Official Title: An Open-Label Study to Evaluate the Efficacy and Safety of Ocrelizumab in Patients With Relapsing Remitting Multiple Sclerosis who Have a Suboptimal Response to an Adequate Course of Disease-Modifying Treatment

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STATISTICAL ANALYSIS PLAN

TITLE: **AN OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**

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STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Events
ALT	Alanine transaminase
ARR	Annualized Relapse Rate
AST	Aspartate transaminase
ATC	Anatomic Therapeutic Chemical
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BMI	Body Mass Index
CDI	Confirmed Disability Improvement
CDP	Confirmed Disability Progression
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMT	Disease Modifying Therapy
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Form
EDA	Evidence of Disease Activity
EDSS	Expanded Disability Status Scale
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FSS	Functional System Score
GGT	Gamma-Glutamyl Transpeptidase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, eye, ear, nose, and throat
IRR	Infusion Related Reactions
ITT	Intent-to-Treat
LTE	Long Term Extension
MedDRa	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effects Model Repeated Measure
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale (29-item scale)

Abbreviation	Definition
NCI	National Cancer Institute
NEDA	No Evidence of Disease Activity
OR	Odd Ratio
PCR	Polymerase Chain Reaction
PDR	Protocol Defined Relapse
PP	Per-Protocol
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
PRO	Patient-reported outcome
PT	Preferred Term
QoL	Quality of Life
RBC	Red blood cell
REML	Restricted Maximum Likelihood method
RMS	Relapsing multiple sclerosis
RRMS	Relapsing Remitting Multiple sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
TEAE	Treatment-Emergent Adverse Events
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
WBC	White Blood Cell
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

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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). Accumulated disability is the fate of most patients with MS when a 20- to 25-year perspective is considered (Trojano et al. 2003). Approximately 85% of MS patients initially present with RRMS (Confavreaux et al. 2000; Leray et al. 2015).

Over the past two decades, there has been an increase in the number and type of available treatments for relapsing multiple sclerosis (RMS). Assessing efficacy and safety in patients who switch to ocrelizumab after a suboptimal response to an adequate course of a disease modifying therapy (DMT) represents an important question for clinicians. Efficacy and safety data in patients who have switched to ocrelizumab are limited. Additional data will also be available on previously treated patients in two completed Phase III studies (NCT01247324 [OPERA I], n=106 and NCT01412333 [OPERA II], n=113), but in a limited number of patients. However, more data from patients who switch to higher efficacy therapies from large scale, prospective studies are needed. Therefore, a dedicated prospective study to specifically evaluate the efficacy and safety of ocrelizumab in patients who have a suboptimal response to an adequate course of a DMT is needed to address this important clinical question.

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

2. STUDY DESIGN

This study is a prospective, multicenter, open-label, efficacy and safety study in patients with RRMS who have had a suboptimal response to an adequate course of a DMT. An adequate course of prior DMT is defined as a stable dose of the same DMT administered for at least 6 months. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the remainder of the study duration.

This study will enroll approximately 750 patients. Patients will be assessed for efficacy and safety every 24 weeks as described in the Schedule of Assessments in Appendix 2.

The study will consist of the following periods:

- Screening period: Up to 4 weeks
- Treatment period: Open-label treatment period of 96 weeks (last dose administered at Week 72)
- A follow-up period of at least 2 years, which is independent of the DMT administered

Follow-up Period: Patients who discontinue treatment early will be followed up for at least 96 weeks after the Early Treatment Discontinuation Visit. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate long term extension (LTE) study, will be followed up for at least 96 weeks after the end of the Treatment Period. Patients who decide to leave the study and switch to commercially marketed ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks 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 Primary Efficacy Outcome Measures

The primary efficacy endpoint is the proportion of patients who have No Evidence of Disease Activity (NEDA), as per protocol defined events during a 96-week period. The magnetic resonance imaging (MRI) activity will be calculated on the events starting from week 8 (baseline reset).

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

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy endpoints are the following:

- Proportions of NEDA patients during the initial 24-week period and the initial 48-week period
- Time to first protocol-defined event of disease activity
- Change in EDSS from baseline to Week 96
- Proportion of patients who, over a 96-week period, have Confirmed Disability Improvement (CDI), CDP or stable disability (i.e. neither CDI nor CDP).
- Annualized rate of protocol-defined relapses at Week 96
- Time to onset of first protocol-defined relapse
- Time to onset of 24 weeks CDP
- Time to onset of first new and/or enlarging T2 lesion
- Total number of T1 Gd-enhanced lesions detected by brain MRI at Weeks 24, 48 and 96

- Change in total T2 lesion volume detected by brain MRI from Week 8 to Week 96
- Volume and number of new and/or enlarging T2 hyperintense lesions from Week 8 to Weeks 24, 48 and 96
- Change in T1 hypointense lesion volume from Week 8 to Weeks 48 and 96
- Percentage change in brain volume from Week 8 measured at Weeks 24, 48 and 96
- Percentage change in white matter volume from Week 8 measured at Weeks 24, 48 and 96
- Percentage change in cortical grey matter volume from Week 8 measured at Weeks 24, 48 and 96
- Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the components of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

2.2.3 Exploratory Outcome Measures

Exploratory outcome measures are used to further assess the efficacy of ocrelizumab 600 mg IV administered every 24 weeks. These include:

- Multiple Sclerosis Impact Scale version 2 (MSIS-29 v2)
- Treatment satisfaction questionnaire for medication (TSQM II)
- SymptoMScreen
- Work Productivity and Activity Impairment (WPAI-SHP) to assess the employment status
- MRI and clinical outcomes
- Severity of relapses (hospitalization for MS relapse, use of corticosteroids, residual disability)
- NEDA status of patients defined from per protocol defined events during a 96-week period and starting from baseline (not from baseline reset week 8)
- Predictors of NEDA and association between NEDA and disability or other efficacy parameters
- NEDA in Year 1 (from Weeks 0/8 to Week 48) and NEDA in Year 2 (from Week 48 to Week 96) by epoch

2.2.4 Pharmacokinetic Efficacy Outcome Measures

Not Applicable

2.2.5 Safety Outcome Measures

The safety and tolerability endpoints are:

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

2.3 DETERMINATION OF SAMPLE SIZE

With a sample size of 750 patients, an observed NEDA rate of 30% will be estimated with a precision (half-width of the 95% CI (Confidence Interval) around the estimate) of 3.3% based on the Clopper-Pearson method, i.e. the 95% CI will be (26.7%, 33.4%). Even if the NEDA rate is different from the assumed rate of 30%, with the proposed sample size the precision of the estimate will remain better than 3.6% (value for a NEDA rate of 50%).

The annualized relapse rate is another relevant outcome measure assessed in this study. Based on results from the pivotal Phase III studies NCT01247324 (OPERA I) and NCT01412333 (OPERA II), in this study the adjusted annualized relapse rate (ARR) assessed over two years is expected to be estimated with a precision of approximately 0.03.

2.4 ANALYSIS TIMING

The primary analyses will be performed after the last Confirmed Disease Progression visit occurred. The results of the statistical analyses described in this SAP will be included in a Clinical Study Report (CSR).

The data collected before CCOD (Clinical Cut–off Date) will be included in the primary analysis. The primary efficacy analysis will be performed on the Treatment period, which is defined as being from the first infusion of treatment (day1) until:

The end of the Treatment Period will be the last visit date of any efficacy measurement at week 96 (including EDSS, MRI or PRO) or withdraw date.

The duration of the treatment period is calculated as

End of Treatment Period – first infusion date +1.

An analysis update of data collected during Safety Follow-up period will be performed once the last patient completed the safety Follow-up period. An addendum to the CSR will include results of selected statistical analyses described in this SAP, if not available at the time of the primary CSR analysis (refer to LoPo for selection of analyses). For each data type collected during the follow-up period (refer to protocol Appendix 2: Follow-up Schedule of Assessments), only listing will be provided If less than 50 patients have data available.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Not Applicable

3.2 INDEPENDENT REVIEW FACILITY

Not Applicable

3.3 DATA MONITORING

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 efficacy variables are detailed in the Efficacy 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 enrolled patients who received any dose of ocrelizumab will be included in the ITT population. Patients who prematurely withdrew from the study for any reason and who did not perform any assessment for any reason will still be included in the ITT population. The ITT population will be used for all analyses except for primary analysis of NEDA and NEDA components.

