, pain, cognition decline)

As health-related QoL is a secondary endpoint of this study all MS-related AEs reported within the patient-reported outcome using the TSQM1.4, Multiple Sclerosis Impact Scale (MSIS-29 v1)and 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 AE have been met this must be reported using the AE eCRF, if not already documented.

As the Pharmacoeconomic outcome '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, leukocytes, platelets), immunoglobulins, liver enzymes (ALT, AST, ALP, GGT), renal status (creatinine, urinalysis), 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 relevant.

Due to the fact that a decrease of CD19+ cells is a therapeutic effect of ocrelizumab, this event will not be considered as an AE for this study.

IRRs should only be recorded as an AE in the eCRF if judged as a serious or life-threatening event. Mild to moderate IRRs are not to be recorded as an AE in the eCRF.

IRs should be recorded as an AE in the eCRF in any case.

Adverse events that occur during or within 24 hours of study drug administration and are considered to be related to injection of the study drug should be recorded as a diagnosis [e.g., "injection reaction" (which applies to local or systemic injection reactions)] in the adverse event eCRF. If possible, ambiguous terms such as "systemic reaction" should be avoided.

8.4 STUDY SIZE

The primary objective of this study is to investigate the occurrence of uncommon AEs in MS patients receiving treatment with ocrelizumab from study start over a maximum time period of 10 years. The sample size is thus planned to allow for the detection of AEs with an incidence 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, the aimed study sample size is 3000 ocrelizumab patients. This will result in a precision of the estimate of AEs with an incidence rate of 0.1% (1 out of 1000 patients) of 0.27%. This precision is based on a pre-defined two-sided alpha level of 5%. In addition, the precision will not exceed 0.76% if AEs are observed in up to 1% of the patients. Even for a sample size of 2800 ocrelizumab patients (conservatively estimated for the recruitment end) the precision will not exceed 3.74% for a worst case scenario of an incidence rate of 50.0%, which is deemed acceptable.

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 185 centers.

With the sample size of 3000 ocrelizumab-exposed patients in this non-interventional study (NIS), the following precision of the estimated incidence in terms of 95% CIs (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
3 (0.1%)	[0.02%; 0.29%]
15 (0.5%)	[0.28%; 0.82%]
30 (1.0%)	[0.67%; 1.43%]

A cohort of 767 patients newly treated for the first time during the course of their MS therapy with a selected MS DMT other than ocrelizumab will result in a precision of the estimate of AEs with an incidence rate of 0.2% (1 out of 500 patients) of 0.91%. This precision is based on a pre-defined two-sided alpha level of 5%. In addition, the precision will not exceed 1.6% if AEs are observed in up to 1% of the patients. For the worst case scenario (incidence of 50% of the patients) the precision will be at most 7.2% which is deemed acceptable for the estimation.

Table 3 95% Confidence Intervals for the Secondary Safety Outcome Measures Based on 767 Patients Receiving Other MS DMT

Number of AE events/observed AE incidence	95% Confidence Interval (Clopper-Pearson) for the incidence
2 (0.2%)	[0.03%; 0.94%]
8 (1.0%)	[0.45%; 2.05%]
16 (2.0%)	[1.20%; 3.37%]

8.5 DATA MANAGEMENT

8.5.1 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 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 and procedures regarding archiving and record management will comply with the requirements of Roche.

8.5.2 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) on their request. Data must be kept with the study records. Acknowledgement of receipt of the data is required.

8.5.3 Source Data Documentation

Site Operations Representative will perform ongoing 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, Xrays, patient files, and records kept at pharmacies, laboratories, and medicotechnical 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 8.7.3.

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.

8.6 DATA ANALYSIS

The statistical analysis will be described in a prospective SAP. 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 by MS treatment at enrolment, i.e. ocrelizumab cohort or pooled other selected MS DMTs cohort, and separately for the MS types RMS and PPMS as well as MS types pooled. In addition, for all safety endpoints time adjusted analyses will be done based on patient years. Analyses of effectiveness will be prepared by MS type for both cohorts.

If the sample sizes allow, further statistical analyses of the other DMT cohort may be performed by DMT in addition.

Data of patients switching their treatment during the course of the study will be examined by analyzing effectiveness and safety variables for the following subsets:

- Set 1: Patients, who received during the whole course of the study ocrelizumab plus those patients having been switched from ocrelizumab to DMT until the treatment switch from ocrelizumab to DMT
- Set 2: Patients, who received during the whole course of the study DMT plus those patients having been switched from DMT to ocrelizumab until the treatment switch from DMT to ocrelizumab
- Set 3: Patients, starting with ocrelizumab treatment after their switch from DMT
- Set 4: Patients, starting with DMT treatment after their switch from ocrelizumab

Due to the long observation time of CONFIDENCE it is anticipated that there will be time frames where a patient does not fit into Set 1-4. For example, if a patient starts with ocrelizumab, switches to a selected other DMT and switches to ocrelizumab afterwards. The handling and analyses of these patients' data will be discussed in the DRMs.

