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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Events
ARR	Annualized Relative Rate
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CCOD	Clinical Cut-off Date
CDP	Confirmed Disability Progression
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
FSS	Functional System Score
IA	Interim Analysis
IFN	Interferon
IRR	Infusion Related Reactions
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale (29-item scale)
NEDA	No Evidence of Disease Activity
NEP	No Evidence of Progression
NEPAD	No Evidence of Progression and Active Disease
PDR	Protocol Defined Relapse
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
PRO	Patient reported outcomes
PT	Preferred Term
RCT	Randomized Clinical Trials
RMS	Relapsing multiple sclerosis

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Abbreviation	Definition
RRMS	Relapsing Remitting Multiple sclerosis
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
TEAE	Treatment-Emergent Adverse Events
US	United States
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
US	United States
T25FW	Timed 25-Foot Walk Test
9HPT	Nine-Hole Peg Test
FLAIR	Fluid-Attenuated Inversion-Recovery
QoL	Quality of Life
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SFU	Safety Follow-up
MH	Medical History
REML	Restricted Maximum Likelihood Method
RBC	Red blood cell
GGT	Gamma-Glutamyl Transpeptidase
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
HEENT	Head, eye, ear, nose, and throat
HBCAb	Hepatitis B core antibody
WBC	White Blood cell

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1. **BACKGROUND**

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 400,000 people in the United States (U.S.) and 2.3 million worldwide ([Tullman et al. 2013](#)). MS is clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression. These include relapsing remitting MS (RRMS), primary progressive MS (PPMS), progressive relapsing MS (PRMS), and secondary progressive MS (SPMS) (([Lublin et al. 1996](#), [Lublin et al. 2014](#)). The most frequent disease course of MS begins with a relapsing-onset presentation in approximately 85% patients developing the so-called relapsing-remitting form of MS ([Confavreaux et al. 2000](#); [Leray et al. 2015](#)).

The phase III randomized clinical trials (RCTs) have demonstrated a favorable benefit-risk ratio of ocrelizumab in RMS and PPMS patients. These studies have completed the controlled treatment period and are in the open label extension phase.

Furthermore, the phase IIIb/IV trials CASTING and ENSEMBLE (the Parent or P-trial studies) evaluated the effectiveness and safety of ocrelizumab in MS patients.

Based on the favorable profile of ocrelizumab, it is justified to offer ocrelizumab to these patients in order to reduce the frequency of relapses and delay disability progression. Furthermore, F. Hoffmann-La Roche (Roche) had committed to provide treatment for above mentioned patients in the P-trial. Thus, patients who complete the treatment period of the P-trials will be offered participation in this Extension study. Providing patients with the opportunity to prolong treatment with ocrelizumab will provide more information on the long-term safety of ocrelizumab in MS, as well as further collection of tolerability and effectiveness information from patients with long-term exposure. Analyzing the long-term safety, tolerability, and effectiveness of ocrelizumab is of critical importance to eventually help clinicians make informed decisions on therapy for patients.

Please refer to the protocol for the references cited above and for further details on ocrelizumab background.

This document will describe the Primary and Final analysis (treatment and follow-up period) for ENSEMBLE patients enrolled in LIBERTO study.

2. **STUDY DESIGN**

This is a single arm, open label, multicenter Extension study in patients on ocrelizumab therapy who are eligible for roll over based on the investigator decision in the Roche Parent trial. Patients will receive treatment with ocrelizumab as single 600 mg infusions in 500 mL 0.9% sodium chloride every 24 weeks up to Week 72 of this study.

The study will consist of the following periods:

- Screening period: The screening visit should be scheduled up to two weeks prior to the first infusion of ocrelizumab. This period of time should not be exceeded.
- Treatment period: The first visit of the Treatment period (first infusion of ocrelizumab) should be 24 weeks (± 14 days) after the last infusion of ocrelizumab in the P-trial. Also, in case if pregnancy/ breastfeeding the Enrolment visit would be done at the same time as the last visit of the P-trial.

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Ocrelizumab will be administered every 24 weeks up to Week 72 of this study and the last visit in the treatment period will be conducted 24 weeks after the last dose of ocrelizumab.

- A safety follow-up period of 48 weeks after the last infusion of the study drug, as explained below.

Safety follow-up Period:

The safety follow-up period is of 48 weeks after the last infusion of study drug (protocol Section 3.1.4 for details). When patients begin an alternative treatment for MS (see protocol section 4.4.1 “Prohibited Therapy”), they will be discontinued from the study.

Patients who decide to leave the study and switch to commercial ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Effectiveness Outcome Measures

The following endpoints will be analyzed to evaluate the effectiveness of ocrelizumab therapy in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial:

Related to disability progression:

- Time to onset of CDP sustained for at least 24 weeks from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)
- Time to onset of CDP sustained for at least 48 weeks from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)
- Proportion of patients who have confirmed disability improvement (CDI), CDP for at least 24 weeks and for at least 48 weeks yearly and over the duration of treatment from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)
- Proportion of patients who have improved, stable or worsened disability compared with baseline (inclusion in Extension study) measured by expanded disability status scale (EDSS) (annually/ by epoch and over duration of treatment) from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)
- Time to 20% increase in timed 25-foot walk test (T25FWT); time to 20% increase in timed nine-hole peg test (9HPT) sustained for at least 24 weeks and for at least 48 weeks and proportion of patients achieving a sustained increase assessed yearly and over the duration of treatment.

Other clinical measures and composite endpoints:

- Time to first protocol-defined event of disease activity from baseline (ENSEMBLE) to week 288 (LIBERTO week 96) : for NEDA, NEP and NEPAD

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- Time to first relapse from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)
- Annualized relapse rate yearly and over the duration of the treatment
- Proportion of patients relapse free yearly and over the duration of the treatment
- Change from baseline (parent trial) in cognitive performance as measured by the Symbol Digit Modalities Test (SDMT)

The definition of a protocol-defined event of disease activity is defined in Section 4.4.1

Related to MRI

- Total number of T1 Gd-enhancing lesions as detected by brain MRI over time (from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96))
- Total number of new and/or enlarging T2 lesion as detected by brain MRI over time (from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96))
- Change in total T1 hypointense lesion volume over time (from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96))
- Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions as detected by brain MRI over time from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96)
- Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time (from ENSEMBLE week 8 to LIBERTO week 96)
- Presence and evolution of leptomeningeal follicles for ENSEMBLE patients with identified FLAIR late enhancing lesions

Other measures related to MS disease

- Time to treatment discontinuation/switch from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)

Patient Reported Outcomes (PROs)

- Employment status (Work Productivity and Activity Impairment Questionnaire [WPAI]) from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)
- SymptoMScreen from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)
- Quality of life (QoL) (Multiple Sclerosis Impact Scale [MSIS]-29) from baseline (ENSEMBLE) to week 288 (LIBERTO week 96)

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2.2.2 Secondary Efficacy Outcome Measures

Not Applicable

2.2.3 Exploratory Outcome Measures

Exploratory outcome measures are used to further investigate the effect of ocrelizumab on antibody and T cell responses in patients administered an approved severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine.

- A separate analysis was performed to analyze the immune response to SARS-CoV-2 vaccine, COVID-19 analyses are therefore not in scope of this SAP. Details were specified in a separate analysis plan.

2.2.4 Pharmacokinetic Efficacy Outcome Measures

Not Applicable

2.2.5 Safety Outcome Measures

- Rate and nature of adverse events
- Changes in vital signs, neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-MS central nervous system [CNS] pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration)

2.3 DETERMINATION OF SAMPLE SIZE

This is an extension study of ocrelizumab where patients will be enrolled from qualifying P-trials (Casting & Ensemble). The final sample size will depend on factors such as the number of participating sites and the number of eligible patients from the respective P-trials. Therefore, no formal determination of sample size was performed.

2.4 ANALYSIS TIMING

This Analysis will be performed on all ENSEMBLE patients who rolled over to LIBERTO.

The analysis will be performed after the last patient's last visit including the safety follow-up period.

Analysis will be performed on the 6-year follow-up from ENSEMBLE/LIBERTO (if applicable), which is defined as the time from the first infusion of Ocrelizumab in ENSEMBLE until LIBERTO week 96/end of treatment for any efficacy measurement and 2-year during the safety follow-period if applicable.

The end of the treatment period will be the last visit date of any efficacy measurement at week 288 (LIBERTO week 96) (including EDSS, MRI, T25FW, 9HPT and PRO) or withdrawal date.

The duration of the treatment period is calculated as: End of treatment Period – first infusion date + 1

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3. STUDY CONDUCT

3.1 RANDOMIZATION

Not Applicable

3.2 INDEPENDENT REVIEW FACILITY

Not Applicable

3.3 DATA MONITORING COMMITTEE

Not Applicable

4. STATISTICAL METHODS

For continuous variables, descriptive statistics (e.g., number of patients [n], mean, standard deviation [SD], median, 25th and 75th percentiles, minimum, maximum) will be calculated and summarized.

For categorical variables, the number and percentage in each category will be displayed.

Statistical methods for analysis of effectiveness variables are detailed in the Effectiveness Analyses section below.

Unless otherwise specified, statistical tests will be two-sided, and the statistical significance level will be 5%. Corresponding 95% CIs will be presented as appropriate. Although multiple statistical tests may be conducted, no adjustments to the Type 1 error rate will be made.

The analyses outlined in this SAP supersede those specified in the protocol.

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

All ENSEMBLE patients that roll over to LIBERTO and receive dose of Ocrelizumab in LIBERTO will be included in the ITT population. Patients who prematurely withdrew from the study for any reason will still be included in the ITT population.

4.1.2 Per Protocol Population

Not Applicable

4.1.3 Pharmacokinetic-Evaluable Population

Not applicable

4.1.4 Safety Population

All patients who rolled over from ENSEMBLE to LIBERTO and received any dose of ocrelizumab in LIBERTO will be included in the safety population (SAF).

4.1.5 Safety Follow-up Population

All patients in ITT population who has at least one non-missing assessment during the safety follow-up period will be included in the safety follow-up population (SFU).