4.1.2 Modified ITT population

The modified intention-to-treat (mITT) population will be defined as all patients from the ITT population excluding patients with both the screening and the baseline EDSS scores missing.

4.1.3 Per Protocol Population

The per-protocol population will consist of the subset of the ITT population defined as all patients who had 96 weeks of treatment and who did not have any major protocol violations that are deemed to potentially affect the efficacy endpoints. The analysis of the primary and secondary endpoints may be repeated if at least 10% patients are excluded from the PP population.

The following patients will also be excluded from the per-protocol population:

- Exclusions related to previous treatments
- Criteria for prior DMTs not met
- Received prohibited concomitant therapy
- Missed, not done MRIs
- MRI done after ocrelizumab infusion
- Missed post-baseline neurological assessment including EDSS

4.1.4 Pharmacokinetic-Evaluable Population

Not applicable

4.1.5 Safety Population

Safety analyses will be done on the ITT population

4.2 ANALYSIS OF STUDY CONDUCT

Patient disposition information will be summarized as follows:

- Number of patients enrolled
- Number of patients in the ITT population and PP population
- Number of patients who complete study treatment
- Number of patients who discontinue study treatment and the reasons for study treatment discontinuation
- Number of patients who discontinue study and the reasons for study discontinuation
- Number of patients entering the safety follow-up
- Number of patients who roll over to the long term extension of Ocrelizumab study
- Number of patients who received any DMT (Disease modifying treatment) after Ocrelizumab discontinuation

Major protocol violations, including violations of inclusion/exclusion criteria collected during the study via PDMS will be summarized and listed.

4.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following demographic and baseline characteristics will be summarized for the ITT population:

- Age (years) as continuous variable and age in the following categories:
  - ≤ 40, > 40
  - ≤ 18, 18< - ≤40, > 40
- Gender
- Self-reported race and ethnicity
- Female reproductive 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.

- Qualifying events for enrollments
  1) Only enrolled due MS Relapse
  2) Only enrolled due to MRI Activity
     - Only T1 Gd-enhanced lesion
     - Only New or enlarging T2 lesion
     - Both
  3) Enrolled due to MS relapse and any MRI activity

Disease activity before enrollment will be summarized as:

1) the number of relapse over the year prior to inclusion (≤ 1, >1) having the date of the last relapse
   - within 6 months: before enrollment
   - within 6 months and 12 months before enrollment
2) EDSS at baseline (<2.5, ≥ 2.5)
3) MRI at Week 8: Number of T2 lesions and presence of T1 Gd+ (Yes/No)

These variables will be summarized for the following groups of patients:

- number of prior DMTs (1,2)
- last DMT prior to study enrolment

Prior DMT Use

- Number of prior DMTs (1, 2)
- Number of patients by last DMT* prior to study enrolment
- Reason for discontinuing the last DMT
- Duration of last DMT and its category (≤6 months, >6 and ≤12 months, > 12 months), overall and by DMT type
- Time from last DMT to first Ocrelizumab infusion, overall and by DMT type

For patients with 2 previous DMT, the following will also be presented

- Number of patients by first DMT
- Duration of first DMT and its category, overall and by DMT type
- Reason for discontinuation for each previous DMT

*for DMT type, the eCRF terms "Interferon β 1a", "Interferon β 1b" and "Peg Interferon β 1a" will be grouped into "Interferon".

Multiple Sclerosis History

- Duration since MS Symptom Onset and its category (≤ 3 years, >3 and ≤5 years, >5 years and ≤10 years, >10years)
- (date of baseline visit – onset date of MS symptoms +1) / 365.25
- Duration since RMS Diagnosis and its category (≤ 2 years, >2 and ≤5 years, >5 years and ≤10 years, > 10years)
- (date of baseline visit – date of diagnosis of RRMS +1) / 365.25
- Baseline EDSS and its category (<2.5 and ≥2.5)

Screening Disease History– Relapse

- 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 and its category (≤ 3 months, >3 and ≤ 6 months, >6 months)
  (date of 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

- 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

Week 8 MRI – Baseline reset MRI

- 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
- Normalized brain volume at Baseline reset

4.4 EFFICACY ANALYSIS

4.4.1 Primary Efficacy Endpoint

Protocol-defined event definition

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 week 8
- A new and/or enlarging T2 hyperintense lesion on MRI after week 8

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

Patient without any of this protocol-defined event of disease activity will be considered as NEDA = Yes (no evidence of disease activity).

The primary endpoint, NEDA, as well as the related disease activities components and combinations listed below, will be evaluated on the mITT population based on the following analysis principles:

- Patients, who discontinued treatment prior week 96 due to death or lack of efficacy, will be considered as having evidence of disease activity at the time of treatment discontinuation (e.g NEDA="NO", Relapse="Yes" and CDP="Yes").

- Patients who discontinued treatment for reasons other than death or lack of efficacy with no evidence of disease activity at the time of early treatment discontinuation will be excluded from the analysis as their disease activity status cannot be ascertained.

This is further summarized in the table below:

Endpoint	Patients who discontinued treatment without related disease activities prior week 96 due to:	
	death or lack of efficacy	**Other reason than death or lack of efficacy with no evidence of disease activity**
NEDA	included with evidence of disease activity (NEDA=NO)	excluded
Relapse	included with evidence of disease activity (Relapse=Yes)	excluded

24-weeks CDP	included with evidence of disease activity (CDP="Yes")	• If discontinuation before confirmation, excluded • If discontinuation after confirmation, included when CDP="Yes"
T1 Gd-enhanced lesions after week 8	included with evidence of disease activity	excluded
New/enlarging T2 lesions after week 8	included with evidence of disease activity	excluded

Analysis of binary NEDA

The proportions of patients with:

- NEDA
- Treatment discontinuation due to lack of efficacy or death without events prior the withdrawal
- Relapses
- No Relapse
- 24-weeks CDP
- No 24 weeks CDP
- T1 Gd-enhanced lesions after week 8
- No T1 Gd-enhanced lesions after week 8
- New/enlarging T2 lesions after week 8
- No New/enlarging T2 lesions after week 8
- MRI activity (T1 Gd-enhanced lesions or new/enlarging T2 lesions)
- No MRI activity
- Relapses or MRI activity
- 24-weeks CDP or MRI activity
- Clinical activity (Relapses or 24-weeks CDP)
- No clinical activity
- Relapses and MRI activity
- 24-weeks CDP and MRI activity
- Relapses and 24-weeks CDP

post-baseline up to the Week 96 visit will be calculated and presented with a two-sided 95% Clopper-Pearson exact confidence interval.

Protocol-Defined 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 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.

24-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 0.0−5.5 inclusive, and a 0.5-increase from a baseline EDSS score higher than 5.5. 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, baseline EDSS is defined as the average of the EDSS scores at the screening and 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 96-week treatment period.

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

1. A sustained change in EDSS for a minimum of 24 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 weeks (⩾168-14 days=154 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 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 patient has a missing assessment at the scheduled visit taking place at 24 weeks (⩾154 days) after an initial progression, the confirmation of the disability progression must be based on the assessment at the next scheduled visit.

For the patients who have the initial progression at week 96 and roll over to the long term extension of Ocrelizumab study, a confirmation EDSS assessment will be collected in t the long term extension (Liberto) study.

Patients who complete the treatment period without confirmed progression of disease will be censored at the date of their last EDSS assessment during the treatment period. Patients 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. 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 (i.e., CDP) at the time of discontinuation.

4.4.2 Secondary Efficacy Endpoints

For all continuous secondary efficacy endpoints, in additional to the model based analyses, they will also be summarized descriptively at each assessment visit. Analysis populations are specified for each endpoint.

4.4.2.1 Proportions of NEDA patients during the initial 24-week and the initial 48-week period

This endpoint will be analyzed on the mITT population using the same approaches as described above in Section 4.4.1, for the proportion of NEDA patients assessed during the initial 24-week period and during the initial 48-week period.

4.4.2.2 Time to first protocol-defined event of disease activity

The analyses will include patients in the mITT population.

Patients with early study discontinuation before any disease activity event will be censored at the withdraw date, which is defined in Section 4.6.1. It will be imputed as having an event if discontinuation reason is lack of efficacy or death.