Set 1 and Set 4 will be compared descriptively.

Patients switching to Ocrelizumab s.c.will be analyzed according to SAP.

Detailed information about handling of patients switching to other DMTs, not specified in this protocol, is given in the SAP.

8.6.1 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 any 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.

All analyses will be done separately for the sets described in the introduction to this chapter. All analyses will be performed for Set 1 to Set 4.

Handling of deviations from the study protocol will be detailed in the SAP or a separate document. It is planned to organize a DRM between database freeze (soft lock) and database hard lock for final analysis. This pre-analysis 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, MS history, status at start of MS treatment, current and previous DMTs, ethnicity and employment status at date of study enrolment) 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 separately for each cohort; results for the other selected MS DMT cohort will be presented as secondary endpoint. The analysis of safety outcomes/variables is based on the incidence and severity (NCI CTCAE grading) of all AEs and SAEs reported.

Incidence of AEs will be calculated on the basis of SOC and preferred term of the MedDRA and presented along with two-sided 95% CIs (Clopper-Pearson). Event incidence rates per 100 patient years (of cumulative treatment exposure) will be determined and calculated along with the corresponding 95% CIs.

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 CIs over time, based on standard units (SI units).

Safety data obtained from this study will be pooled with data from the ocrelizumab-exposed cohort in the U.S. (study BA39731) and EU (study BA39730) for comparisons of incidence of selected AEs (e.g. malignancies) between patients treated with ocrelizumab and those treated with other selected MS DMTs. These comparisons will be made using internal and external comparator MS populations, and with general population malignancy incidence and mortality rates as part of the study BA39731 analyses.

8.6.2 Effectiveness Analyses

Effectiveness analyses will be conducted on the Full Analysis Set.

Descriptive statistics of the secondary endpoints will be provided. 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 distribution curves and the median survival time. The time to endpoint will be calculated as time interval between the date of baseline (date of first treatment) 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 baseline (date of first treatment) 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 (e.g. a cox model) 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.

A negative binomial model will investigate the annualized relapse rates. The model will include the total number of protocol-defined relapses per patient since treatment start. The different treatment durations for each patient will be considered as individual log-transformed exposure time for the computation of relapse rates. Annualized relapse rates will be presented along with their two-sided 95% CIs (95% CI). The detailed model will be specified by the SAP.

Corresponding 95% CIs will be provided, where appropriate.

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

8.6.3 Other analyses

The number/percentage of patients with a change in MS/ RMS type at any time during the study will be summarized and the time to change in years will be calculated. The number/percentage of patients with relapses any time and per visit during study will be calculated. Methods of survival analysis (Kaplan-Meier summary and corresponding Kaplan-Meier plot) will be done. A logistic regression model may evaluate how far the probability for treatment success is

influenced by covariates like EDSS baseline score, age (continuous), gender, categories based on enrolment date, MS type. The full model will be specified in the SAP. Treatment exposure, the total dose per patient, and the number of patients still under treatment at each visit will be summarized as numeric variables. Additionally, the number of administrations per patient and the time between doses will be analyzed for all patients treated with ocrelizumab.

Subgroup Analyses

- Subgroup analyses for all outcome measures will be performed according to SAP and will comprise:
  - EDSS at baseline (0-3.5 / ≥4 for RMS, 0-5.5 / >5.5–6.5 /≥7 for PPMS)
  - By pre-treatment
  - Age (≤55 / >55 years for RMS, ≤40 / 41-55 / >55 years for PPMS)
  - Gender (male vs. female vs undifferentiated)

Sensitivity analyses

In order to investigate the relationship between potential prognostic or risk factors and the main outcome, various exploratory analyses are imaginable. For selected DMTs of the other selected DMTs cohort subpopulations by treatment may be analyzed. Further details will be given in the SAP.

8.6.4 Interim/Final Analysis and Timing of Analyses

Annual interim analyses are planned starting when 1-year data of at least 500 patients treated with ocrelizumab are available. Analysis of the second cohort will be included when at least baseline data of 500 patients treated with other DMTs are available.

The final analysis is planned after final database lock and will include all analyses planned for all endpoints and will be delivered in tables, listings and figures.

Interim analysis will include selected analyses and will be delivered in tables, listings and figures. The selection of analyses will be documented in the DRM minutes. No adjustment for multiplicity will be done.

8.7 QUALITY CONTROL

8.7.1 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.

8.7.2 Site Audits and Inspections

The physician will permit the MAH of ocrelizumab to audit facilities and records relevant to this study.

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

8.7.3 Retention of Records

Records and documents pertaining to the conduct of this study, Informed Consent Forms and if applicable eCRFs, 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.