4.2 ANALYSIS OF STUDY CONDUCT

Patient disposition information will be summarized as follows:

- Number of patients enrolled in ENSEMBLE ITT Population
- Number of ENSEMBLE patients enrolled in LIBERTO
- Number of ENSEMBLE patients in the LIBERTO ITT population
- Number of ENSEMBLE patients in the LIBERTO Safety (SAF) population
- Number of ENSEMBLE patients who completed parent study and did not enroll in LIBERTO
- Number of ENSEMBLE patients who completed week 288 (LIBERTO) study treatment
- Number of patients who discontinue study treatment and the reasons for study treatment discontinuation during the treatment period
- Number of ENSEMBLE patients in the Safety Follow-up (SFU) population
- Number of ENSEMBLE patients who completed LIBERTO Safety Follow-up period
- Number of ENSEMBLE patients who discontinue LIBERTO Safety Follow-up period the reasons for study discontinuation during safety Follow-up period

A list of patients who discontinued from study treatment during the treatment period and a list of patients who discontinued the safety follow-up period will be provided.

Major protocol violations from ENSEMBLE, including violations of inclusion/exclusion criteria collected during the study will be summarized and listed on ITT and SFU population.

4.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

4.3.1 LIBERTO Baseline Information

The following demographic and baseline characteristics will be summarized for the ITT population based on LIBERTO baseline information:

- Age (years) as continuous variable and age in the following categories:
 - ≤ 40, > 40
 - ≤ 18, 18 - ≤ 40, > 40
- Gender
- Education status
- Female fertility status
- LIBERTO Baseline MRI (MRI at week 192 visit from ENSEMBLE)
 - Number of Gd-enhancing T1 lesions at Baseline as continuous and in categories (0,1,2,3,>=4)
 - Volume of T2 lesions at Baseline
- Baseline EDSS (continuous and its category (<2.5 and ≥2.5))

4.3.2 ENSEMBLE Baseline Information

The following demographic and baseline characteristics will be summarized for the ITT based on ENSEMBLE baseline information and also for patients who completed ENSEMBLE treatment period but did not roll over to LIBERTO:

- Age (years) as continuous variable and age in the following categories:
 - ≤ 40 , > 40
 - ≤ 18 , $18 - \leq 40$, > 40
- Gender
- Female fertility status
- Country
- Height (cm), weight (kg), and Body Mass Index (BMI: kg/m²)
- Smoking history (never, current, previous); if previous, years since last use and years relative to MS diagnosis; if current or previous, years of smoking.
- Education status
- Qualifying events for enrollments
 - 1) Only enrolled due MS Relapse
 - 2) Only enrolled due to MRI Activity
 - ≥ 1 T1 Gd-enhanced lesion (only)
 - ≥ 2 New or enlarging T2 lesion (only)
 - Both
 - 3) Enrolled due to MS relapse and any MRI activity

Disease activity before enrollment will be summarized only on ITT population as:
 the number of relapses over the year prior to baseline (1, >1) having the date of the last relapse

- within 6 months before baseline
- within 6 months and 12 months before baseline

Multiple Sclerosis History

- Duration since MS Symptom Onset (years)
 (Date of ENSEMBLE baseline visit – onset date of MS symptoms +1) / 365.25
- Duration since RRMS Diagnosis (years)
 (Date of ENSEMBLE baseline visit – date of diagnosis of RRMS +1) / 365.25
- Baseline EDSS (defined as the average of the EDSS scores at the screening and baseline visits) and its category (<2.5 and ≥ 2.5)

Screening Disease History– Relapse on ITT and SFU population

- Number of relapses in the last year as continuous and in categories (0, 1, 2, 3, ≥ 4) and (≤ 1 and > 1)
- Duration since last onset of MS relapse prior to enrollment (months) and its category (≤ 3 months, > 3 and ≤ 6 months, > 6 months)
- (Date of ENSEMBLE baseline visit – date of last onset of MS relapse prior to enrollment +1) / 30.4375
- Sites and symptoms for the most recent relapse

Note that for this analysis, if the date of the relapse is completely missing or if only the year is available, this will not be included in the analysis. If the day is missing, it will be imputed to the first day of the month.

Screening Disease History – MRI on ITT and SFU population

- Presence of T1 Gd+ at screening MRI

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- Number of Gd-enhancing T1 lesions at Screening as continuous and in categories (0, 1, 2, 3, >=4) at Screening
- Number of T2 lesions at Screening

ENSEMBLE Week 8 MRI – Baseline reset MRI only on ITT population

- presence of T1 Gd+ (Yes/No)
- Number of Gd-enhancing T1 lesions at Baseline reset as continuous and in categories (0, 1, 2, 3, >=4)
- Volume of T2 lesions at Baseline reset

Demographics and relevant baseline characteristics will be listed on the ITT and SFU population.

4.3.3 Medical history

For each previous and concurrent medical history recorded medical history (MH), the term entered by the investigator describing the event (the “reported term”) will be assigned a standardized term (the “Preferred Term” [PT]) and assigned to a superclass term (the “System Organ Class” [SOC]) on the basis of the MedDRA World Health Organization (WHO) dictionary of terms.

Previous and concurrent medical history collected in the P-trial (ENSEMBLE study) will be summarized in the ITT by SOC and PT.

Previous medical history is defined as an event with an end date before the date of first dose in ENSEMBLE study.

Concurrent medical history is defined as an event with an onset date before the date of first dose in ENSEMBLE study (and no worsening after onset) and an unknown end date or an end date after the date of first dose or an onset date on or after the date of first dose of study drug from ENSEMBLE period and before last dose from LIBERTO period.

Previous and concurrent medical history will be also listed.

4.4 EFFECTIVENESS ANALYSES

4.4.1 Effectiveness Definition

All the effectiveness endpoints will be performed using the ITT population.

4.4.1.1 Protocol-defined event definition (corresponding to EDA)

The definition of a protocol-defined event of disease activity is the occurrence of at least one of the following individual events while on treatment with ocrelizumab:

- A protocol-defined relapse defined as an occurrence of new or worsening neurological symptoms attributable to MS. Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications), and immediately be preceded by neurological stability for at least 30 days.
- 24-weeks CDP based on increase in EDSS while on treatment with ocrelizumab
- A new T1 Gd-enhanced lesion on MRI after ENSEMBLE week 8
- A new and/or enlarging T2 hyperintense lesion on MRI after ENSEMBLE week 8 visit compared to the ENSEMBLE Week 8 visit MRI scan

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The MRI activity will be calculated on the events starting from ENSEMBLE week 8 (baseline reset).

4.4.1.2 Protocol-defined event definition (corresponding to EP)

The definition of a protocol-defined event of progression is the occurrence of at least one of the following individual events sustained 24 weeks while on treatment with ocrelizumab:

- 24-weeks CDP based on increase in EDSS while on treatment with ocrelizumab
- Confirmed $\geq 20\%$ increase in timed T25FWT sustained for 24 weeks
- Confirmed $\geq 20\%$ increase in 9HPT sustained for 24 weeks

4.4.1.3 Protocol-defined event definition (corresponding to EPAD)

The definition of a protocol-defined event of progression or disease activity is the occurrence of at least one of the following individual events sustained 24 weeks while on treatment with ocrelizumab:

- 24-weeks CDP based on increase in EDSS while on treatment with ocrelizumab
- Confirmed $\geq 20\%$ increase in timed T25FWT sustained for 24 weeks
- Confirmed $\geq 20\%$ increase in 9HPT sustained for 24 weeks
- A protocol-defined relapse defined as an occurrence of new or worsening neurological symptoms attributable to MS. Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications), and immediately be preceded by neurological stability for at least 30 days
- A new T1 Gd-enhanced lesion on MRI after ENSEMBLE week 8 visit
- A new and/or enlarging T2 hyperintense lesion on MRI after ENSEMBLE week 8 visit compared to the ENSEMBLE Week 8 visit MRI scan

The MRI activity will be calculated on the events starting from ENSEMBLE week 8 (baseline reset).

4.4.1.4 Protocol-defined MS Relapse definition

A protocol-defined MS relapse is an occurrence of new or worsening neurological symptoms attributable to MS that meets the following criteria:

- Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications)
- Symptoms should be preceded by neurological stability for at least 30 days
- Symptoms should be accompanied by new objective neurological worsening determined with a timely EDSS/ Functional Systems Score (FSS) assessment, consistent with an increase of at least:
 - ≥ 0.5 points on EDSS scale
 - or ≥ 2 points on one of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual
 - or ≥ 1 point on two or more of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual

Information related to a Protocol-Defined Relapse (PDR) will be captured on a clinical relapse event case report form (CRF) page (Multiple Sclerosis Relapse). If the following criteria are satisfied, the clinical relapse will qualify as a PDR:

1. Clinical relapse is reported on eCRF.
2. Check-box of “Did symptoms persist for >24 hours and were not being attributable...” on the Clinical MS relapse event is checked.
3. Check if the first EDSS assessment at a visit (unscheduled or scheduled) on or after the onset date of the relapse is increased by ≥ 0.5 steps from the previous EDSS; or selected FSS domains relevant to the relapse event (pyramidal, ambulation, cerebellar, brainstem, sensory, or converted visual) are increased by ≥ 2 points on one domain or ≥ 1 point on two or more domains. When deriving this step do the following:
 - Take the last EDSS/FSS score before each clinical relapse onset date
 - Take the first EDSS/FSS score on or after each clinical relapse onset date
 - Calculate the difference between the two scores
 - Select clinical relapses where there is an increase of ≥ 0.5 in EDSS or ≥ 2 on one appropriate FSS domain or ≥ 1 on two or more appropriate FSS domains
4. For each relapse that satisfies the 3 criteria above, check if the following relapses are within 30 days (i.e., the onset dates are ≤ 30 days apart). If they are within 30 days, then the later relapses are not PDR.

4.4.1.5 24-Week/48-Week Confirmed Disability Progression (CDP) definition

Disability Progression as measured by EDSS is defined a ≥ 1 -point increase in EDSS score from a baseline EDSS score of 1–5 inclusive, a 0.5-increase from a baseline EDSS score higher than 5 and a 1.5-increase from a baseline EDSS score from 0 to 1 exclusive. Because of the variability of EDSS, a single measurement at the baseline visit might not provide a sufficiently reliable baseline EDSS. Therefore, using an average score from two separate measurements may improve the reliability of baseline EDSS and the reliability of confirmed disability progression seen in the study. In the analysis of CDP,

- From ENSEMBLE baseline to week 288 (LIBERTO week 96: 6-year analysis), baseline EDSS is defined as the average of the EDSS scores at the ENSEMBLE screening and ENSEMBLE baseline visits (of note, any baseline visits occurring after the first dosing date will be disregarded in the computation of the baseline EDSS score), without rounding. If one of the EDSS scores from the screening or baseline visit was missing, the other was used for baseline EDSS.