1) Kaplan-Meier analysis of time to first protocol-defined event (refer to section 4.4.1), with estimates (Greenwood 95% confidence intervals using a log-log transformation) of proportion of patients with NEDA determined at week 96 and week 104 (or time of the last event/censoring if that is before week 104). Kaplan-Meier plots will be produced up to the last available time of censoring or event.

2) Life-table analysis will be used to estimate the survival probability of time to first protocol-defined event, with estimates and Greenwood 95% confidence intervals using a log-log transformation by using time intervals which correspond to planned MRI assessments (weeks 24, 48 and 96). Thus, exact time of protocol-defined relapses and 24-weeks CDP will fall within MRI time intervals such as [week 8-week 24), [week 24-week 48), [week48-week96) and [week 96, -end of study]. Life-table plots will be produced.

Sample SAS code can be found below (SAS code is regarded as “draft” until fully validated at the analysis stage):

a) Binary method

```
ods output binomial=dataset BinomialTest=tpvalue;
proc freq data=event  ate;
      tables eventyn / binomial (level='1') alpha=0.05;
run;
```

b) Kaplan-Meier method

```
proc lifetest data=dataset method=km conftype=loglog outsurv=surv  plots=none notable STDERR;
      time aval*eventyn(1);
run;
```

c) Life -Table method

```
proc lifetest data=dataset method=life conftype=loglog intervals=24 48 96 outsurv=surv plots=none STDERR;
       time aval*eventyn(1);
run;
```

4.4.2.3 Change in EDSS from baseline to week 96

EDSS (actual value, change, percentage change from baseline) will be summarized at each visit (up to week 96) for the ITT population. The change in the eight function scores from baseline up to week 96 will also be summarized for the ITT population.

Additionally, summary statistics will also be presented at week 96 for the following categories of change in EDSS:

- worsened (>0.5),
- stable (-0.5, 0 ,0.5)
- improved (<-0.5)

Change from baseline in EDSS at Weeks 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:

- Baseline EDSS (continuous variable),
- Duration since MS Symptom Onset (≤ 3 years, >3 and ≤5 years, >5 years and ≤10 years, >10years)",
- Presence of T1 Gd-enhanced lesions at Screening (Yes/No).
- Number of previous DMTs (1 ,>1)
- Enrollment reasons (relapse only, MRI only or both relapse and MRI)

Visit will be treated as a repeated variable within a patient. Patient 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 doesn't converge, other variance−covariance structures can be considered.

Sample SAS code can be found below (SAS code is regarded as “draft” until fully validated at the analysis stage):

```
proc mixed data=data method=REML;
    class VISIT USUBJID [covariates];
    model change = [covariates] VISIT/ ddfm= satterthwaite;
    repeated VISIT / type=un subject = USUBJID;
    lsmeans VISIT / cl;
    ods output lsmeans = lsm; * contains the adjusted means;
run;
```

4.4.2.4 Proportion of patients who have CDI

This endpoint will be analyzed on the ITT population.

For patients with a baseline EDSS score ≥ 2, disability improvement is defined as a reduction in EDSS score ≥ 1.0 compared to baseline EDSS score. 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 96-week period, have CDI will be presented along with a two-sided 95% Clopper-Pearson exact confidence interval.

Additionally, for patients with a baseline EDSS score ≥ 2, the time to CDI will be defined as the number of days from baseline to CDI. The Kaplan–Meier method will be used to estimate the survival function for the time to CDI. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented at 24 weeks, 48 weeks and 96 weeks. Kaplan-Meier plots will be produced.

4.4.2.5 Annualized rate of protocol-defined relapses at Week 96

This endpoint will be summarized for the ITT population.

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 length of treatment period).

In addition, the adjusted annualized relapse rate will be estimated using a negative binomial model, adjusting for:

- Duration since MS Symptom Onset (≤ 3 years, >3 and ≤5 years, >5 years and ≤10 years, >10years),
- presence of T1 Gd-enhanced lesions at Screening (Yes/No),
- presence of relapses prior screening as per CRF (Yes/No)
- number of previous DMTs (1, >1)

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.

Sample SAS code can be found below (SAS code is regarded as “draft” until fully validated at the analysis stage):

```
proc genmod data=ARR;
     class [covariates];
      model N_PDR = [covariates]/offset=EXPLOG link=log dist=negbin type3;
      estimate “Annualized rate” intercept 1  DISDUR xx xx  T2VOL <mean value > T1GD xx xx RELAPSE xx xx  PDMT xx xx/ exp cl;
                ods output ParameterEstimates=est;
run;
```

As sensitivity analyses, the analyses specified above will be repeated on the annualized rate of clinical relapses at Week 96 (see section 4.4.4).

4.4.2.6 Time to onset of first protocol-defined relapse

This endpoint will be analyzed for patients in the ITT population. All protocol-defined relapses, as defined in section 4.4.1, that occurred during the treatment period will be considered.

Patients who did not experience an event at the end of the treatment period are censored at the last available clinical visit up to week 96. 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 first protocol-defined event. Kaplan-Meier rates and Greenwood 95% CI using log-log transformation will be presented at 24 weeks, 48 weeks and 96 weeks. Kaplan-Meier plots will be produced.

4.4.2.7 Time to onset of 24 weeks CDP

This endpoint will be analyzed for patients in the ITT population. All 24-weeks CDP that occurred during the treatment period will be considered.

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.

This endpoint will be analyzed using the same approach as described above in Section 4.4.2.6.

4.4.2.8 Time to onset of first new and/or enlarging T2 lesion

This endpoint will not be analyzed as the measurement of T2 lesion by MRI is only performed at week 24, 48 and 96, while the actual onset time can be very different from the MRI visit.

4.4.2.9 Time to onset of first T1 Gd-enhanced lesion

This endpoint will not be analyzed as the measurement of T1 lesion by MRI is only performed at week 24, 48 and 96, while the actual onset time can be very different from the MRI visit.

4.4.2.10 Total number of T1 Gd-enhanced lesions detected by brain MRI at Weeks 24, 48 and 96

The analyses will include patients in the ITT population. Data from unscheduled assessments will not be included in this summary or analysis.

The following analyses will be presented:

- Number and percentage of patients having 0, 1, 2, 3, and greater than 1 and greater than 3 lesions at weeks 24, 48 and 96.
- Number and percentage of patients having 0, 1, 2, 3, and greater than 1 and greater than 3 lesions in total detected at week 24, 48 and 96.
- The unadjusted and adjusted rates of lesion occurrence at weeks 24, 48 and 96 and the unadjusted and adjusted rate combining week 24, 48, 96 will be calculated:
    - The unadjusted rate will be the ratio of the total number of T1 Gd-enhanced lesions divided by the total number of interpretable MRI scans at each visit.
    - The adjusted rate will be derived using a negative binomial 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:
        - disease duration
        - presence of T1 Gd-enhanced lesions at screening (Yes/No),
        - presence of relapses prior screening as per CRF (Yes/No)
        - number of previous DMTs (1, >1).

      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”.
    - For the analysis above using negative binomial model for adjusted rate, if the model doesn’t converge due to a high number of zero T1 Gd-enhanced lesion counts, other models, such as logistic regression model will be considered based on the same baseline variables. Patients having zero T1 Gd-enhanced lesions (but not missing) up to withdrawal will be considered as not having an event.

- Histogram of the count (0, 1, 2, 3, >1, >3) of T1 Gd-enhanced lesions at Weeks 24, 48 and 96, and during all visits (Weeks 24, 48 and 96) combined will be produced.

A descriptive analysis on the number of T1 Gd-enhanced lesions at screening and week 8 will also be performed.

4.4.2.11 Change in total T2 lesion volume detected by brain MRI from Week 8 to Week 96

The analyses will include patients in the ITT population.

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

Change and percentage change from week 8 in total T2 lesion volume detected by brain MRI will be summarized.

4.4.2.12 Volume and number of new and/or enlarging T2 hyperintense lesions at Week 24, 48 and 96

The analyses will include patients in the ITT population.

The number of new and/or enlarging T2 lesions at week 24, 48 and 96 will be calculated as the sum of the individual number of new and/or enlarging lesions at each visit. Data from other unscheduled assessments will not be included in this summary or analysis.

The volume of new/or enlarging T2 lesions will also be analyzed at week 24, 48 and 96.

The same analysis as total number T1-Gd enhanced lesions and will be provided for the number of new and /or T2 lesions and a summary descriptive will be provided for the volume of new/or enlarging T2 lesions.