Records and documents pertaining to the conduct of this study must be retained by the MAH/study initiator for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of 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.

8.7.4 Administrative Structure

[redacted] Scientific Responsible of this non-interventional study is Prof. Dr. [redacted], University Clinic Dresden.

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

8.8 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 encouraged to enroll patients into both treatment cohorts and to include patients representing the site´s general population regarding patient disposition and treatment regimen.

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 the SAP.

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 as new users, at the time of ocrelizumab treatment initiation or newly starting other selected MS DMTs, 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.

Recruitment of patients is dependent on several factors: Uptake of new medications such as ocrelizumab is unpredictable and has the potential to impact the feasibility of meeting the recruitment targets in 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.

8.9 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 current MS treatment 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 of Current MS Treatment

The decision for discontinuation of current MS 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 their current MS DMT 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. At least three documented follow-up contact attempts should be made before considering the patient to be lost to follow-up. If a patient does not respond, attempts will be made to contact the patient's primary health care physician to obtain follow-up information.

If contact with a missing patient is re-established, follow-up should continue according to the protocol, and exposure and outcome variable information for the missed periods should be collected to the extent possible. The handling of data from patients whose missed data collection period is longer than 20 months will be described in the SAP.

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 GPPs 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 PASstudies.

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 by the site or via their primary care physician in case of contact discontinuation to the study site, and the possibility of monitoring activities. It is the accountability of the physician for ascertaining that the patient has comprehended the information and to obtain written informed consent from each patient participating in the study. 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, AEs 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.

Roche, including affiliates, collaborators and licensees may use study data labeled with the patient ID numbers. Study data may also be shared with independent researchers or government agencies, but only after personal information that can identify the patient has been removed. Patients' study data may be combined with other patients' data and/or linked to other data collected from the patients. Patients' study data may be used to help better understand why people get diseases, how to best prevent, diagnose and treat diseases, and to develop and deliver access to new medicines, medical devices, and healthcare solutions to advance patient care

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., 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 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., ECG, Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.
- Adverse events that occur during or within 24 hours of study drug administration and are considered to be related to injection of the study drug should be recorded as a diagnosis [e.g., "injection reaction" (which applies to local or systemic injection reactions)] in the adverse event eCRF. If possible, ambiguous terms such as "systemic reaction" should be avoided.

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

- Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Appendix 3.3.7).

- 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

Symptoms of the MS which are expected during the course of the disease are not to be reported as AEs but only recorded in the eCRF section MS symptoms.

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 AEs 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 Gd enhancing lesion in spinal or cerebral MRI)

- MS signs and symptoms

- Disability caused by MS

- Events originating from patient questionnaires (e.g. fatigue, pain, cognition decline)

As health-related QoL is a secondary endpoint of this study all AEs reported within the patient-reported outcome using the TSQM1.4, Multiple Sclerosis Impact Scale (MSIS-29 v1), and 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 AE have been met this must be reported using the AE eCRF, if not already documented.

As the Pharmacoeconomic outcome '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, leukocytes, platelets, immunoglobulins, liver enzymes (ALT, AST, ALP, GTT), renal status (creatinine, urinalysis), 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 relevant.

Due to the fact that a decrease of CD19+ cells is a therapeutic effect of ocrelizumab, this event will not be considered as an AE for this study.

IRRs should only be recorded in the eCRF as an AE if judged as a serious or life-threatening event. Mild to moderate IRRs are not to be recorded as an AE in the eCRF.

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 from enrollment or first administration of ocrelizumab or other selected MS DMT (whatever is earlier) 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 MAH 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
- Injection Reactions
- Diagnosis versus signs and symptoms
- AEs occurring secondary to other AEs
- Persistent or recurrent AEs
- Abnormal Laboratory Values
- Abnormal Vital Sign Values
- Abnormal Liver Function Tests
- Deaths
    - All events with an outcome or consequence of death should be classified as SAES and reported to Roche immediately. 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 effectiveness
- Lack of efficacy (Drug Ineffective)
- 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 MAH (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 of patients treated with ocrelizumab 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 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 QoL is a secondary endpoint of this study all AEs reported within the patient-reported outcome using the TSQM1.4, Multiple Sclerosis Impact Scale (MSIS-29 v1), and 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 AE have been met this must be reported using the AE eCRF, if not already documented.

As the Pharmacoeconomic outcome '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

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 MAH 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 AEs (Special Situation Events):

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy (drug ineffective)
- 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.

10.3 REPORTING OF PRODUCT COMPLAINTS WITHOUT ADVERSE EVENTS

Roche product complaints without AEs have to be reported by the physicians to grenzach.complaint_pharma@roche.com. A product complaint is any written or oral information received from a complainant that alleges deficiencies related to Identity, Quality, Safety, Strength, Purity, Reliability, Durability, Effectiveness or Performance of a product after it has been released and distributed to the commercial market. Non-Roche-product complaints have to be reported as per local regulation.