Initial progression can happen at any scheduled or unscheduled visit during the treatment period in LIBERTO or the ENSEMBLE treatment period.

An initial disability progression becomes confirmed if the following conditions are met:

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1. A sustained change in EDSS for a minimum of 24 weeks or 48 weeks (-2 weeks) from the initial progression event i.e. the change in EDSS must be sustained at all available (scheduled or unscheduled) visits for a minimum of 24/48 weeks ($\geq 168/336 - 14 \text{ days} = 154/322 \text{ days}$) after initial progression. A “Early Discontinuation” visit can be used as a confirmation visit if it falls into the visit window (defined in the protocol) of any scheduled visit. The EDSS assessments (if any) between the initial disability progression and the confirmation of disability progression should be at least as high as the minimum change required for progression.
2. Scheduled visits within 30 days after the onset of a clinical relapse that meets conditions 1, 2 and 3 of a protocol-defined relapse definition cannot be used for confirmation of disability progression. The confirmation of the disability progression must then be based on the EDSS assessment at the next scheduled visit (which is not within 30 days of a protocol defined relapse).
3. If a subject has a missing assessment at the scheduled visit taking place at 24/48 weeks ($\geq 154/322 \text{ days}$) after an initial progression, the confirmation of the disability progression must be based on the assessment at the next scheduled visit.

Subjects who reach week 288 (week 96 in LIBERTO) without confirmed progression of disease will be censored at the date of their last EDSS assessment at week 288 (LIBERTO week 96). Subjects with an initial assessment of disease progression who subsequently discontinue from the study without further assessments will not be considered to have confirmed disease progression, if the discontinuation reason is not lack of efficacy or death. Subjects who discontinue from the study due to lack of efficacy or death without confirmed progression of disease will be imputed as having an event (i.e., CDP) at the time of discontinuation.

4.4.1.6 Definition of Confirmed $\geq 20\%$ increase in T25FWT sustained for 24 weeks/48 weeks.

T25FWT (seconds) is computed by taking the average scores of two 25-Foot Timed Walk trials. If one of the trials was missing, then the other is used.

Initial $\geq 20\%$ increase in T25FWT can happen at any scheduled or unscheduled visit between ENSEMBLE baseline to week 288 (LIBERTO week 96).

An initial $\geq 20\%$ increase in T25FWT becomes confirmed if the following conditions are met:

1. A sustained change in T25FWT for a minimum of 24/48 weeks (-2 weeks) from the initial event i.e. the change in T25FWT must be sustained at all available (scheduled or unscheduled) visits for a minimum of 24/48 weeks ($\geq 168/336 - 14 \text{ days} = 154/322 \text{ days}$) after initial progression. An “Early Discontinuation” visit can be used as a confirmation visit if it falls into the visit window (defined in the

protocol) of any scheduled visit. The T25FWT assessments (if any) between the initial change and the confirmation should be $\geq 20\%$.

2. Scheduled visits within 30 days after the onset of a clinical relapse that meets conditions 1, 2 and 3 of a protocol-defined relapse definition cannot be used for confirmation. The confirmation must then be based on the T25FWT assessment at the next scheduled visit (which is not within 30 days of a protocol defined relapse).

3. If a patient has a missing assessment at the scheduled visit taking place at 24/48 weeks ($\geq 154/322$ days) after an initial $\geq 20\%$ change, the confirmation must be based on the assessment at the next scheduled visit.

Patients who complete the treatment period without confirmed $\geq 20\%$ change will be censored at the date of their last T25FWT assessment during the treatment period.

Patients with an initial $\geq 20\%$ change who subsequently discontinue from the study without further assessments will not be considered to have the $\geq 20\%$ change confirmed, if the discontinuation reason is not lack of efficacy or death. Patients who discontinue from the study due to lack of efficacy or death without confirmed $\geq 20\%$ change will be imputed as having the event (i.e., $\geq 20\%$ increase in T25FWT sustained for 24/48 weeks) at the time of discontinuation.

Missing data will be imputed as follows. If the test results are not available due to a "physical limitation," impute the maximum possible value for the scale. If the test results are not available but it is NOT due to a "physical limitation," use the result from the other trial to impute the missing value. In the case of outliers, the lower bound is set to be 2.2 seconds and upper bound is set to be 180 seconds.

4.4.1.7 Definition of Confirmed $\geq 20\%$ increase in 9HPT sustained for 24 weeks/48 weeks

9HPT (seconds) is computed by taking the average scores from the four trials on the 9HPT (the two trials for each hand are averaged).

Initial $\geq 20\%$ increase in 9HPT can happen at any scheduled or unscheduled visit between ENSEMBLE baseline to LIBERTO week 96.

An initial $\geq 20\%$ increase in 9HPT becomes confirmed if the following conditions are met:

1. A sustained change in 9HPT for a minimum of 24/48 weeks (-2 weeks) from the initial event i.e. the change in 9HPT must be sustained at all available (scheduled or unscheduled) visits for a minimum of 24/48 weeks ($\geq 168/336 - 14$ days = 154/322 days) after initial progression. An "Early

Discontinuation" visit can be used as a confirmation visit if it falls into the visit window (defined in the protocol) of any scheduled visit. The 9HPT assessments (if any) between the initial change and the confirmation should be $\geq 20\%$.

2. Scheduled visits within 30 days after the onset of a clinical relapse that meets conditions 1, 2 and 3 of a protocol-defined relapse definition cannot be used for confirmation. The confirmation must then be based on the 9HPT assessment at the next scheduled visit (which is not within 30 days of a protocol defined relapse).

3. If a patient has a missing assessment at the scheduled visit taking place at 24/48 weeks ($\geq 154/322$ days) after an initial $\geq 20\%$ change, the confirmation must be based on the assessment at the next scheduled visit.

Patients who complete the treatment period without confirmed $\geq 20\%$ change will be censored at the date of their last 9HPT assessment during the treatment period.

Patients with an initial $\geq 20\%$ change who subsequently discontinue from the study without further assessments will not be considered to have the $\geq 20\%$ change confirmed, if the discontinuation reason is not lack of efficacy or death. Patients who discontinue from the study due to lack of efficacy or death without confirmed $\geq 20\%$ change will be imputed as having the event (i.e., $\geq 20\%$ increase in 9HPT sustained for 24/48 weeks) at the time of discontinuation.

Missing data will be imputed as follows. If the test results are not available due to a "physical limitation," impute the maximum possible value for the scale. If the test results are not available but it is NOT due to a "physical limitation," impute the missing test score using the result from the other trial of the same hand. If the result from the other trial of the same hand is also missing, use the average score from the other hand (or available score from one trial if the result from one trial only is available).

In the case of outliers, the lower bound is set to be 10 seconds and the upper bound is set to be 300 seconds.

4.4.2 Effectiveness Endpoints

Effectiveness of ocrelizumab will be evaluated by means of a set of endpoints addressing different facets of MS. There are no primary endpoints defined in this study. All effectiveness coxanalyses will be performed on the ITT population.

4.4.2.1 Related to Disability Progression

4.4.2.1.1 Time to onset of CDP sustained for at least 24 weeks

All 24 weeks CDP, as defined above, that occurred before week 288 (week 96 of LIBERTO) including the ENSEMBLE treatment period will be considered.

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Patients without a 24-week CDP will be censored at the last EDSS assessment. Patients who discontinue from the study due to lack of efficacy or death without confirmed progression of disease will be imputed as having an event at the time of discontinuation.

The Kaplan–Meier methods will be used to estimate the survival function for the time to 24-week CDP. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented from week 24 to week 288 (LIBERTO week 96). Kaplan-Meier plots will be produced.

Same analysis will be provided for the time to 20% increase in T25FWT sustained for at least 24 weeks and for the time to 20% increase in 9HPT sustained for at least 24 weeks.

4.4.2.1.2 Time to onset of CDP sustained for at least 48 weeks

All 48 weeks CDP, as defined above, that occurred before week 96 of LIBERTO including the ENSEMBLE treatment period will be considered.

Patients without a 48-week CDP will be censored at the last EDSS assessment. Patients who discontinue from the study due to lack of efficacy or death without confirmed progression of disease will be imputed as having an event at the time of discontinuation.

The Kaplan–Meier methods will be used to estimate the survival function for the time to 48-week CDP. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented at 24 weeks, 48 weeks, 72 weeks, 96 weeks, 120 weeks, 144 weeks, 168 weeks, week 192, week 216, week 240, week 264 and week 288. Kaplan-Meier plots will be produced.

Same analysis will be provided for the time to 20% increase in T25FWT sustained for at least 48 weeks and for the time to 20% increase in 9HPT sustained for at least 48 weeks.

4.4.2.1.3 Proportion of patients who have confirmed disability improvement (CDI) for at least 24 weeks yearly and over the duration of treatment

For patients with a baseline EDSS score ≥ 2 , disability improvement is defined as an improvement of ≥ 1 point on the EDSS score confirmed at a regular scheduled visit at least 24 weeks after the initial documentation of neurological status when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is above 5.5. The same approach to data derivation of CDP will be used for the derivation of CDI, in particular the confirmation of the disability improvement at 24 weeks. For patients with baseline EDSS score < 2 , CDI will not be defined.

The proportion of patients who, over a 6-year period (from ENSEMBLE baseline to week 288: LIBERTO week 96), have 24-week CDI will be presented along with a two-sided 95% Clopper-Pearson exact confidence interval.

Patients who discontinue from treatment (for any reason) without confirmed CDI will be excluded from the analysis.

The same analysis will be provided for the following timepoint: baseline (ENSEMBLE) to week 48 (ENSEMBLE), week 48 (ENSEMBLE) to week 96 (ENSEMBLE), week 96 (ENSEMBLE) to week 144 (ENSEMBLE), week 144 (ENSEMBLE) to week 192 (ENSEMBLE), week 192 (LIBERTO baseline) to week 240 (LIBERTO week 48), week 240 (LIBERTO week 48) to week 288 (LIBERTO week 96) and week 192 (LIBERTO baseline) to week 288 (LIBERTO week 96).