4.4.2.13 Change in T1 hypointense lesion volume from Week 8 to Weeks 48 and 96

The analyses will include patients in the ITT population.

The volume of T1 hypointense lesions at week 8, 48 and 96 along with the change from week 8 to week 48 and to week 96 will be summarized descriptively. In addition, change and percentage change from Week 8 in T1 hypointense lesion volume detected by brain MRI at Weeks 48 and 96 will be analyzed using a longitudinal MMRM. These MMRM analyses will be undertaken using the same approach as described above in Section 4.4.2.3.

4.4.2.14 Percentage Change in brain volume from Week 8 measured at Weeks 24, 48 and 96

This endpoint will be analyzed on the ITT population.

Brain volume is recorded as an absolute “normalized” (refer to “Electronic Data File Format & Transfer Specifications”) value at week 8 (baseline reset) then recorded at subsequent visits as a percentage change relative to the normalized brain volume value

at 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 considering as missing. Same rule applies to cortical grey matter volume and white matter volume.

Percentage change in brain volume relative to Week 8, as detected by brain MRI scan, will be summarized at weeks 24, 48 and 96 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 week 8
- percentage change in brain volume at weeks 24, 48 and 96

For the assessment of differences in the mean percentage change in brain volume at week 24, 48 and 96, a Mixed-Effect Model Repeated Measures analysis (MMRM) incorporating data collected up to 96 weeks of treatment will be used to assess all data collected over time with consideration of the variance−covariance matrix of the repeated measures. This method allows for a general unstructured variance−covariance matrix and will include data from patients with incomplete data from some scheduled time points.

The model will be implemented in SAS using the MIXED procedure and will include the percentage change at subsequent visits (weeks 24, 48 and 96) in brain volume as the dependent variable. The fixed effects in the model will include independent variables visit (nominal post - baseline visits at week 24, 48 and 96), along with the following covariates:

- normalized brain volume at week 8 (continuous variable),
- Duration since MS Symptom Onset (≤ 3 years, >3 and ≤5 years, >5 years and ≤10 years, >10years),
- T2 volume at week 8 (continuous variable),
- presence of T1 Gd-enhanced lesions at screening (Yes/No)
- Number of previous DMTs (1 ,>1)

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

Graphical presentations for least square means and 95% confidence intervals will be used to illustrate trends over time.

Sample SAS code can be found below (SAS code is regarded as "draft" until fully validated at the analysis stage):

```
proc mixed data=MRINBV method=REML;
    class VISIT USUBJID [covariates];
    model change = [covariates] VISIT / ddfm=   satterthwaite;
    repeated VISIT / type=un subject = USUBJID;
    lsmeans VISIT /cl;
```

```
        ods output lsmeans = lsm; * contains the adjusted means;
run;
```

4.4.2.15 Percentage Change in cortical grey matter volume from Week 8 measured at Weeks 24, 48 and 96

This endpoint will be analyzed on the ITT population. Note, this is an additional endpoint as compared with the protocol (refer to “Electronic Data File Format & Transfer Specifications”). 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 considering as missing.

Descriptive statistics will be used to summarize the following:

- “normalized” and “pre-normalized” cortical grey matter volume at week 8
- percentage change in cortical grey matter volume at weeks 24, 48 and 96

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

For the assessment of differences in the mean percentage change in cortical grey matter volume on MRI scans during the 96-week from week 24 up to week 96, an MMRM analysis will be undertaken using the same approach as described in Section 4.4.2.13, adjusting for covariates here will be as follows:

- cortical grey matter volume at week 8 (continuous variable),
- Duration since MS Symptom Onset (≤ 3 years, >3 and ≤5 years, >5 years and ≤10 years, >10years),
- T2 volume at week 8 (continuous variable),
- presence of T1 Gd-enhanced lesions at screening (Yes/No).
- Number of previous DMTs (1 ,>1)

4.4.2.16 Percentage Change in white matter volume from Week 8 measured at Weeks 24, 48 and 96

This endpoint will be analyzed on the ITT population. Note, this is an additional endpoint as compared with the protocol (refer to “Electronic Data File Format & Transfer Specifications”). 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 considering as missing.

Descriptive statistics will be used to summarize the following:

- “normalized” and “pre-normalized” white matter volume at week 8
- percentage change in white matter volume at weeks 24, 48 and 96

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

For the assessment of differences in the mean percentage change in white matter volume on MRI scans during the 96-week from week 24 up to week 96, an MMRM analysis will

be undertaken using the same approach as described in Section 4.4.2.13, adjusting for covariates:

- white matter volume at week 8
- Duration since MS Symptom Onset (≤ 3 years, >3 and ≤5 years, >5 years and ≤10 years, >10years),
- T2 volume at week 8,
- presence of T1 Gd-enhanced lesions at screening (Yes/No).
- Number of previous DMTs (1 ,>1)

4.4.2.17 Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS

This endpoint will be analyzed on the ITT population.

BICAMS analysis will be using three measures collected in the eCRF:

- The total number of correct symbols over 90 seconds recorded in the Symbol Digit Modalities Test (SDMT score)
- The total learning score from the California Verbal Learning Test (CVLT-II)
- The total learning score from the Brief Visuo-spatial Memory Test (BVMT-R)

These three measures will be summarized at each visit as the test value, the change from baseline and the % change from baseline values.

Additionally, the SDMT score analysis will be repeated for patients with no missing SDMT score at any visits. The BVMT-R score analysis will be repeated for patients with no missing BVMT-R score at any visits.

4.4.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include patient-reported outcomes (PROs) related to health-related quality of life (QoL), treatment satisfaction and other clinical endpoints. Summaries for change from baseline in these exploratory efficacy endpoints at Weeks 24, 48 and 96 will be provided.

In additional to the model based analyses, all PRO exploratory endpoints will be summarized descriptively at each assessment visit for individual question or domain as well as total scores as appropriate.

4.4.3.1 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 21-29, see below for missing data handling

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

	Calculation for transformed score	Range
Physical Scale	[(domain score-20)/(80-20)]*100, see below for missing data handling	0-100
Psychological Scale	[(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.

A summary table will present, by visit, the number of patients with:

- All items completed in the physical scale
- A minimum of 10 completed items in the physical scale
- All items completed in the psychological scale
- A minimum of 5 completed items in the psychological scale

The mean change in the physical and psychological MSIS-29 v2 domain scores from baseline to weeks 24, 48 and 96 will be summarized descriptively.

4.4.3.2 Treatment satisfaction questionnaire for medication (TSQM II)

The TSQM II consists of 11 questions and 4 domains. Scores are rated on a 5 – or 7-point likert scale. Items within a domain are summed and then transformed to a 0 – 100 scale, where a lower score corresponds to lower satisfaction.

Domain	Item #	Item Score	Transformed Domain Score	Range

Effectiveness	1-2	1 = Extremely Dissatisfied 2 = Very Dissatisfied 3 =Dissatisfied 4 = Somewhat Satisfied 5 = Satisfied 6 = Very Satisfied 7 = Extremely Satisfied	([(Items #1 + #2) – 2] divide by 12) * 100 If one item is missing: ([(Use the completed item)) – 1] divide by 6) * 100	0-100
Side Effects	3	1 = Yes 0 = No*	All 'not applicable' responses in items #4 – #6 will be scored as 5 for the derivation of the side effect domain score	
	4-6	1 = Extremely Dissatisfied 2 = Very Dissatisfied 3 = Somewhat Dissatisfied 4 = Slightly Dissatisfied 5 = Not at all Dissatisfied	([Sum(Items #4,#5,#6) – 3] divide by 12) * 100 If one item is missing: ([(Sum(*the two completed items*)) – 2] divide by 8) * 100	0-100
Convenience	7-9	1 = Extremely Dissatisfied 2 = Very Dissatisfied 3 =Dissatisfied 4 = Somewhat Satisfied 5 = Satisfied 6 = Very Satisfied 7 = Extremely Satisfied	([Sum(Items #7, #8, #9) – 3] divided by 18) * 100 If one item is missing: ([(Sum(*the two completed items*)) – 2] divided by 12) * 100	0-100
Global Satisfaction	10-11	1 = Extremely Dissatisfied 2 = Very Dissatisfied 3 =Dissatisfied 4 = Somewhat Satisfied 5 = Satisfied 6 = Very Satisfied 7 = Extremely Satisfied	([(Item #10 + #11) – 2] divide by 12) * 100 If one item is missing, then Domain score is missing	0-100

** note, if response to item #3 is "No", questions # 4, #5 and #6 are "not applicable"*

A summary table will present, by domain and visit, the number of patients with all items completed.