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.

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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 8.3.2.

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 ageappropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately lifethreatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting selfcare 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.

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

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

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

Appendix 3.3.2 Diagnosis versus Signs and Symptoms

For SAEs, AESIs, and NMSCs, other than infusion-related reactions (see Appendix 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 BP), 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 Effectiveness

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 Lack of Efficacy (Drug Ineffective)

Any failure of expected pharmacological action (applies to any scenario where the product did not work as expected, while being used within its marketed authorization) 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).

Appendix 3.3.12 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 3.3.13 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 3.3.14 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 3.3.15 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 3.3.16 Safety data other than Adverse Events

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

Appendix 4

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MSIS-29

In den folgenden Fragen geht es darum, wie MS sich Ihrer Ansicht nach **in den letzten 14 Tagen** auf Ihr Alltagsleben ausgewirkt hat.
Kreuzen Sie bitte zu jeder Frage die Antwort an, die **am besten** auf Sie zutrifft.
Beantworten Sie bitte alle Fragen.

Wie schwer fiel es Ihnen in den letzten zwei Wochen...	gar nicht	ein bisschen	mäßig	ziemlich	sehr
1. körperlich anstrengende Dinge zu tun?	1	2	3	4	5
2. Dinge fest anzufassen (z.B. Hahn aufdrehen)?	1	2	3	4	5
3. Dinge zu tragen?	1	2	3	4	5

Hatten Sie in den letzten zwei Wochen...	gar nicht	ein bisschen	mäßig	ziemlich	sehr
4. Probleme mit dem Gleichgewicht?	1	2	3	4	5
5. Schwierigkeiten, sich in der Wohnung zu bewegen?	1	2	3	4	5
6. das Gefühl ungeschickt zu sein?	1	2	3	4	5
7. ein Steifigkeitsgefühl?	1	2	3	4	5
8. schwere Arme und/oder Beine?	1	2	3	4	5
9. Zittern der Arme oder Beine?	1	2	3	4	5

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10. Krämpfe der Extremitäten?	1	2	3	4	5
11. das Gefühl, dass ihr Körper nicht tat, was sie wollten?	1	2	3	4	5
12. Beeinträchtigung im sozialen und Freizeitleben zu Hause?	1	2	3	4	5
13. Probleme mit den Händen bei Alltagstätigkeiten?	1	2	3	4	5
14. Probleme sich fortzubewegen (Auto, Bus, Taxis, Zug)?	1	2	3	4	5
15. länger gebraucht, Dinge zu tun?	1	2	3	4	5
16. Schwierigkeiten, Dinge spontan zu machen?	1	2	3	4	5
17. das Gefühl, ganz schnell zur Toilette zu müssen?	1	2	3	4	5
18. sich allgemein unwohl gefühlt?	1	2	3	4	5
19. Schlafprobleme?	1	2	3	4	5
20. sich geistig/mental müde gefühlt?	1	2	3	4	5
21. Sorgen bezogen auf ihre MS?	1	2	3	4	5
22. sich angespannt und ängstlich gefühlt?	1	2	3	4	5
23. sich ungeduldig und aufbrausend gefühlt?	1	2	3	4	5

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24. Konzentrationsprobleme?	1	2	3	4	5
25. keine Zuversicht?	1	2	3	4	5
26. sich traurig/depressiv gefühlt?	1	2	3	4	5
Waren Sie in den letzten zwei Wochen...	gar nicht	ein bisschen	mäßig	ziemlich	sehr
27. davon abhängig, dass andere Dinge für Sie erledigten?	1	2	3	4	5
28. gezwungen, zu Hause zu bleiben?	1	2	3	4	5
29. gezwungen die Zeit für Arbeit oder Alltagsaktivitäten einzuschränken?	1	2	3	4	5

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Appendix 5

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SDMT

Beschreibung
Der Symbol Digit Modalities Test überprüft die anhaltende Aufmerksamkeit und Konzentration.

Material
Formular (siehe S. 2), Stoppuhr, SDMT Anleitung (W-129C)

Durchführung
Legen Sie Ihrem Patienten das Testformular vor und erklären Sie die den Ablauf folgendermaßen:
„Betrachten Sie bitte diese Kästchen."
➜ Zeigen Sie das Beispiel.

„Wie Sie sehen, besteht jedes Kästchen aus zwei Teilen. Im oberen Teil erkennen Sie ein Symbol, im unteren Teil steht eine Zahl. Zu jedem Symbol gehört eine Zahl. Schauen Sie nun bitte nach unten."
➜ Zeigen Sie nach unten.

„In diesem Kästchen sehen Sie im oberen Teil die Symbole. Im unteren Bereich fehlen jedoch die Zahlen. Bitte sagen Sie mir, welche Zahl zu welchem Symbol gehört, z. B. so ..."
➜ Demonstrieren Sie die Aufgabe mit den ersten zwei Symbolen.