4.4.2.1.4 Proportion of patients who have confirmed disability improvement (CDI) for at least 48 weeks yearly and over the duration of treatment

Disability improvement will use the same definition in section 4.4.2.1.3;

The proportion of patients who, over a 6-year period from baseline (ENSEMBLE) to week 288 (LIBERTO week 96), have 48-week CDI will be presented along with a two-sided 95% Clopper-Pearson exact confidence interval.

Patients who discontinue from treatment (for any reason) without confirmed CDI will be excluded from the analysis.

The same analysis will be provided for the following timepoint: baseline (ENSEMBLE) to week 48 (ENSEMBLE), week 48 (ENSEMBLE) to week 96 (ENSEMBLE), week 96 (ENSEMBLE) to week 144 (ENSEMBLE), week 144 (ENSEMBLE) to week 192 (ENSEMBLE), week 192 (LIBERTO baseline) to week 240 (LIBERTO week 48), week 240 (LIBERTO week 48) to week 288 (LIBERTO week 96) and week 192 (LIBERTO baseline) to week 288 (LIBERTO week 96).

4.4.2.1.5 Mean change from baseline in EDSS score over the course of the study

Change in EDSS from ENSEMBLE baseline to week 288 (LIBERTO week 96) will be analyzed using a longitudinal mixed effects model repeated measure (MMRM). The model's fixed effects will include visit along with the following covariates:

- Age at disease diagnosis
- Gender
- History of smoking
- Baseline EDSS
- Presence or absence of T1 Gd-enhanced lesions at ENSEMBLE screening
- Presence or absence of LEM/FLAIR lesions at ENSEMBLE screening
- Number of relapses 1 year prior to enrollment

Visit will be treated as a repeated variable within a patient. Patients and visit will be treated as factor variables. An unstructured variance-covariance structure will be applied to model the within-patient errors. The model will be fitted using the Restricted Maximum Likelihood method (REML). Denominator degrees of freedom will be estimated using Satterthwaite's approximation. If the model does not converge, other variance-covariance structures can be considered.

4.4.2.1.6 Proportion of patients achieving a sustained increase for at least 24-week of T25FW /9HPT yearly and over the duration of treatment

The proportion of patients who, over a 6-year period (from ENSEMBLE baseline to week 288 (LIBERTO week 96), have a sustained increase of T25FW / 9HPT during a 24-week period will be presented along with a two-sided 95% Clopper-Pearson exact confidence interval.

Patients who discontinue from treatment (for any reason) without confirmed T25FW / 9HPT will be excluded from the analysis.

The same analysis will be provided for the following timepoint: ENSEMBLE baseline to ENSEMBLE week 48, ENSEMBLE week 48 to ENSEMBLE week 96, ENSEMBLE week 96 to ENSEMBLE week 144, ENSEMBLE week 144 to ENSEMBLE week 192, LIBERTO baseline (ENSEMBLE week 192) to LIBERTO week 48 (week 240), LIBERTO week 48 (week 240) to LIBERTO week 96 (week 288) and LIBERTO baseline (ENSEMBLE week 192) to LIBERTO week 96 (week 288).

The same analysis will be done on the proportion of patients who have a sustained increase during a 48-week period for T25FW and 9HPT.

4.4.2.2 Other clinical measures and composite endpoints

4.4.2.2.1 Time to first protocol-defined event of disease (NEDA, NEP, NEPAD)

Patients with early study discontinuation before any disease activity event will be censored at the withdrawal date. It will be imputed as having an event (EDA, EP, EPAD), if the discontinuation reason is lack of efficacy or death.

The Kaplan–Meier methods will be used to estimate the survival function for the time to first protocol-defined relapse. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented from week 24 to week 288 (LIBERTO week 96). Kaplan-Meier plot will not be provided.

This endpoint will be analyzed using the same approach as described above in section 4.4.2.1.1.

Same analysis will be provided for the time to first protocol-defined event of no evidence of progression (NEP) and for time to first protocol-defined event of no evidence of progression and active disease (NEPAD).

4.4.2.2.2 Time to first relapse

All protocol-defined relapses, as defined in section 4.4.1.4, that occurred during the treatment period (from ENSEMBLE baseline to week 288: LIBERTO week 96) will be considered.

Patients who did not experience an event at week 288 (LIBERTO week 96) are censored at the last available clinical visit up to week 288 (LIBERTO week 96). Patients who discontinue from the study due to lack of efficacy or death without relapse will be imputed as having an event at the time of discontinuation.

The Kaplan–Meier methods will be used to estimate the survival function for the time to first protocol-defined relapse. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented from 24 weeks to 288 weeks (LIBERTO week 96). Kaplan-Meier plot will not be produced.

4.4.2.2.3 Annualized relapse rate yearly and over the duration of the treatment

The unadjusted annualized protocol-defined relapse rate will be defined as the total number of protocol-defined relapses for all patients divided by the total years of drug exposure (defined as the duration of treatment period: first day of infusion (ENSEMBLE period) until week 288 (LIBERTO week 96) treatment period).

In addition, the adjusted annualized relapse rate will be estimated using a poisson regression model (from ENSEMBLE baseline to week 288: LIBERTO week 96), adjusting for:

- Age at disease diagnosis
- Baseline EDSS
- Presence of T1 Gd-enhanced lesions at ENSEMBLE screening (Yes/No)
- Presence of relapses in the last year prior to ENSEMBLE screening (Yes/No)

and including the log-transformed years of drug exposure time (in years) as an “offset” variable. The adjusted rates along with the two-sided 95% confidence interval will be presented.

The unadjusted ARR will be provided for the following period: from ENSEMBLE Baseline to LIBERTO week 96, from ENSEMBLE Baseline to ENSEMBLE week 48, from ENSEMBLE Week 48 to ENSEMBLE week 96, from ENSEMBLE week 96 to ENSEMBLE week 144, from ENSEMBLE week 144 to ENSEMBLE week 192, from LIBERTO baseline (ENSEMBLE week 192) to week 240 (LIBERTO week 48), from week 240 (LIBERTO week 48) to week 288 (LIBERTO week 96).

4.4.2.2.4 Proportion of patients relapse free, yearly and over the course of treatment (from ENSEMBLE baseline to week 288: LIBERTO week 96)

The proportion of patients without relapse from ENSEMBLE baseline to week 288 (LIBERTO week 96) will be performed on the ITT population and the corresponding two-sided Clopper-Pearson 95% confidence interval (CI) will be presented.

The proportion will be presented also from baseline (ENSEMBLE) to week 48 (ENSEMBLE), from Week 48 (ENSEMBLE) to week 96 (ENSEMBLE), from week 96 (ENSEMBLE) to week 144 (ENSEMBLE), from week 144 (ENSEMBLE) to week 192 (ENSEMBLE), from week 192 (LIBERTO baseline) to week 240 (LIBERTO week 48), from week 240 (LIBERTO week 48) to week 288 (LIBERTO week 96) and from ENSEMBLE week 192 (LIBERTO baseline) to week 288 (LIBERTO week 96).

4.4.2.2.5 Cognitive performance as measured by the Symbol Digit Modalities Test (SDMT)

Proportion of patients with ≥ 8 -point increase/decrease in SDMT (total number of correct symbols over 90 seconds) from ENSEMBLE baseline to week 288 (LIBERTO week 96)

A time to event for an 8-point change in the SDMT will be also provided.

Patients without a ≥ 8 -point change in the SDMT will be censored at the last SDMT assessment.

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The Kaplan–Meier methods will be used to estimate the survival function for the time to ≥ 8 -point change in the SDMT. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented from week 24 to week 288 (LIBERTO week 96). Kaplan-Meier plots will be produced.

4.4.2.3 Related to MRI

4.4.2.3.1 Total number of T1 Gd-enhancing lesions as detected by brain MRI over time

Data from unscheduled assessments will not be included in this summary or analysis.

The following analyses will be presented:

- Summary statistics for the number of T1 lesions (actual value) at each scheduled visit from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96)
- Number and percentage of patients from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96) having 0, 1, 2, 3, >1 , >3 .
- The unadjusted and adjusted rates of lesion occurrence combining all post-baseline week 8 (from week 8(ENSEMBLE) to week 288/LIBERTO week 96) will be calculated:
- The unadjusted rate will be the ratio of the total number of T1 Gd-enhanced lesions for all patients divided by the total number of brain MRI scans.
- The adjusted rate will be derived using a Poisson model. The dependent variable in the model will be the total number of T1-Gd-enhanced lesions.

The model will be adjusted for the following covariates:

- Presence or absence of T1 lesion Count at ENSEMBLE screening
- Baseline EDSS (<2.5 vs ≥ 2.5)

In order to account for patients potentially receiving varying numbers of brain MRI scans during the study, the log-transformed number of brain MRI scans received will be included in the model as an “offset”.

4.4.2.3.2 Total number of new and/or enlarging T2 lesion as detected by brain MRI over time

The number of new and/or enlarging T2 lesions from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96) will be calculated as the sum of the individual number of new and /or enlarging T2 lesions at each visit.

Data from unscheduled assessments will not be included in this summary or analysis.

The same analysis as total of T1 Gd-enhancing lesions in section 4.4.2.3.1 will be provided for the number of new and/or enlarging T2 lesions from ENSEMBLE week 8 to week 288 (LIBERTO week 96).

4.4.2.3.3 Change in total T1 hypointense (unenhancing) lesion volume over time (from week 8 (ENSEMBLE) to week 288/LIBERTO week 96)

Change from ENSEMBLE week 8 in T1 hypointense lesion volume detected by brain MRI from ENSEMBLE week 8 to week 288 (LIBERTO week 96) will be analyzed using a longitudinal MMRM.

These MMRM analyses will be undertaken using the same approach as described above in Section 4.4.2.1.5.

4.4.2.3.4 Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions (with leakage) as detected by brain MRI from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96)

The total number of FLAIR late enhancing lesions from week 8 (ENSEMBLE) to week 288 (LIBERTO week 96) will be summarized descriptively.

Data from unscheduled assessments will not be included in this summary.

The same analysis as the total of T1 Gd-enhancing lesions will be provided for the number of FLAIR.