Each TSQM II transformed domain score will be summarized descriptively by visit. No imputation of missing data will be performed. This analysis will be repeated on the last DMT prior to study enrollment subgroup.

The mean change in each TSQM II transformed domain score from baseline to weeks 24, 48 and 96 will be summarized descriptively for completers only.

A separate analysis on the answer to Question 3: "As a result of taking this medication, do you experience any side effect at all?" will be performed. A shift table (cross tabulate) on the answer will be present from baseline to week 24, 48 and 96. These two analyses will be repeated on the last DMT prior to study enrollment subgroup.

4.4.3.3 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 a higher score corresponds to worse symptom limitations.

	Items #	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. No imputation of missing data will be performed. The mean change of SymptoMScreen total score from baseline to weeks 24, 48 and 96 will be summarized descriptively.

Proportion of patients with at least one symptom causing moderate limitation (>=4) and above will be calculated at baseline and at follow up weeks 24, 46 and 96.

4.4.3.4 Employment status: Work Productivity and Activity Impairment (WPAI)

The WPAI is a PRO formed 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 (%)
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.

4.4.3.5 MRI and clinical outcomes at 6 months and 1 year

MRI data including total number of Gd-enhanced lesions up to Weeks 24 *(i.e. 6-months)* and 48 *(i.e. 1-year)*, changes in total T2 lesion volume at Weeks 48 and changes in total T1 hypointense volume at Week 48 have been described as secondary efficacy endpoints.

Total number of new and/or enlarging T2 hyperintense lesions up to Weeks 24 and 48 will be summarized similarly to total number of T1 Gd-enhanced lesions (see section 4.4.2.10).

4.4.3.6 Severity of relapses (hospitalization for MS relapse, use of corticosteroids, residual disability)

Severity of protocol defined relapses including hospitalization longer than 5 days (yes/no), use of corticosteroid (yes/no) and residual disability (yes/no) will be summarized at baseline, weeks 24, 48 and 96 using frequency tables (number and percentage with total number of relapses as denominator).

For protocol defined relapses, a descriptive analysis of the EDSS change between before and after relapse will be performed. This change in EDSS (referred as Chg-$EDSS_{(after-before)}$) will be defined as difference between EDSS collected at the last scheduled EDSS measurement available prior to relapse and the EDSS collected at the first scheduled or unscheduled EDSS measurement on or after relapse. Descriptive summary of Chg-$EDSS_{(after-before)}$ will be presented along with the number of patients by EDSS change categories (<=0.5, 0.5-1.0, 1.0-2.0 and >2.0).

To investigate the evolution of EDSS after relapse, the change between the first EDSS measurement after the relapse and the next scheduled EDSS measurement will be summarized as above. This will be repeated for the change between the first EDSS measurement after the relapse and the second next scheduled EDSS measurement.

To investigate the duration of post relapse residual disability, the number and proportion of patients with an EDSS $_{\text{after relapse+<24;48> weeks}}$ > $\text{EDSS}_{\text{before relapse}}$ +0.5*$\text{Chg-EDSS}_{\text{(after-before)}}$ will be provided. This is illustrated in an example below:

$\text{EDSS}_{\text{before relapse}}$	$\text{EDSS}_{\text{after relapse}}$	$\text{Chg-EDSS}_{\text{(after-before)}}$	EDSS $_{\text{after relapse+ <24 ; 48> weeks}}$	retained at least 50% of $\text{Chg-EDSS}_{\text{(after-before)}}$
3	4	1	4.5	Yes
3	4	1	3.5	No

4.4.3.7 Proportion of patients who have NEDA, as per protocol defined events during a 96-week period and starting from baseline

This analysis can be considered as a sensitivity analysis of primary endpoint looking at clinical and MRI events in- between baseline visit and week 96. The MRI activity (T1 Gd-enhanced lesion and new/or enlarging T2 hyperintense lesion) will be evaluated from baseline to week 96.

Number and percentage of patients who have NEDA (yes, no) according to the presence of T1 Gd-enhanced lesion at Week 8 will be provided.

This endpoint will be analyzed similarly to the primary endpoint as described in section 4.4.1.

4.4.3.8 Predictors of NEDA and association between NEDA and disability or other efficacy parameters

Logistic regression models will be used to identify predictors of response to treatment (freedom from events). Variables that will be considered include:

- Duration since MS Symptom Onset (≤ 3 years, >3 and ≤5 years, >5 years and ≤10 years, >10years),
- T2 volume at week 8 (since not available at screening),
- presence of T1 Gd-enhanced lesions at screening,
- presence of relapses prior screening as per CRF (Yes/No)
- number of previous DMTs (1, >1)
- baseline EDSS
- gender.

4.4.3.9 Epoch analysis of NEDA in Year 1 (Weeks 0 to Week 48) and Year 2 (Week 48-96)

This analysis will be performed on the mITT population. Note, this is an additional endpoint as compared with the protocol.

The analysis of NEDA in Year 1 will follow the same rule as in Section 4.4.2.1. For the definition of EDA events in Year 2, a new baseline at week 48 for CDP and MRI activity

will be considered. A cross tabulation table of patients with NEDA = Yes/No in Year 1 and Y2 will be also presented.

4.4.4 Sensitivity Analyses

All analyses (binary endpoint, Kaplan-Meier, Life Table) listed for the primary endpoint in section 4.4.1 will be repeated for a modified protocol defined event definition, where any clinical MS relapses will contribute for a more comprehensive analysis of relapses as collected during the study.

For the primary endpoint, several sensitivity analysis will be performed:

- This analysis will be repeated for ITT population without imputation of missing values i.e. patients who discontinued treatment prior week 96, regardless of the reason, will be excluded from the analysis as their disease activity status cannot be ascertained.

- The analysis will also be repeated on the NEDA defined from MRI at screening visit instead of using MRI at week 8 as baseline. For this analysis, the number of new or enlarged T2 hyperintense lesionat week 24 visit will corresponds to the sum of the number of new or enlarged T2 hyperintense lesions at week 8 and 24.

- The analysis will also be repeated on the NEDA defined from MRI at week 8 as baseline and from protocol defined relapses occurred from Week 8 (only protocol defined relapses with study day>=57 will be considered).

- The analysis will be performed regarding the MRIs are done after infusion at the same visit. We will manually remove the measurement on T1 Gd-enhancing lesions from these MRIs if zero T1 Gd-enhancing lesions from these MRIs are reported, because the premedication corticosteroids potentially has impact on this MRI (Barkhof F, Neuroradiology. 1994) We will impute the presence of T1 Gd-enhanced lesion based on those MRIs if there is no T1 Gd-enhancing lesions identified. We consider this is a more conservative way than the primary analysis.

To summarize, five sensitivity analysis will be performed for NEDA:

Sensitivity Analysis	Modificantion
A	No imputation of missing values, regardless of the discontinuation reason.
B	MRI baseline at screening (week 0)
C	Use clinical relapse not the protocol defined relapse in the definition.
D	Rebaseline relapse (PDR) from week 8 (exclude the relapses occuring in the first 8 weeks)
E	If the number of T1 Gd-enhanced lesion from the MRI that done after infusion equals zero, it will be imputed

Modified protocol-defined event definition

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

- Any reported clinical MS relapse
- 24-weeks CDP based on increase in EDSS while on treatment with ocrelizumab
- A T1 Gd-enhanced lesion on MRI after week 8
- A new and/or enlarging T2 hyperintense lesion on MRI after week 8

Additionally, analyses of secondary efficacy endpoints from sections 4.4.2.5 and 4.4.2.6 will be repeated for all reported clinical MS relapses.