„Zum Üben sagen Sie mir bitte, welche Zahlen in welche Kästchen gehören, und zwar bis zur Doppellinie."
➜ Zeigen Sie die Doppellinie.

Während der Patient die Zahlen nennt, markieren Sie die richtigen Antworten des Patienten auf dem Formular.
In der Übungsphase (bis zur Doppellinie) wird der Patient nach jeder falschen Antwort korrigiert.
Wenn für die Übungssymbole die richtigen Zahlen genannt wurden, beginnen Sie mit dem Test:
„Wenn ich ‚jetzt' sage, arbeiten Sie bitte so schnell wie möglich und sagen mir, welche Zahl in welches Kästchen gehört. Fangen Sie hier an, und lösen Sie bitte soweit wie möglich. Bitte lassen Sie kein Kästchen aus! Sie können mit dem Finger den Symbolen folgen, um nicht aus der Reihe zu kommen. Wenn Sie eine Reihe beendet haben, machen Sie einfach bei der nächsten weiter. Arbeiten Sie dabei so schnell wie möglich, ohne einen Fehler zu machen, und zwar so lange, bis ich, nach 90 Sekunden, ‚Stopp' sage."

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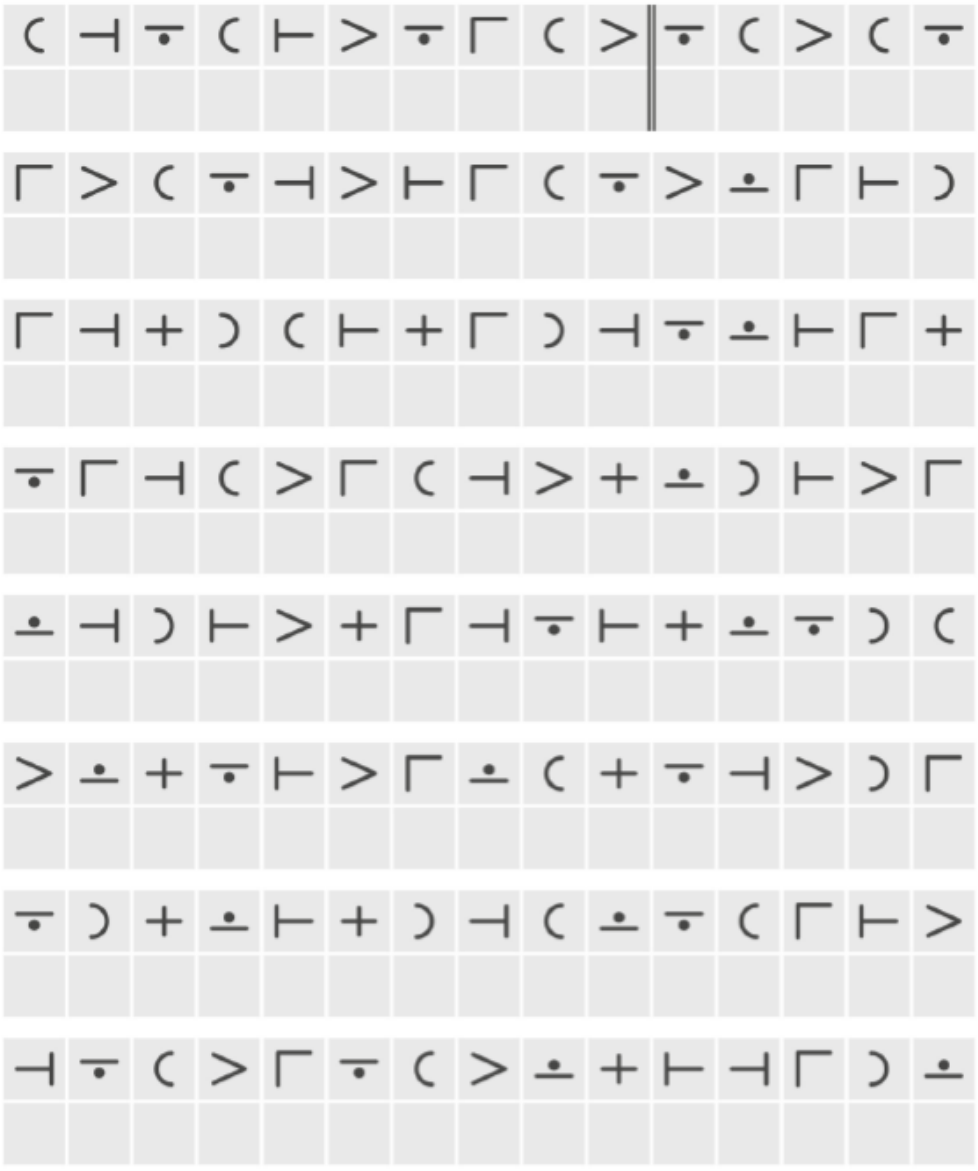
CONFIDENCE