4.4.2.3.5 Change in Brain volume as detected by brain MRI over time (from week 8 (ENSEMBLE) to week 288/LIBERTO week 96)

Brain volume is recorded as an absolute “normalized” (refer to “Electronic Data File Format & Transfer Specifications”) value at ENSEMBLE week 8 (baseline reset) then recorded at subsequent visits as a percentage change relative to the normalized brain volume value at ENSEMBLE week 8. Any volume measurement from the MRIs that were done after infusion at the same visit will not be included in the analysis, i.e., manually considered as missing.

Change and Percentage change in brain volume relative to ENSEMBLE Week 8, as detected by brain MRI scan, will be summarized at weeks 24, 48, 96, 144, 192, 216, 240 and 288 using descriptive statistics.

Data from other unscheduled assessments will not be included in this summary or analysis.

Descriptive statistics will be used to summarize the following:

- “normalized” and “pre-normalized” Brain volume at ENSEMBLE week 8
- Change and percentage change in brain volume at weeks 24, 48, 96, 144, 192, 216, 240 and 288.

In addition, change from ENSEMBLE week 8 in Brain volume detected by brain MRI from ENSEMBLE week 8 to week 288 (LIBERTO week 96) will be analyzed using a longitudinal MMRM.

These MMRM analyses will be undertaken using the same approach as described above in Section 4.4.2.1.5.

4.4.2.3.6 Change in white matter volume as detected by brain MRI over time (from ENSEMBLE week 8 to week 288/LIBERTO week 96)

Any volume measurement from the MRIs that were done after infusion at the same visit will not be included in the analysis, i.e., manually considered as missing.

Descriptive statistics will be used to summarize the following:

- Change and percentage change in white matter volume at ENSEMBLE weeks 24, 48, 96, 144 and 192 and LIBERTO weeks 24, 48 and 96 (week 216, 240 and 288).

In addition, change from ENSEMBLE week 8 in white matter volume detected by brain MRI from ENSEMBLE week 8 to week 288 (LIBERTO week 96) will be analyzed using a longitudinal MMRM.

These MMRM analyses will be undertaken using the same approach as described above in Section 4.4.2.1.5.

Data from other unscheduled assessments will not be included in this summary or analysis.

4.4.2.3.7 Change in grey matter volume as detected by brain MRI over time (from ENSEMBLE week 8 to week 288/LIBERTO week 96)

Any volume measurement from the MRIs that were done after infusion at the same visit will not be included in the analysis, i.e., manually considered as missing.

Descriptive statistics will be used to summarize the following:

- Change and percentage change in white matter volume at ENSEMBLE weeks 24, 48, 96, 144 and 192 and LIBERTO weeks 24, 48 and 96 (week 216, 240 and 288).

In addition, change from ENSEMBLE week 8 in grey matter volume detected by brain MRI from ENSEMBLE week 8 to week 288 (LIBERTO week 96) will be analyzed using a longitudinal MMRM.

These MMRM analyses will be undertaken using the same approach as described above in Section 4.4.2.1.5.

Data from other unscheduled assessments will not be included in this summary or analysis.

4.4.2.3.8 Presence and evolution of leptomeningeal follicles

The analysis will include patients with identified FLAIR late enhancing lesions with leakage.

Descriptive statistics of presence of leptomeningeal follicles at available visit will be provided.

Actual value will be summarized at all available visit.

4.4.2.4 Other measures related to MS disease

4.4.2.4.1 Time to treatment discontinuation/switch

Time to treatment discontinuation is defined as the time between the first treatment start date in LIBERTO until the discontinuation date.

Patients who did not discontinue the treatment during LIBERTO treatment period will be censored at week 288 (LIBERTO week 96).

The Kaplan–Meier methods will be used to estimate the survival function for the time to treatment discontinuation. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented at 24 weeks, 48 weeks, 72 weeks, 96 weeks, 120 weeks, 144 weeks, 168 weeks and 192 weeks from ENSEMBLE and at 216 weeks, 240 weeks and 288 weeks (respectively 24 weeks, 48 weeks and 96 weeks from LIBERTO).

4.4.2.5 Patients reported outcomes (PROs)

4.4.2.5.1 Employment status (Work Productivity and Activity Impairment Questionnaire [WPAI])

The WPAI is a PRO form of 6 items, used to assess working status, specifically the impact of MS on absenteeism, presentism, work productivity loss and activity impairment over the past 7 days.

Response options are:

Item #	Item Score	Details
1	Yes No	
2-4	Numerical	number of hours: ● missed from work because of problems associated with MS ● missed from work because of any other reason; ● actually worked
5-6	numerical rating scale	Ranging from 0 to 10, where a higher score corresponds to MS problems highly impacting work/regular daily activities.

Four sub scores are calculated and presented as a percentage.

WPAI sub scores	Calculation for score (%)
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Absenteeism (Percent work time missed due to problem)	$(Q2/(Q2+Q4)) * 100$
Presenteeism (Percent impairment while working due to problem)	$(Q5/10) * 100$
Work productivity (Percent overall work impairment due to problem)	$(Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4))x(Q5/10))]) * 100$
Activity Impairment (Percent activity impairment due to problem)	$(Q6/10) * 100$

Each WPAI sub-score will be summarized descriptively by visit from ENSEMBLE baseline to week 288 (LIBERTO week 96).

4.4.2.5.2 SymptoMScreen

The SymptoMScreen is formed of 12 distinct domains which list common MS symptoms including mobility, dexterity, vision, fatigue, cognition, bladder function, sensation, dizziness, spasticity, body pain, depression and anxiety. Extent of limitations affected by symptoms is scored on a 7-point likert scale. Item scores are summed to form a total score and higher score corresponds to worse symptom limitations.

	Item #	Item Scores
SymptoMScreen score	1-12	0 = Not affect at all 1 = Very mild limitation / I make minor adjustments 2 = Mild limitation/ I make frequent adjustments 3 = Moderate limitation/ I reduced my daily activities 4 = Severe limitation/ I gave up some activities 5 = Very severe limitation/ I'm unable to do many daily activities 6 = Total limitation/ I'm unable to do most daily activities

A total score will be calculated

	Calculation for total score	Range
SymptoMScreen score	The 12 items are summed for patients with all 12 questions non missing	0-72

The SymptoMScreen total score will be summarized descriptively by visit on the ITT population as continuous and categorical as follows: 0-12, 13-24, 25-36, 37-48, 49-60 and 61-72.

No imputation of missing data will be performed, i.e. only questionnaires with no missing items will be evaluated. The mean change of SymptoMScreen total score from ENSEMBLE baseline to week 288 (LIBERTO week 96) will be summarized.

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Descriptive statistics and change from baseline (ENSEMBLE) to week 288 (LIBERTO week 96) will be provided for each domain.

4.4.2.5.3 Quality of Life (Multiple Sclerosis Impact Scale [MSIS-29])

The MSIS-29 V2 is a 29-item PRO designed to measure the physical and psychological impact of MS. Items are rated on a 4-point Likert scale and are summed for each domain. These summed scores are transformed for ease of interpretability. Lower transformed scores correspond to better HRQoL.

Domain	Items #	Item scores	Domain score
Physical Scale	1-20	1 = Not at all 2 = A little 3 = Moderately 4 = Extremely	Sum of items 1-20, see below for missing data handling
Psychological Scale	21-29	1 = Not at all 2 = A little 3 = Moderately 4 = Extremely	Sum of items 1-20, see below for missing data handling

A transformed score will be calculated from each domain score, respectively

	Calculation for transformed score	Range
Physical Scale	$[(\text{domain score} - 20) / (80 - 20)] * 100$, see below for missing data handling	0-100
Psychological Scale	$[(\text{domain score} - 9) / (36 - 9)] * 100$, see below for missing data handling	0-100

Missing data handling:

- Respondents must have a minimum of 10 completed items in the physical scale, or a minimum of 5 completed items in the psychological scale in order to use the imputing process above to impute the missing individual items
- Missing scores in the specific scale are imputed as the average of the scores of all (completed) items in that scale. For example, if a patient has completed 15 items (item 1-15) in the physical scale and the values for item 16-20 are missing. Then first sum the completed items 1-15 and then divide by 15 to get his respondent-specific mean score. Then use this value as the score for each of the missing 5 items 16-20. Then generate a total score as usual by summing the values of the 15 completed items 1-15 and the 5 imputed items 16-20 based on the score calculation for physical scale above.

For any analyses of domain scores, transformed domain scores will be used as they have range of 0-100 and intuitive to understand.

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The mean change in the physical and psychological MSIS-29 v2 domain scores from ENSEMBLE baseline to week 288 (LIBERTO week 96) will be summarized descriptively.

4.4.3 Exploratory Effectiveness Endpoints

NA

4.4.4 Sensitivity Analyses

NA

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

No pharmacokinetic or pharmacodynamics analyses are planned in this study

4.6 SAFETY ANALYSES

The safety outcome measures comprise the following: the incidence and nature of all adverse events, including findings on vital sign measurements, physical and neurological examinations, clinical laboratory tests, locally reviewed MRI for safety (non-MS CNS pathology), and concomitant medications.

The safety analysis will be performed on the Safety population (SAF).

4.6.1 Exposure of study medication

Definitions:

Dose: Ocrelizumab dose is given as one infusion, or two infusions administered 2 weeks apart. Patients will be considered to have received a Dose of treatment if at least part of one infusion of that Dose (either Day 1 or Day 15 for dual infusions) was given. If a dose is completely missed instead of delayed, the next dose number will be based on the number of previous doses received.

Treatment duration (in weeks) for a patient will be calculated as follows:

$[(\text{Date of last contact}^* - \text{Date of first dose (ENSEMBLE)} + 1) / 7]$

- *Earliest
- 1) date of last contact from the study completion page or study early termination page
 - 2) date of death
 - 3) DBL

Exposure Analysis

The following measures of exposure of ocrelizumab will be summarized using descriptive statistics from ENSEMBLE baseline to week 288 (LIBERTO week 96) on SAF and SFU population:

- Treatment duration (weeks)
- Number of doses received (day 1 and day 15 infusions are considered as one dose)
- Total cumulative dose (mg)

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4.6.2 **Adverse Events**

All AE tables will be generated on :

- SAF population once for the 6-year follow up (from baseline (ENSEMBLE) to week 288/LIBERTO week 96), once from baseline (ENSEMBLE) to week 288/LIBERTO week 96 including safety follow-up period and once for the LIBERTO 2-year follow up (from LIBERTO baseline to week 288/LIBERTO week 96).
- SFU population once for the 6-year follow up (from baseline (ENSEMBLE) to week 288/LIBERTO week 96 including safety follow-up period) and once for the LIBERTO 2-year follow up (from LIBERTO baseline to week 288/LIBERTO week 96 including safety follow-up period).