4.4.5 Subgroup Analyses

The primary and the secondary efficacy endpoints will be summarized by the following subgroups, provided that they include at least 50 patients:

- Last DMT prior to study enrolment
  - Interferons (Interferon ß 1a, Interferon ß 1b, Peg Interferon ß 1a)
  - Glatiramer acetate
  - Teriflunomide
  - Fingolimod
  - Dimethyl fumarate
  - Natalizumab
- Age (≤ 40 years, > 40 years)
- Disease severity at inclusion and in disease history:
  - EDSS at baseline (<2.5, ≥ 2.5)
  - Number of relapses over the year prior to inclusion (≤ 1, >1)
  - MRI at Week 8: presence of T1 Gd+ (Yes/No)
  - time between the qualifying disease activity event (last relapse prior to study) while on last DMT and 1st dose of ocrelizumab (<6 months, >=6 months)

In addition, changes in EDSS and ARR at week 96 will be summarized separately for patients with and without NEDA upto week 96. ARR will be only be repeated on the patients without NEDA up to week 96.

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 ITT population.

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:

[(Date of last contact*−Date of first dose) + 1]/7

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

[(Date of last contact*−Date of first dose) + 1]/365.25

*Earliest 1) date of last contact from the study completion page or study early termination page

2) date of death

3) CCOD

Exposure Analysis

Exposure of ocrelizumab will be summarized using descriptive statistics with the following data:

- treatment duration (weeks),
- number of doses received (day 1 and day 15 infusions are considered as one dose)
- total cumulative dose (mg).

4.6.2 Adverse Events

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.

Treatment emergent adverse events (TEAEs) will be summarized by SOC and PT. 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. The table results will be sorted by descending frequency of SOC and PT within each SOC.

Summary of TEAEs will be repeated for the following subgroups, provided that they include at least 50 patients:

- Last DMT prior to study enrolment
  - Interferons (Interferon ß 1a, Interferon ß 1b, Peg Interferon ß 1a)
  - Glatiramer acetate
  - Teriflunomide
  - Fingolimod
  - Dimethyl fumarate
  - Natalizumab

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.

An adverse event will be considered as treatment-emergent in the period “baseline to week 24”, if the AE onset date occurred on or after the start date of trial treatment and before start date of trial treatment + 24 weeks. An adverse event will be considered as treatment-emergent in period “>= week X – week Y”, if the AE onset date occurred on or after the start date of trial treatment + week X and before start date of trial treatment + Y weeks. If the emergence of an AE cannot be clearly assigned to a period, the AE will be considered emergent across all appropriate periods.

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
  - If the day and months are missing, impute to 01JAN
  - If the date is completely missing, it is considered treatment-emergent
- If the end date is incomplete:
  - If the day is missing, impute to the last day of the month
  - If the day and month are missing, impute to 31DEC
  - If the date is completely missing, it is considered treatment emergent

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

Dose assigned to an AE: only applicable if the AE onset date is on or after the date of the first infusion of that dose but before the first infusion of the next treatment dose. AEs that are reported during the safety follow-up period will be assigned to the last dose received. AEs that start prior to the first dose and worsen during treatment (i.e., treatment-emergent) will be assigned to the first treatment dose.

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). All summaries and listings of AEs will be based on the ITT population. Summaries of AEs will be generated to summarize the incidence of treatment-emergent AEs only (TEAE and AE are used exchangeable).

A listing of all AEs will be provided, including all relevant information (including -but not limited to- start date, end date and the corresponding study days, related to treatment, seriousness, Grade, treatment-emergence).

Incidence Analysis on number of the events and number of patients with at least one event:

Overview of TEAE, including

- 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 infection (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 $\geqslant$ 3

  An epoch summary (baseline to week 24, week 24 to week 48, and week 48 to week 96) of TEAEs will be repeated including the number of events and number and proportion of patients with adverse events emerging and serious AE in each of the period (baseline to week 24, >=week 24 – week 48, >= week 48 – week 96) will be provided.

Summary tables presenting the number of patients who experienced a TEAE will be summarized by SOC and PT for the following:

- **All TEAEs**

  An epoch summary (baseline to week 24, week 24 to week 48, and week 48 to week 96) of TEAEs. The number and proportion of patients with adverse events emerging in each of the period (baseline to week 24, >=week 24 – week 48, >= week 48 – week 96) will be provided.
- If an AE cannot be allocated to
- **Most Common TEAEs** reported by 5% or more of patients
- **TEAEs related to study drug** (“Yes” for the “Even suspected to be caused by ocrelizumab?” field on the “Adverse Event/IRR/MS Relapse” eCRF form)
- **TEAEs by Intensity Grade** (“1”, “2”, “3”, “4”, “5” for the “AE most extreme NCI CTCAE grade” field in the “Adverse Event/IRR/MS Relapse” 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).
- **TEAEs by intensity Grade ≥ 3** (“3”, “4”, “5” for the “AE most extreme NCI CTCAE grade” field in the “Adverse Event/IRR/MS Relapse” eCRF form)
- **Serious TEAEs** (“Serious” for the “Is this event non-serious or serious?” field in the “Adverse Event/IRR/MS Relapse” eCRF form),
- **Serious TEAE related to study drug**
- **Serious TEAE by intensity Grade ≥ 3**
- **TEAEs 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” eCRF form)
- **TEAEs 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” eCRF form)

- **Non-serious TEAEs reported by 5% or more of patients** (Note: table required for EudraCT and CT.gov disclosure registries)

Adverse events rates per 100 patient-years of exposure are defined as:
(total number of adverse events/total duration in the study) × 100.

Event rate per 100 PY will be presented on the following events:

- AE with fatal outcome
- infusion related reaction (IRR)
- Serious infusion related reaction (IRR)
- infections (based on SOC)
- serious infection (based on SOC)
- 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 $\geqslant$ 3.

All serious adverse events and deaths will be also listed.

4.6.2.1 Selected Adverse events

Infusion Related Reactions (IRR)

The number and percentage of patients with at least one IRR will be presented by infusion (patients with multiple events within an infusion will count only once). IRR will be selected based on AE CRF page flag. In addition, the total number of IRRs will be summarized (multiple events will be counted). The total and percentage (based on the total number of patients with at least one IRR) will be summarized by most extreme intensity.

IRRs will be summarized by intensity and by infusion. For multiple events within a patient, the most extreme intensity will be taken.

IRRs will also be summarized by intensity, by infusion and by previous DMT

Infections

A summary table by SOC and PT and listing of all TEAEs and Serious TEAEs infections occurring during the study will be provided. Infections will be selected based the MedDRA SOC of “Infections and Infestations”.

Pregnancies

All pregnancies occurring during the study will be listed.

4.6.3 Delayed return of B cells

Listings of patients whose B-cells have not been repleted after 96 weeks of Follow-up (Prolonged B-cell monitoring) will be provided and added to the CSR report as an appendix, once the data available.

4.6.4 Laboratory Data

Laboratory assessments are performed in local laboratory:

- Hematology (hemoglobin, hematocrit, platelet count, red blood cell [RBC] count, white blood cell [WBC] count, percent and absolute differential count [neutrophils, bands, 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)
- Viral serology and detection:
  - Hepatitis B (HBsAg and HBcAb confirmed, if positive, by positive viral DNA PCR)
  - For enrolled patients with negative HBsAg and positive total HBcAb, Hepatitis B virus (HBV) DNA (by PCR) must be repeated every 24 weeks
  - Hepatitis C virus (HCV) antibody
- 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 and urine analysis) will be summarized or listed when applicable.

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. 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.

In addition, for the liver laboratory parameters, the number and percentage of patients with an elevated post-baseline AST or ALT level during the 96-week treatment period will be summarized and a Hy's law analysis will be performed.

4.6.4.2 Lymphocytes evaluation

All lymphocytes parameters (CD4, CD8 and CD19) will be summarized using absolute count and change from baseline values at each visit.

In addition, the median CD19 cell count will be displayed graphically over time from the first infusion of study medication. At each time point, a summary of the number and percentage of patients whose CD19 counts have repleted will be produced. Repletion is defined as the CD19 count having returned to their baseline value or lower limit of normal, whichever is lowest.

4.6.5 Vital Signs

Vital signs will include measurements of heart rate, systolic and diastolic blood pressures, and temperature.

Each parameter of vital sign will be summarized using descriptive statistics at all timepoints.

4.6.6 Physical and neurological examinations

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").

4.6.7 Locally reviewed MRI

Non-MS pathology that is reported by the local safety radiologist will be listed.

4.6.8 Concomitant medications

Concomitant medications (defined as treatment started after baseline visit) will be summarized by frequency tables according to the Anatomic Therapeutic Chemical (ATC) classification system using the WHO Drug dictionary.

4.7 MISSING DATA

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

4.8 INTERIM ANALYSES

An analysis of the Year 1 data on some selected endpoints will be performed in 2019.