SDMT-Erhebungsbogen Patient



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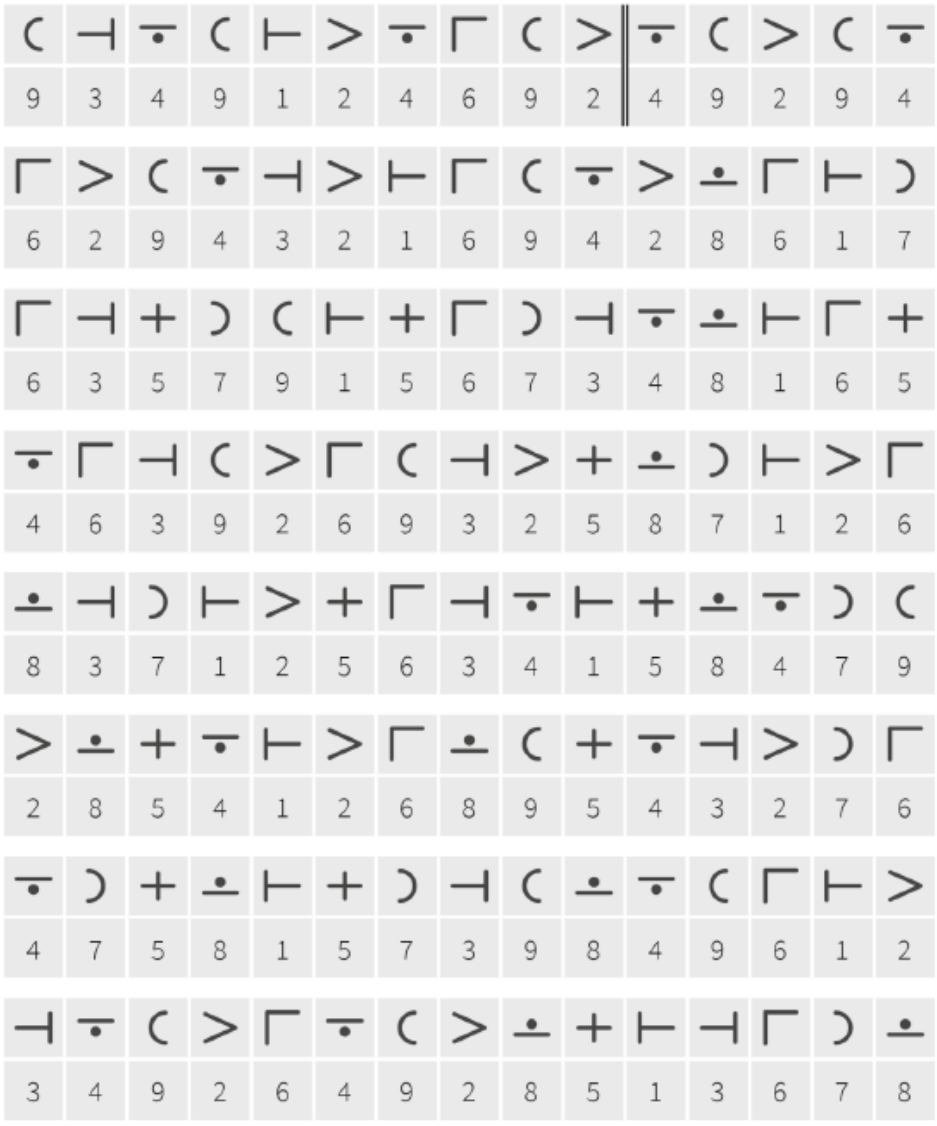
SDMT-Dokumentations- und Auswertungsbogen

Bitte dokumentieren Sie im unteren Feld die Anzahl der innerhalb von 90 Sekunden richtig eingetragenen Antworten.



Anzahl korrekter Antworten: ☐

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TSQM Version 1.4

Anleitung: Bitte nehmen Sie sich einen Moment Zeit und überlegen Sie, wie zufrieden oder unzufrieden Sie mit dem Medikament sind, das Sie im Rahmen dieser klinischen Studie nehmen. Wir möchten gerne wissen, wie Sie die Wirksamkeit und die Nebenwirkungen des Medikaments beurteilen und wie einfach und bequem es einzunehmen ist. Berücksichtigen Sie dabei *die letzten zwei bis drei Wochen, oder die Zeit, seit Sie es zum letzten Mal genommen haben*. Bitte kreuzen Sie bei jeder Frage die Antwort an, die Ihren eigenen Erfahrungen am besten entspricht.