For each recorded adverse event (AE), the term entered by the investigator describing the event (the “reported term”) will be assigned a standardized term (the “Preferred Term” [PT]) and assigned to a superclass term (the “System Organ Class” [SOC]) on the basis of the MedDRA World Health Organization (WHO) dictionary of terms version 27.0

Treatment emergent adverse events (TEAEs) will be summarized by SOC and PT. At each level of summarization (at least one event, SOC and PT), subjects reporting more than one AE will be counted only once. The table results will be sorted by descending frequency of SOC and PT within each SOC.

Definitions

Treatment-emergent adverse events (TEAE): AEs with an observed or imputed date of onset on or after the start date of trial treatment. If the onset date of the AE is prior to the day of first dose, the AE will be considered treatment-emergent only if the most extreme intensity is greater than the initial intensity (i.e., the intensity for a given AE increases and its end date is on or after the date of the first dose). An AE with a completely missing, non-imputed start date will be assumed to be treatment emergent unless the AE has a complete, non-imputed end date that is prior to the date of the first dose.

Imputation of incomplete date: in order to evaluate if an AE is treatment-emergent, incomplete dates will be imputed as follows:

- If the start date is incomplete:
 - If the day is missing, impute to 01, or to the day of first dose of ocrelizumab if the month and year is the same as the dosing date.
 - If month is missing, impute to JAN, or to the month of first dose of ocrelizumab if the year is the same as the year of dosing.
 - If the date is completely missing, then the date will remain missing
- If the end date is incomplete:
 - If the day is missing, impute to the last day of the month
 - If the month is missing, impute to DEC
 - If the date is completely missing, then the date will remain missing

If the imputed start date of an AE is post first intake, it is considered treatment emergent.

If the imputed start date of an AE is prior first intake, it is considered non-treatment emergent.

In case of a missing start date and an (imputed) end date prior to first intake, the AE is considered non-treatment emergent.

Otherwise, the AE is considered treatment emergent.

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Serious Adverse events (SAEs): all SAEs reported in the eCRF and including serious MS relapses and serious Infusion Related Reactions (IRRs).

Output Conventions

All analyses of AE data will be performed using the PTs unless otherwise specified.

For all summary tables, the AEs will be sorted by SOC (in decreasing order of overall incidence) and then by PT (in decreasing order of overall incidence). At each level of summarization (at least one event, SOC and PT), patients reporting more than one AE will be counted only once. For TEAEs by grade (intensity), the highest grade will be reported. All AE summaries will be based on TEAEs only.

An overview table displaying the total number of events, the number of patients with the respective AE will be created for the following type of AE:

- AE
- Serious AE
- Death
- AE with fatal outcome
- Infusion related reaction (IRR)
- Serious Infusion related reaction (IRR)
- Infections (using the MedDRA SOC of “Infections and Infestations.”)
- Serious infections (using the MedDRA SOC of “Infections and Infestations.”)
- AE leading to study drug discontinuation (“Drug Withdrawn” for the “Action taken with ocrelizumab due to SAE/AE” field in the “Adverse Event/IRR/MS Relapse” eCRF form)
- Serious AE leading to study drug discontinuation (“Drug Withdrawn” for the “Action taken with ocrelizumab due to SAE/AE” field in the “Adverse Event/IRR/MS Relapse” eCRF form)
- AE leading to dose modification/interruption
- Serious AE leading to dose modification/interruption
- AE related to study medication
- AE of Grade ≥ 3
- Malignancies (using Adverse events falling into the Standard MedDRA Query 'Malignant tumours (narrow)')
- Serious malignancies (using Adverse events falling into the Standard MedDRA Query 'Malignant tumours (narrow)')
- Non-serious premalignant disorders event (using Adverse events falling into the Standard MedDRA Query Premalignant disorders (narrow)')
- AE of Special Interest (AESI) defined as follows:
 - Cases of potential drug-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 Section 5.3.5.7 of Protocol).
 - Suspected transmission of an infectious agent by the study drug, 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 applies only when a contamination of the study drug is suspected.

The summary table will be generated once using all AEs and once using serious AEs.

All adverse events, serious adverse events, infusion related reaction, multiple sclerosis relapse, infection, adverse events leading to withdrawal, pregnancies, adverse events of special interest and death will be also listed on both population (SAF and SFU) and from baseline (ENSEMBLE) to SFU (LIBERTO) period.

Summary tables presenting the number of patients who experienced a AE will be summarized by SOC and PT from baseline (ENSEMBLE) to SFU (LIBERTO) on SAF and SFU population as stated above for the followings:

- AEs related to study drug (“Yes” for the event “AE suspected to be caused by Ocrelizumab?” field on the “Adverse Event/IRR/MS Relapse” and “Adverse Events – Ongoing from Parent Study” eCRF form)
- AEs by intensity Grade (“1”, “2”, “3”, “4”, “5” for the “AE most extreme NCI CTCAE grade” field in the “Adverse Event/IRR/MS Relapse” and “Adverse Events – Ongoing from Parent Study” eCRF form). Multiple occurrences of the same event within a patient will be counted once at the greatest intensity/highest grade for this PT. For AEs leading to death, the most extreme intensity will be overwritten by Grade 5 (death). Any AEs and the SOC overall rows of the summary table will count patients according to AEs by intensity (grade).
- AEs by intensity Grade ≥ 3 (“3”, “4”, “5” for the “AE most extreme NCI CTCAE grade” field in the “Adverse Event/IRR/MS Relapse” and “Adverse Events – Ongoing from Parent Study” eCRF form)
- AEs that led to study drug discontinuation (“Drug Withdrawn” for the “Action taken with ocrelizumab due to SAE/AE” field in the “Adverse Event/IRR/MS Relapse” and “Adverse Events – Ongoing from Parent Study” eCRF form)
- AEs that led to modification or interruption of study drug (“Dose reduced” or “Dose temporarily interrupted” for the “Action taken with ocrelizumab due to SAE/AE” field in the “Adverse Event/IRR/MS Relapse” and “Adverse Events – Ongoing from Parent Study” eCRF form)
- AE of Special Interest (AESI)
- IRR by Visit from ENSEMBLE baseline (first infusion date) to week 264/LIBERTO week 72 (last infusion date) on SAF population

4.6.3 Delayed return of B cells

Not Applicable

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4.6.4 Laboratory Data

Laboratory assessments are performed in local laboratory in SAF population and SFU population:

- Hematology (hemoglobin, hematocrit, platelet count, red blood cell [RBC] count, white blood cell [WBC] count, percent and/or absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells]).
- Serum chemistries (AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin, creatinine, random glucose, potassium, sodium)
- Urine dipstick at site (glucose, protein, ketones, blood)]
- Lymphocytes subtypes: whole-blood samples will be collected to determine the duration of B-cell depletion and recovery (CD19+) and T-cell counts (CD4+, CD8+)

4.6.4.1 General Laboratory evaluation

All laboratory assessments (hematology, biochemistry, urine analysis) will be summarized or listed when applicable from baseline (ENSEMBLE) to safety follow-up visit.

Absolute value and change from baseline values at each visit will be summarized using standard unit. The baseline value will be the last value prior to the first dose of study medication (ENSEMBLE study). When laboratory data are presented over time, these laboratory values will be time-windowed into a common visit structure. If multiple values of the same laboratory parameter occur within the same time window, the worst value for that parameter will be presented in the summary table.

A summary of the number and percentage of patients with normal/abnormal laboratory outcomes based on normal laboratory ranges will be produced for each parameter and visit. A list will also be provided.

A summary of the number and percentage of patients with each result category will also be presented for the urine laboratory tests.

4.6.5 Vital Signs

Vital signs during infusion and non-infusion visit will include measurements of heart rate, systolic and diastolic blood pressures and temperature.

- Each parameter of vital sign will be summarized using descriptive statistics (actual value and change) from baseline (ENSEMBLE) to Safety Follow-up (LIBERTO) at each schedule time on safety population.
- Each parameter of vital sign will be summarized using descriptive statistics (actual value and change) from baseline (ENSEMBLE) to Safety Follow-up (LIBERTO) at each visit on safety population.

4.6.6 Physical and neurological examinations

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Physical examinations will include an evaluation of head, eye, ear, nose and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory and gastrointestinal systems. Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder.

In case of abnormality, number and percentage of patients in each category ("MS relapse", "Disease progression" and "Other") will be provided from baseline (ENSEMBLE) to week 288 (LIBERTO week 96) on SAF population.

4.6.7 Locally reviewed MRI

Not Applicable

4.6.8 Concomitant medications

Prior medication (defined as treatment ended before baseline visit) and Concomitant medications (defined as treatment started or ongoing after baseline visit) will be summarized by frequency tables according to the Anatomical Therapeutic Chemical (ATC) classification system using the WHO Drug dictionary as follow:

- Prior medication will be summarized during the treatment period (from ENSEMBLE baseline to week 288/LIBERTO week 96) on SAF population.
- Concomitant medications will be summarized during the treatment period and safety follow-up on SAF population: from baseline (ENSEMBLE) to SFU (LIBERTO)

4.7 MISSING DATA

All methods for handling missing data are described above, section by section, for each endpoint. If not otherwise specified, missing values are not imputed.

4.8 INTERIM ANALYSES

NA.

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Appendix 1: Protocol Synopsis

<u>PROTOCOL SYNOPSIS</u>	
TITLE:	A SINGLE ARM, OPEN LABEL MULTICENTRE EXTENSION STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS PREVIOUSLY ENROLLED IN A F. HOFFMANN-LA ROCHE SPONSORED OCRELIZUMAB PHASE IIIb/IV CLINICAL TRIAL
PROTOCOL NUMBER:	MN39158
VERSION NUMBER:	6.0
EUDRACT NUMBER:	2017-004886-29
IND NUMBER:	100,593
NCT NUMBER:	NCT03599245
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase IIIb/IV
INDICATION:	Multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This extension study will evaluate the effectiveness and safety of ocrelizumab in multiple sclerosis (MS) patients who were previously enrolled in a F. Hoffmann-La Roche (Roche) sponsored ocrelizumab phase IIIb/IV trial (i.e. the Parent, P-trial). Specific objectives and corresponding endpoints for the study are outlined in the table below.