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Appendix 1: Protocol Synopsis

PROTOCOL SYNOPSIS TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**
PROTOCOL NUMBER:	MA30005
VERSION NUMBER:	5
EUDRACT NUMBER:	2015-005597-38
IND NUMBER:	Not applicable
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase IIIb
INDICATION:	Relapsing remitting multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of ocrelizumab in patients with relapsing remitting multiple sclerosis (RRMS) who have a suboptimal response to an adequate course of a disease modifying treatment (DMT). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objective

The primary objective for this study is to assess the efficacy of ocrelizumab 600 mg intravenous (IV) given every 24 weeks on the basis of the following endpoint:

- Proportion of patients who have no evidence of disease activity (NEDA, as per protocol defined events) during a 96-week period. The magnetic resonance imaging (MRI) activity will be calculated on the events starting from week 8 (baseline reset) when drug is fully active.

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

- A protocol-defined relapse as defined below
- 24 weeks confirmed disability progression based on increases in Expanded Disability Status Scale (EDSS) while on treatment with ocrelizumab
- A T1 gadolinium (Gd)-enhanced lesion after Week 8
- A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan

A protocol-defined multiple sclerosis (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

Episodic spasms, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse (Please note: Sexual dysfunction and fatigue need not be scored).
The secondary objective for this study is to evaluate the efficacy of ocrelizumab 600 mg IV given every 24 weeks on the basis of the following endpoints:

- The proportions of patients free from a protocol-defined event of disease activity during a 24-week period and a 48-week period
- Time to first protocol-defined event of disease activity
- Change in EDSS from baseline to Week 96
- Proportion of patients who, over a 96-week period, have Confirmed Disability Improvement (CDI), Confirmed Disability Progression (CDP) or stable disability (i.e. neither CDI nor CDP)
- Annualized rate of protocol-defined relapses at Week 96
- Time to onset of first protocol-defined relapse
- Time to onset of 24 weeks CDP
- Time to onset of first new and/or enlarging T2 lesion
- Total number of T1 Gd-enhanced lesions detected by brain MRI at Weeks 24, 48 and 96
- Change in total T2 lesion volume detected by brain MRI from baseline to Week 96
- Volume and number of new and/or enlarging T2 hyperintense lesions from baseline to Weeks 24, 48 and 96
- Change in T1 hypointense lesion volume from baseline to Weeks 48 and 96
- Change in brain volume from baseline measured at Weeks 24, 48 and 96
- Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis)

Safety Objective
The safety objective for this study is to evaluate the safety and tolerability of ocrelizumab 600 mg IV given every 24 weeks on the basis of the following endpoints:

- Rate and nature of adverse events
- Changes in vital signs, physical and 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).

Exploratory Objectives
The exploratory efficacy objective for this study is to further assess the efficacy of ocrelizumab 600 mg IV given every 24 weeks by monitoring patient-reported outcomes (PROs) related to quality of life (QoL), treatment satisfaction and other endpoints and analyses as follows:

- Multiple Sclerosis Impact Scale (MSIS)-29 (MS-specific QoL questionnaire)
- Treatment satisfaction questionnaire for medication (TSQM II)
- Patient reported outcome: SymptoMScreen
- MRI and clinical outcomes at 6 months and 1 year
- Predictors of NEDA and association between NEDA and disability or other efficacy parameters
- Severity of relapses (hospitalization for MS relapse, use of corticosteroids, residual disability)
- Employment status (WPAI)
- Proportion of patients who have no evidence of disease activity (NEDA, as per protocol defined events) during a 96-week period and starting from baseline.

Study Design

Description of Study
This study is a prospective, multicenter, open-label, efficacy, and safety study in patients with RRMS who have a suboptimal response to an adequate course of a DMT. An adequate course of prior DMT is defined as a stable dose of the same DMT administered for at least 6 months. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the study duration.
Patients will be assessed for efficacy and safety every 24 weeks. The study will consist of the following periods:

- Screening period: Up to 4 weeks
- Treatment period: Open-label treatment period of 96 weeks (last dose administered at Week 72)
- A follow-up period of at least 2 years, which is independent of the DMT administered

Follow-up Period: Patients who discontinue treatment early will be followed up for at least 96 weeks after the Early Treatment Discontinuation Visit. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate long-term extension (LTE) study, will be followed up for at least 96 weeks after the end of the Treatment Period. Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

Patients whose B-cells have not been repleted after 96 weeks of Follow-up Period will continue with visits every 24 weeks, and telephone contacts every 8 weeks, until B-cell repletion (Prolonged B-cell monitoring). If the patients are receiving other B-cell targeted therapies, then the Follow-up Period will be stopped at 96 weeks regardless of their B-cell count.

A structured telephone interview will be conducted by site personnel every 8 weeks between the study visits during the treatment period and follow-up to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections.
Number of Patients
This study will enroll 750 patients with RRMS who have had a suboptimal response to an adequate course of a DMT.

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
- Age 18 − 55 years, inclusive
- Have a definite diagnosis of RRMS, confirmed as per the revised McDonald 2010 criteria (Polman et al. 2011)
- Have a length of disease duration, from first symptom, of < 10 years. If the date of first symptom is unknown, then the diagnosis of RRMS should be of $\leqslant$ 5 years
- Have received no more than two prior DMTs, and the discontinuation of the most recent DMT was due to lack of efficacy
- Suboptimal disease control while on a DMT; a suboptimal response is defined by having at least one of the following events while being on a stable dose of the same DMT for at least 6 months:

− One or more clinically reported relapse(s)

− OR one or more T1 Gd-enhanced lesion(s)

− OR two or more new and/or enlarging T2 lesions on MRI

In addition, in patients receiving stable doses of the same approved DMT for more than a year, at least one of the above events must have occurred within the last 12 months of treatment with this DMT.

- EDSS of 0.0 to 4.0, inclusive, at screening
- For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 6 months after the last dose of study drug. 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 following are acceptable contraceptive methods: progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, and cap, diaphragm, or sponge with spermicide. A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods) is considered acceptable

Exclusion Criteria

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

- Secondary progressive multiple sclerosis (SPMS) or history of primary progressive or progressive relapsing MS
- Inability to complete an MRI (contraindications for MRI include but are not restricted to pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, inability to tolerate Gadolinium-based contrast agents etc.)
- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 (HTLV-1), herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

Exclusions Related to General Health

- Pregnancy or lactation
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study

- History or currently active primary or secondary immunodeficiency
- Lack of peripheral venous access
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Significant or uncontrolled somatic disease or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (New York Heart Association [NYHA] III or IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection, excluding fungal infection of nail beds

  Note: Active infections should be treated and effectively controlled before possible inclusion in the study
- History of major opportunistic infections (i.e. cryptococcosis, Pneumocystis pneumonia, progressive multifocal leukoencephalopathy [PML])
- History or known presence of recurrent or chronic infection (e.g., hepatitis B or C, human immunodeficiency virus [HIV], syphilis, tuberculosis [TB])
- History of malignancy, including solid tumors and hematological malignancies, except basal cell carcinoma, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been previously completely excised with documented, clear margins
- History of alcohol or drug abuse within 24 weeks prior to baseline
- History or laboratory evidence of coagulation disorders

Exclusions Related to Medications*

- Receipt of a live vaccine or attenuated live vaccine within 6 weeks prior to the baseline visit.

  In rare cases when patient requires vaccination with a live vaccine, the screening period may be extended but cannot exceed 8 weeks
- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or five half-lives of the investigational drug (whichever is longer) or treatment with any experimental procedures for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Contraindications to or intolerance of oral or IV corticosteroids, according to the country label, including:

  a) Psychosis not yet controlled by a treatment;

  b) Hypersensitivity to any of the constituents
- Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Systemic corticosteroid therapy within 4 weeks prior to screening
- Any previous treatment with alemtuzumab (Campath/Mabcampath/Lemtrada), cladribine, mitoxantrone, daclizumab, laquinimod, total body irradiation, or bone marrow transplantation.
- Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine or methotrexate
- Previous treatment with natalizumab unless natalizumab was discontinued because of persistent anti-natalizumab antibodies
- Treatment with IV immunoglobulin (Ig) within 12 weeks prior to baseline
- Any previous treatment with an investigational MS DMT not yet approved at time of screening.