1. Wie zufrieden oder unzufrieden sind Sie damit, wie gut das Medikament zur Vorbeugung oder Behandlung Ihrer Erkrankung geeignet ist?	1 Sehr unzufrieden 2 Ziemlich unzufrieden 3 Unzufrieden 4 Einigermaßen zufrieden 5 Zufrieden 6 Ziemlich zufrieden 7 Sehr zufrieden
2. Wie zufrieden oder unzufrieden sind Sie damit, wie das Medikament Ihre Beschwerden lindert?	1 Sehr unzufrieden 2 Ziemlich unzufrieden 3 Unzufrieden 4 Einigermaßen zufrieden 5 Zufrieden 6 Ziemlich zufrieden 7 Sehr zufrieden

Seite **1** von **5**

Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12. Those seeking information regarding or permission to use the TSQM are directed to IQVIA at www.iqvia.com/TSQM or TSQM@iqvia.com 03/2018, Version 2.0

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3. Wie zufrieden oder unzufrieden sind Sie damit, wie lange es dauert, bis das Medikament anfängt zu wirken?	1 Sehr unzufrieden 2 Ziemlich unzufrieden 3 Unzufrieden 4 Einigermaßen zufrieden 5 Zufrieden 6 Ziemlich zufrieden 7 Sehr zufrieden
4. Verspüren Sie Nebenwirkungen, weil Sie dieses Medikament nehmen?	1 Ja 0 Nein (falls Nein, bitte mit Frage 9 weitermachen)
5. Wie sehr machen Ihnen die Nebenwirkungen des Medikaments zu schaffen, das Sie zur Behandlung Ihrer Erkrankung nehmen?	1 Sehr 2 Ziemlich 3 Mäßig 4 Ein wenig 5 Überhaupt nicht
6. Wie sehr beeinträchtigen die Nebenwirkungen Ihren körperlichen Gesundheitszustand und wie Sie im Alltag zurechtkommen (d.h. Ihre Kraft, Energie, usw.)?	1 Sehr 2 Ziemlich 3 Etwas 4 Sehr wenig 5 Überhaupt nicht

Seite **2** von **5**

Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12. Those seeking information regarding or permission to use the TSQM are directed to IQVIA at www.iqvia.com/TSQM or TSQM@iqvia.com 03/2018, Version 2.0

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7. Wie sehr wirken sich die Nebenwirkungen auf Ihren geistigen Zustand aus (d.h. auf die Fähigkeit, klar zu denken, wach zu bleiben, usw.)?	1 Sehr 2 Ziemlich 3 Etwas 4 Sehr wenig 5 Überhaupt nicht
8. Wie sehr haben sich die Nebenwirkungen des Medikaments auf Ihre allgemeine Zufriedenheit mit dem Medikament ausgewirkt?	1 Sehr 2 Ziemlich 3 Etwas 4 Sehr wenig 5 Überhaupt nicht
9. Wie einfach oder schwierig ist es, das Medikament in seiner derzeitigen Form zu nehmen?	1 Sehr schwierig 2 Ziemlich schwierig 3 Schwierig 4 Es geht so 5 Einfach 6 Ziemlich einfach 7 Sehr einfach

Seite **3** von **5**

Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12. Those seeking information regarding or permission to use the TSQM are directed to IQVIA at www.iqvia.com/TSQM or TSQM@iqvia.com 03/2018, Version 2.0

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10. Wie einfach oder schwierig ist es, zu planen, wann Sie das Medikament jeweils nehmen?	1	Sehr schwierig
	2	Ziemlich schwierig
	3	Schwierig
	4	Es geht so
	5	Einfach
	6	Ziemlich einfach
	7	Sehr einfach
11. Wie einfach und bequem ist es, das Medikament wie verschrieben einzunehmen?	1	Sehr schwierig und unbequem
	2	Ziemlich schwierig und unbequem
	3	Schwierig und unbequem
	4	Es geht so
	5	Einfach und bequem
	6	Ziemlich einfach und bequem
	7	Sehr einfach und bequem
12. Wie überzeugt sind Sie davon, dass es gut für Sie ist, dieses Medikament zu nehmen?	1	Überhaupt nicht überzeugt
	2	Nicht ganz überzeugt
	3	Einigermaßen überzeugt
	4	Ziemlich überzeugt
	5	Sehr überzeugt

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Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12. Those seeking information regarding or permission to use the TSQM are directed to IQVIA at www.iqvia.com/TSQM or TSQM@iqvia.com 03/2018, Version 2.0

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13. Wie sicher sind Sie sich, dass die guten Seiten des Medikaments gegenüber den schlechten Seiten überwiegen?	1 Überhaupt nicht sicher 2 Nicht ganz sicher 3 Einigermaßen sicher 4 Ziemlich sicher 5 Sehr sicher
14. Wie zufrieden oder unzufrieden sind Sie insgesamt gesehen mit diesem Medikament?	1 Sehr unzufrieden 2 Ziemlich unzufrieden 3 Unzufrieden 4 Einigermaßen zufrieden 5 Zufrieden 6 Ziemlich zufrieden 7 Sehr zufrieden

Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12. Those seeking information regarding or permission to use the TSQM are directed to IQVIA at www.iqvia.com/TSQM or TSQM@iqvia.com 03/2018, Version 2.0

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WPAI:MS

Fragebogen zur Beeinträchtigung von Arbeitsproduktivität und Aktivität: Multiple Sklerose V2.0

Die folgenden Fragen beziehen sich auf die Auswirkungen Ihrer multiplen Sklerose auf Ihre Fähigkeit zu Arbeiten und normalen Aktivitäten nachzugehen. *Antworten bitte in die freien Stellen eintragen oder eine Zahl einkreisen, je nachdem.*

1. Stehen Sie derzeit in einem Arbeitsverhältnis (bezahlte Tätigkeit)?	☐ NEIN ☐ JA *Falls NEIN, "NEIN" ankreuzen und zu Frage 6 weitergehen.*

Die nächsten Fragen beziehen sich auf die **vergangenen sieben Tage** (den heutigen Tag nicht eingeschlossen).

2. Wie viele Stunden fehlten Sie in den vergangenen sieben Tagen bei der Arbeit aufgrund von Problemen im Zusammenhang mit Ihrer multiplen Sklerose? *Alle Stunden einbeziehen, die Sie aufgrund Ihrer multiplen Sklerose an Krankenstandstagen, Tagen, an denen Sie später kamen oder früher gingen etc., fehlten. Rechnen Sie die Zeit, die Sie wegen der Teilnahme an dieser Studie fehlten, bitte nicht ein.*	_____ STUNDEN

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5): 353-65. 12/2017, Version 1.0

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3. Wie viele Stunden fehlten Sie in den vergangenen sieben Tagen aus anderen Gründen bei der Arbeit – z.B.: Urlaub, Feiertage, freigenommene Zeit für die Teilnahme an der Studie? _____ STUNDEN

4. Wie viele Stunden haben Sie in den vergangenen sieben Tagen tatsächlich gearbeitet? _____ STUNDEN

(Falls "0", zu Frage 6 weitergehen.)

5. Wie sehr wirkte sich Ihre multiple Sklerose in den vergangenen sieben Tagen auf Ihre Produktivität während der Arbeit aus?

Denken Sie hierbei an Tage, an denen das Arbeitspensum oder die Art der Arbeit, die Sie ausführen konnten, eingeschränkt war, Tage, an denen Sie weniger leisten konnten als Sie wollten, oder Tage, an denen Sie Ihre Arbeit nicht so sorgfältig wie sonst erledigen konnten. Falls sich Ihre multiple Sklerose nur wenig auf Ihre Arbeit auswirkte, wählen Sie eine niedrige Zahl. Wählen Sie eine hohe Zahl, falls sich Ihre multiple Sklerose stark auf Ihre Arbeit auswirkte.

Erwägen Sie nur, wie stark sich Ihre multiple Sklerose auf Ihre Produktivität während der Arbeit ausgewirkt hat.

Meine multiple Sklerose hatte keinen Einfluss auf meine Arbeit	0	1	2	3	4	5	6	7	8	9	10	Meine multiple Sklerose hielt mich völlig von der Arbeit ab

EINE ZAHL EINKREISEN

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5): 353-65. 12/2017, Version 1.0

PID: _____ **Datum:** ___. ___ . _____ **Visite** _____

6. Wie sehr wirkte sich Ihre multiple Sklerose in den vergangenen sieben Tagen auf Ihre normalen täglichen Aktivitäten aus (Berufstätigkeit ausgenommen)?

Mit normalen Aktivitäten meinen wir die üblichen Aktivitäten wie Hausarbeit, Einkaufen, Kinderversorgung, Sport, Lernen etc. Denken Sie hierbei an Zeiten, an denen das Pensum oder die Art der Aktivität, die Sie ausführen konnten, eingeschränkt war, und die Zeiten, in denen Sie weniger tun konnten als Sie wollten. Falls sich Ihre multiple Sklerose nur wenig auf Ihre Aktivitäten auswirkte, wählen Sie eine niedrige Zahl. Wählen Sie eine hohe Zahl, falls sich Ihre multiple Sklerose stark auf Ihre Aktivitäten auswirkte.

Erwägen Sie nur, wie stark sich die multiple Sklerose auf Ihre normalen täglichen Aktivitäten ausgewirkt hat (Berufstätigkeit ausgenommen).

Meine multiple Sklerose hatte keinen Einfluss auf meine täglichen Aktivitäten	0	1	2	3	4	5	6	7	8	9	10	Meine multiple Sklerose hielt mich völlig von meinen täglichen Aktivitäten ab

EINE ZAHL EINKREISEN

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Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5): 353-65. 12/2017, Version 1.0