Objectives	Corresponding Endpoints
Primary Objective:	
To evaluate the effectiveness of ocrelizumab therapy in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial	Evaluate clinical measures related to disease progression over <i>the duration of treatment</i> in MS patients
Overview of the effectiveness measures:	
Different effectiveness measures evaluated for ocrelizumab in MS patients who were	Related to disability progression:

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Objectives	Corresponding Endpoints
previously enrolled in a Roche sponsored phase IIIb/IV-trial	• Time to onset of confirmed disability progression (CDP) sustained for at least 24 weeks and for at least 48 weeks • Proportion of patients who have confirmed disability improvement (CDI), CDP for at least 24 weeks and for at least 48 weeks yearly and over the duration of <i>treatment</i> • Proportion of patients who have improved, stable or worsened disability compared with baseline (inclusion in Extension study) measured by expanded disability status scale (EDSS) (annually/by epoch and over duration of <i>treatment</i>) Stable EDSS is defined as EDSS change +/- 0.5. Worsening is > 0.5 increase of EDSS, Improvement is >0.5 decrease of EDSS. • Mean change from inclusion in <i>the parent</i> study in EDSS score over the course of <i>treatment</i> • Time to 20% increase in timed 25-foot walk test (T25FWT); time to 20% increase in timed nine-hole peg test (9HPT) sustained for at least 24 weeks and for at least 48 weeks, and proportion of patients achieving a sustained increase assessed yearly and <i>over the duration of treatment</i> Other clinical measures and composite endpoints: • Time to first protocol-defined event of disease activity • Time to first relapse • Annualized relapse rate • Proportion of patient relapse free, yearly and over the course of <i>treatment</i> • Proportion of patients with no evidence of protocol-defined disease activity (NEDA) yearly and over the <i>duration</i> of the <i>treatment</i> where disease activity is defined as at least one the following events: protocol-defined relapse; 24 weeks CDP based on increases in EDSS; a T1 Gadolinium (Gd)-enhanced lesion; or a new and/or enlarging T2 hyperintense lesion on magnetic resonance imaging (MRI). • Proportion of patients with no evidence of progression (NEP) defined as no progression sustained for at least 24 weeks on all of the following three components (CDP; 20% increase in timed T25FWT; 20% increase in timed 9HPT yearly and over the course of <i>treatment</i> • Proportion of patients with no evidence of progression sustained for at least 24 weeks and no active disease (NEPAD) defined as no progression on all of the three components of NEP (CDP, T25FWT, 9HPT), no new relapse and no enlarging or new T2 or T1 Gd-enhancing lesion yearly and over the course of <i>treatment</i> • Change from baseline (<i>parent trial</i>) in cognitive performance as measured by the Symbol digit modalities test (SDMT) Related to MRI • Total number of T1 Gd-enhancing lesions as detected by brain MRI over time

Objectives	Corresponding Endpoints
	• Total number of new and/or enlarging T2 lesion as detected by brain MRI over time • Change in total T1 hypointense lesion volume over time • Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions as detected by brain MRI over time (<i>pertinent to CASTING/MA30005 patients only</i>) • <i>Total number of FLAIR late enhancing lesions as detected by brain MRI at the end of the treatment period</i> • Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time • Presence and evolution of leptomeningeal follicles (<i>pertinent to ENSEMBLE/MA30143 patients with identified FLAIR late enhancing lesions and CASTING/MA30005 patients</i>) Other measures related to MS disease: • Time to treatment discontinuation/switch Patient reported outcomes (PROs) • Employment status (Work Productivity and Activity Impairment Questionnaire [WPAI]) • SymptoMScreen • Quality of life (QoL) (Multiple Sclerosis Impact Scale [MSIS]-29)
Exploratory Objective:	
• To investigate the effect of ocrelizumab on antibody and T cell responses in patients administered an approved severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine	• Analysis of immune response (SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses) to SARS-CoV-2 vaccine
Safety Objective:	
• To evaluate the safety and tolerability of ocrelizumab therapy in MS patients who were previously enrolled in a Roche sponsored phase IIIb/IV-trial	• Rate and nature of adverse events • Changes in vital signs, neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-MS central nervous system [CNS] pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration)

Study Design

Description of Study

This is a single arm, open label, multicenter Extension study in patients on ocrelizumab therapy *who are eligible for roll over based on the investigator decision in the Roche Parent trial*. Patients will receive treatment with ocrelizumab as single 600 mg infusions in 500 mL 0.9% sodium chloride every 24 weeks up to Week 72 of this study. In patients who did not experience a serious infusion-related reaction (IRR) with any previous conventional ocrelizumab infusion (~3.5 hours), the next 600 mg infusion can be administered as a shorter (~2 hours) infusion for subsequent doses, after providing written informed consent. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit.

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The study will consist of the following periods:

- Screening period: The screening visit should be scheduled up to two weeks prior to the first infusion of ocrelizumab. This period of time should not be exceeded.
- Treatment period: The first visit of the Treatment period (first infusion of ocrelizumab) should be 24 weeks (± 14 days) after the last infusion of ocrelizumab in the P-trial. Ocrelizumab will be administered every 24 weeks up to Week 72 of this study and the last visit in the treatment period will be conducted 24 weeks after the last dose of ocrelizumab.
- A safety follow-up period of 48 weeks after the last infusion of the study drug, as explained below

Safety follow-up period:

The safety follow-up period is of 48 weeks after the last infusion of study drug (Section 3.1.4 for details). When patients begin an alternative treatment for MS (see Section 4.4.1 "Prohibited Therapy"), they will be discontinued from the study.

Patients who decide to leave the study and switch to ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

Number of Patients

Any patients with MS who were previously enrolled in a Roche sponsored P-trial, and with a positive benefit risk ratio as determined by treating neurologist can be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- *Eligible for roll-over into the MN39158/LIBERTO study (including the female patients who were pregnant during the parent studies and are still in the safety follow up period) based on the investigator decision in a Roche sponsored ocrelizumab P-trial upon risk/benefit assessment for continuous treatment with ocrelizumab*
- Meet re-treatment criteria with ocrelizumab (Please see Section 3.1.3)
- Patients who became pregnant by chance between the last visit of the parent study and screening of this study, as confirmed by pregnancy tests at screening, will enter the safety follow-up immediately and re-start the treatment after birth and breastfeeding are over, as per re-treatment criteria in Section 3.1.3
- For women of childbearing potential:

Agreement to remain abstinent or use an acceptable birth control method during the treatment period and for at least 6 months or longer after the final dose of ocrelizumab, as applicable in the ocrelizumab package leaflet.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- The following contraceptive methods are considered acceptable (failure rate $>1\%$ [Clinical Trial Facilitation Group (CTFG)]): (1) progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; (2) male or female condom with or without spermicide; (3) cap, diaphragm, or sponge with spermicide; (4) combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).
- Birth control methods that are highly effective (i.e. failure rate $<1\%$ [CTFG]) may also be used but are not required, and include: (1) oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation; (2) oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6) vasectomised partner; (7) sexual abstinence.

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Exclusion Criteria

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

- Hypersensitivity to ocrelizumab or to any of its excipients.
- Patients in a severely immunocompromised state until the condition resolves.
- Evidence of any adverse event potentially attributable to ocrelizumab, for which the summary of product characteristics (SmPC) recommends permanent discontinuation
- Existence of a contra-indication as per SmPC
- Prohibited concomitant medication as specified in Section 4.4.1.
- Patients intending to become pregnant during the study or within 6 months after the last dose of the study drug in the parent study.
- Patients who discontinued ocrelizumab in the P-trial (exemption made for treatment discontinuation due to unplanned pregnancy and breastfeeding for patients who continued clinical study assessments in the safety follow-up of the parent study).

End of Study

The end of the study is defined as the last patient last visit (LPLV) in the Safety Follow-up Period or the last patient completing the week 96 visit whichever comes later. Patients who decide to leave the study and switch to ocrelizumab outside of the study or an alternative disease modifying therapy (DMT), either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

Length of Study

The total length of the study is expected to be dependent on the end of treatment of the last patient rolling over from the last parent study. For each patient, the treatment period is two years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Ocrelizumab will be administered as one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the duration of the study.

Non-Investigational Medicinal Products

The following premedications must be administered prior to each infusion of ocrelizumab to reduce the frequency and severity of IRRs:

- 100 mg intravenous methylprednisolone (or an equivalent) administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion.
- Antihistamine, via oral, intramuscular or IV route to be completed approximately 30-60 minutes and not less than 25 minutes prior to each ocrelizumab infusion (the antihistamine should be the first premedication to be administered).
- The addition of an antipyretic (e.g., acetaminophen/ paracetamol) may also be considered.

Statistical Methods

The analysis of this study will be exploratory and primarily make use of descriptive statistical methods.

The intent-to-treat (ITT) population will include all enrolled patients who received any dose of ocrelizumab and will be used for the primary analyses of effectiveness and safety. The last 48-week and 24-week CDP / CDI confirmatory assessment will be performed at the End of Treatment visit (week 96).

Effectiveness of ocrelizumab will be evaluated by means of a set of endpoints addressing different facets of MS. There is no primary endpoint defined in this study. The effectiveness endpoints include time to onset of confirmed CDP sustained for at least 24 and for at least 48 weeks, proportion of patients who have CDI, CDP for at least 24 and for at least 48 weeks, change from baseline in EDSS score over time of the parent study and this extension study, relapse rates, MRI-based measures of disease activity and progression or degeneration, measures of cognition, and patient reported outcomes. For a full list of effectiveness endpoints refer to Section 2.

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The primary study analysis will be performed *in subpopulations of the P-trials* after the last patient from the corresponding P-trial completes the last (End of Treatment) visit *in this MN39158/LIBERTO study*. The evaluation of the clinical effectiveness of ocrelizumab will be based upon the events and assessments in-between the baseline (start of *parent* study) and end of Treatment period visit. A descriptive analysis based on the Kaplan-Meier method will be performed for the time to CDP and other time-to-event endpoints, such as the time to first relapse or to first event of disease activity. Change of EDSS from baseline till end of treatment will be analyzed based on statistical models such as mixed models for repeated measures. Details will be specified in the statistical analysis plan (SAP).

Determination of Sample Size

This is an extension study of ocrelizumab where patients will be enrolled from qualifying P-trials. A formal determination of sample size was therefore not performed.

Interim Analyses

No formal confirmatory effectiveness or safety interim analyses are planned. Exploratory interim analyses of selected endpoints, and in particular periodic analyses of safety data are planned to be performed during the course of the study

Appendix 2: Schedule of Assessments: Screening through the End of Treatment Period

Visit ^a	Screening	Treatment Period ^a					Early study treatment discontinuation evaluation ^c	Safety Follow-Up 48 weeks after last dose of study drug ^d Refer to Appendix 2
	1	2 (Enrolment) ^b	3	4	5 (last infusion of study drug)	6 (End of Treatment period)		
Week	-2 weeks	0	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
Informed consent ^e	X							
Review inclusion & exclusion criteria	X	X						
Review of retreatment criteria ^f	X	X	X	X	X			
Physical examination ^g	X	X	X	X	X	X	X	
Vital signs ^h		X	X	X	X	X	X	
Neurological examination ⁱ		X	X	X	X	X	X	
EDSS score ^j		X	X	X	X	X	X	
T25FWT and 9HPT ^k		X	X	X	X	X	X	
SDMT		X		X		X	X	
Brain MRI ^l			X ^u	X		X	X	
Recording of potential relapses		X	X	X	X	X	X	
WPAI		X	X	X	X	X	X	
SymptoMScreen		X		X		X	X	

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	Screening	Treatment Period					Early study treatment discontinuation evaluation ^c	Follow-Up 48 weeks after last dose of study drug ^d Refer to Appendix 2
	1	2 (Enrolment) ^b	3	4	5 (last infusion of study drug)	6 (End of Treatment period)		
Week	-2 weeks	0	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
MSIS-29		X		X		X	X	
Hematology, chemistry, urinalysis ^m	X	X	X	X	X	X	X	
Pregnancy test ⁿ	X	X	X	X	X	X		
Lymphocytes subtypes ^o		X	X	X	X	X	X	
HBV DNA measured by PCR in patients with positive HBcAb ^p		X	X	X	X			
Adverse event assessment ^q	X	X	X	X	X	X	X	
Concomitant treatment review		X	X	X	X	X	X	
Methylprednisolone and antihistaminic drug premedication ^r		X	X	X	X			
Ocrelizumab administration ^s		X	X	X	X			
Optional whole blood and serum samples for SARS-CoV-2 vaccine immunological assessments ^t	Please see Figure 3 for details.							

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDP = confirmed disability progression; DMT = disease modifying treatment; DNA = deoxyribonucleic acid; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS = Multiple sclerosis impact scale; 9HPT = nine hole peg test; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; RBC = red blood cell; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SDMT = symbol digit modalities test; T25FWT = Timed 25-foot walk test; WBC = white blood cell; WPAI = Work productivity and activity impairment questionnaire

- ^a The study visits during the treatment period may be spread over more than one day to complete all the assessments before study drug administration. The first infusion of ocrelizumab in this study should be 24 weeks (± 14 days) after the last infusion of ocrelizumab in the Parent-trial. Ocrelizumab will be administered every 24 weeks up to Week 72 of this study and the last visit in the treatment period will be conducted 24 weeks after the last dose of ocrelizumab.
- ^b All assessments performed at the last visit of the parent trial do not have to be repeated if they were performed within 14 days (within 22-26 weeks for the MRI).
- ^c In case of discontinuation per Section 4.6 every effort should be made that the patient completes the early treatment discontinuation assessments per Appendix 1
- ^d The safety follow-up period is of 48 weeks after the last infusion of the study drug. When patients begin an alternative treatment for MS, they will be discontinued from the study. Patients who leave the study and switch to ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period. For patients who complete the study treatment period, the week 96 visit will include the 24-week safety follow-up assessments.
- ^e Written informed consent will be obtained from all patients during screening in order to be eligible for the study.
- ^f *Decisions on re-treatment criteria will be made in accordance with standard of care and the local ocrelizumab label.*
- ^g A physical examination should be performed at the screening, baseline visits and at all visits during the treatment period. Any abnormality identified or changes from previously reported abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF.
- ^h Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and temperature. Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or an equivalent) infusion and administration of antihistaminics. In addition, vital signs should be measured prior to the ocrelizumab infusion then every 15 minutes (± 5 minutes) for the first hour, followed by every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study.
- ^j The last 48-week and 24-week CDP confirmatory assessments will be performed at the End of Treatment visit (week 96). For patients who discontinue the study (e.g., switch to ocrelizumab outside of the study, or start treatment with another DMT), the EDSS CDP confirmatory assessments will not be performed.
- ^k Not expected from patients coming from CASTING/MA30005 study.
- ^l MRI readings should be available before dosing with ocrelizumab for safety reasons.
- ^m *Routine laboratory assessments (performed in local laboratory and according to standard of care) will include: Hematology: hemoglobin, hematocrit, RBCs, WBC absolute, percent and/or absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), and quantitative platelet count; Chemistry: AST, ALT, GGT, creatinine, total bilirubin. Urine dipstick will be done at site locally.*

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- ⁿ At the screening visit, urine beta-hCG [sensitivity of at least 25 mIU/mL] will be performed. On infusion visits, the urine pregnancy test should be performed prior to prophylactic medication in all women of childbearing potential. If positive, the patient will not receive the scheduled dose until a serum pregnancy test is performed for confirmation. If the serum pregnancy test is negative, the patient can receive the scheduled ocrelizumab dose. The FSH test is only applicable to confirm postmenopausal status in female patients. Patients who became pregnant by chance between the last visit of the parent study and screening of this study, as confirmed by pregnancy tests at screening, will enter the safety follow-up immediately and re-start the treatment after birth and breastfeeding are over, as per retreatment criteria.
- ^o Lymphocytes subtypes samples should be collected prior to ocrelizumab infusion to screen for CD19+ and T-cell counts (CD4+, CD8+) at a local laboratory.
- ^p If total HBcAb was positive at screening of a subject rolled over from any parent studies, HBV DNA measured by PCR must be negative in order for a patient to be dosed with ocrelizumab in the MN39158 study. For enrolled patients rolling over from any of the parent studies with negative HBsAg and positive total HBcAb, HBV DNA testing (by PCR) must be repeated every 24 weeks and evaluated prior to ocrelizumab administration. If it becomes positive, treatment with ocrelizumab must be discontinued but the patient should remain in the safety follow up.
- ^q Adverse events will be reported throughout the study and until 48 weeks after the last dose of ocrelizumab as provided during the study period. After this period, the Investigator should report any serious and non-serious adverse events that are believed to be related to prior study drug treatment. At the end-of-treatment evaluation, reasons for study discontinuation will be captured via telephone call unless a site visit is requested by the Investigator.
- ^r All patients must receive prophylactic treatment with 100 mg methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion and an antihistamine, via oral, intramuscular or IV route to be completed approximately 30–60 minutes and not less than 25 minutes prior to each infusion of ocrelizumab (the antihistamine should be the first premedication to be administered). The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered.
- ^s Ocrelizumab will be administered as one 600-mg infusion in 500 mL 0.9% sodium chloride every subsequent dose (i.e., every 24 weeks) for a period of two years. In patients who did not experience a serious IRR with any previous conventional ocrelizumab infusion (~3.5 hours), the next 600 mg infusion can be administered as a shorter (~2 hours) infusion for subsequent doses, after providing written informed consent. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit. Ocrelizumab will not be administered to pregnant/breastfeeding patient. Treatment with ocrelizumab should also be stopped if the patient decides to become pregnant.
- ^t For the optional procedure related to SARS-CoV-2 vaccination only: Whole blood and serum samples collected on the day of the infusion must be collected prior to the IV methylprednisolone administered as premedication. Samples will be collected up to 18 months after the last vaccine dose.
- ^u *Week 24 MRI is only applicable for patients who have consented to Protocol/Informed Consent Form v5.0 or lower.*

Note: All lab samples can be taken up to 2 weeks prior to the scheduled study visit. If laboratory results are required to confirm retreatment criteria, these need to be available prior to dosing.

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Appendix 3: Safety Follow-up Schedule of Assessments

(Including Additional B-Cell Monitoring, if required)

The safety follow-up period is of 48 weeks after the last infusion of the study drug. When patients begin an alternative treatment for MS, they will be discontinued from the study. Patients who decide to leave the study and switch to ocrelizumab outside of the study, either after completion of the 96-week Treatment Period or after early discontinuation from the 96-week Treatment Period, will not enter the safety follow-up period.

Assessment	Safety Follow-Up		
	Patients who complete the 96 weeks Treatment Period	Patients who discontinue the study treatment early	
		Week 24 after the last infusion of study drug (± 14 days)	Week 48 after the last infusion of study drug (± 14 days)
Routine safety laboratory tests ^a	X	X	X
Lymphocytes subtypes ^b	X	X	X
Vital signs	X	X	X
EDSS score	X	X	X
Adverse events ^c	X	X	X
Concomitant medication	X	X	X

EDSS = Expanded Disability Status Scale

^a Routine safety lab: hematology, chemistry and urinalysis.

^b Lymphocytes subtypes samples for CD19+ and T-cell counts (CD4+, CD8+)

^c All adverse events should be reported until 48 weeks after the last dose of study drug. After this period, the Investigator should report any serious and non-serious adverse event that are believed to be related to prior study drug treatment.

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- ich kann die Auskunft auf Papier ausdrucken oder sie an einen Ort schicken, wo ich sie ausdrucken kann, um sie aufzubewahren und zukünftig zu konsultieren; und
- außer wenn oder bis ich den Eigentümer des Accounts wie oben beschrieben informiere, stimme ich zu, alle Mitteilungen, Auskünfte, Genehmigungen, Bestätigungen und sonstigen Dokumente, die mir vom Eigentümer des Accounts übermittelt oder zur Verfügung gestellt werden müssen, während der Geschäftsbeziehung mit Ihnen ausschließlich auf elektronischem Wege zu erhalten.
- Ich erkenne die in den [DocuSign-Datenschutzrichtlinien](#) enthaltenen Informationen an.

Signature Page for 1151892-csr-mn39158-1619

System identifier: RIM-CLIN-1206766

Approval Task	 Company Signatory 30-Apr-2026 12:04:10 GMT+0000
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