- History of recurrent aspiration pneumonia requiring antibiotic therapy
- Patients previously treated with teriflunomide, unless an accelerated elimination procedure is implemented before screening visit

  Accelerated elimination procedure after stopping treatment with teriflunomide:
  - cholestyramine 8g is administered 3 times daily for a period of 11 days, or cholestyramine 4g three times a day can be used, if cholestyramine 8g three times a day is not well tolerated,
  - alternatively, 50g of activated powdered charcoal is administered every 12 hours for a period of 11 days

  In cases where no pregnancy is expected teriflunomide plasma concentrations of 0.03-0.04 mg/ml are accepted to include the patient in study.
- Previous treatment with fingolimod or dimethyl fumarate if at baseline the lymphocyte count is below lower limit of normal (LLN). The provisions for stopping therapy as described in the respective SmPCs should be followed.
- Treatment with fampridine/dalfamipridine (Fampyra®)/Ampyra®) unless on stable dose for ⩾ 30 days prior to screening. Wherever possible, patients should remain on stable doses throughout the 96-week treatment period.

* Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.

Exclusions Related to Laboratory Findings*

- Positive serum β human chorionic gonadotropin (hCG) measured at screening
- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C (HepCAb)
- Lymphocyte count below LLN
- CD4 count<250/µL.
- Aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT)⩾ 3.0 × the upper limit of normal (ULN)
- Platelet count <100,000/µL (<100 × 109/L)
- Absolute neutrophil count <1.0 × 103/µL

*Re-testing before baseline: any abnormal screening laboratory value that is clinically relevant should be retested in order to rule out any progressive or uncontrolled underlying condition. The last value before baseline visit must meet study criteria.
Please note: based on local Ethics Committees or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or selected centers to exclude tuberculosis, Lyme disease, HTLV-1 associated myelopathy (HAM), acquire immunodeficiency syndrome (AIDS), hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the Investigator.

End of Study

The end of the study treatment period has been defined as the date on which the last patient receiving the full study treatment reached the 96-week visit. Exception will be made for patients who have EDSS change at Week 96 and need confirmation of EDSS score after a further 24 weeks.

The end of the study is defined as the last patient last visit in the B-cell monitoring of the Follow-up Period.

At the end of the study treatment, patients will be encouraged to be included in a separate LTE study to further evaluate the efficacy and safety of their DMT treatment and this is independent of the DMT administered. This LTE will also aim to evaluate the relationship between the primary endpoint of this study and long-term outcome.

Length of Study
The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years. This includes an enrollment period of approximately 12 months.

Investigational Medicinal Products
Test Product (Investigational Drug)
The first dose of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15), followed by one 600-mg IV infusion in 500 mL 0.9% sodium chloride every subsequent dose (i.e., every 24 weeks) for a maximum of 4 doses.

Non-Investigational Medicinal Products
Premedicate with 100 mg of methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes prior to each ocrelizumab infusion, and an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of infusion-related reactions (IRRs). The addition of an antipyretic (e.g., acetaminophen/ paracetamol) may also be considered.

Statistical Methods
Primary Analysis
The primary efficacy analyses will include all enrolled patients who received any dose of ocrelizumab (intent-to-treat population). The analysis will be performed after the last CDP and CDI confirmation visit. The per-protocol population, defined as all patients who had 96 weeks of treatment and who did not have any major protocol violations that are deemed to potentially affect the efficacy and safety endpoints, will be used for supportive efficacy analyses of the primary endpoint.
The evaluation of the clinical efficacy of ocrelizumab will be based upon the events in-between the baseline visit and week 96 visit. The MRI activity is evaluated from week 8 to week 96.
The proportion of patients free from protocol-defined events up to Week 96 (i.e. patients with NEDA) will be calculated and the corresponding two-sided Clopper-Pearson 95% confidence interval (CI) will be presented. Logistic regression models will be used to identify predictors of response to treatment (freedom from protocol-defined events of disease activity). Variables that will be considered are: region, line of treatment (previous DMTs), gender, and baseline EDSS. In addition, specific efficacy endpoints, such as CDP, will be compared between patients with or without evidence of disease activity up to Week 96. Details about the missing data handling, as well as sensitivity analyses, will be specified in the statistical analysis plan.

Determination of Sample Size
With a sample size of 750 patients, an observed NEDA rate of 30% will be estimated with a precision (half-width of the 95% CI around the estimate) of 3.3% based on the Clopper-Pearson method, i.e. the 95% CI will be (26.7%, 33.4%). Even if the NEDA rate is different from the assumed rate of 30%, with the proposed sample size the precision of the estimate will remain smaller than 3.6% (value for a NEDA rate of 50%).
The annualized relapse rate is another relevant outcome measure assessed in this study. Based on results from the pivotal Phase III studies NCT01247324 (OPERA I) and NCT01412333 (OPERA II), in this study the adjusted annualized relapse rate assessed over two years is expected to be estimated with a precision of approximately 0.03.

Interim Analyses

No formal confirmatory efficacy interim analyses are planned. Exploratory analyses of selected endpoints may be performed during the course of the study, e.g. after all patients have completed the first 6 and 12 months of the treatment phase and the necessary data are available.

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

Visit	Screening	Treatment Period							Early study treatment discon-tinuation evaluation[q]	Follow-Upa Refer to Appendix 3
	1	2 (Baseline)	3	4	5	6	7	8		
Week	–4 to –1 weeks	1	2 (±2 days)	8 (±3 days)	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
Informed consent [b]	X									
Medical history and demographic data [c]	X									
Review inclusion & exclusion criteria	X	X								
Physical examination [d]	X	X	X		X	X	X	X	X	
Height and weight	X									
Vital signs [e]	X	X	X		X	X	X	X	X	
Laboratory Assessments										
Hematology, chemistry, urinalysis [f]	X	X	X		X	X	X	X	X	
Pregnancy test [g]	X	X	X		X	X	X	X		
Hepatitis screening [h]	X									
Hepatitis B virus DNA test [h]	X									
Lymphocytes subtypes sample [i]		X	X		X	X	X	X	X	
Plasma anti-JCV antibodies sample [j]		X				X		X	X	
EDSS score [k]	X	X			X	X	X	X	X	
Brain MRI [r]	X [s]			X	X	X		X	X	
Neurological examination [l]	X	X	X		X	X	X	X	X	
Recording of potential relapses		X	X		X	X	X	X	X	
Adverse event assessment [m]		X	X		X	X	X	X	X	
Patient Reported Outcomes		X			X	X		X	X	
BICAMS assessment [t]		X				X		X		

Visit	Screening	Treatment Period							Early study treatment discon-tinuation evaluation[q]	Follow-Upa Refer to Appendix 3
	1	2 (Baseline)	3	4	5	6	7	8		
Week	–4 to –1 weeks	1	2 (±2 days)	8 (±3 days)	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
Concomitant treatment review		X	X		X	X	X	X		
Methylprednisolone and antihistaminic drug premedication [n]		X	X		X	X	X			
Ocrelizumab administration [o]		X	X		X	X	X			
Telephone contact every 8 weeks[p]				X					(X)	

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BICAMS= Brief International Cognitive Assessment for Multiple Sclerosis; 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; HepCAb = hepatitis C; IV = intravenous; JCV = John Cunningham virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; RBC = red blood cell; WBC = white blood cell.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] The follow-up period will begin when the patient discontinues from the study for any reason. Patients should remain in follow-up for 96 weeks following the last infusion of ocrelizumab. (if discontinued early) or after the end of the Treatment Period. Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

[b] Written informed consent will be obtained from all patients during screening in order to be eligible for the study. ICF signature needs to be obtained before any study related procedure; the screening visit date is the date of the first screening procedure (e.g. lab sampling, neurological exam, etc.).

[c] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 6 weeks prior to the screening visit. Demographic data will include age, sex, and self-reported race/ethnicity.

[d] A complete physical examination should be performed at the screening and baseline visits and at all dosing visits during treatment. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline 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.

[e] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and oral or auricular temperature while the patient is in a seated position. Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone infusion. In addition, vital signs should be obtained 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 abnormalities observed before enrollment on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute and differential, ANC, and quantitative platelet count. Chemistry will include AST, ALT, GGT, creatinine, total bilirubin, random glucose, potassium and sodium. Urine dipstick will be done at site locally.

[g] Serum b-hCG must be performed at screening in women of childbearing potential. Subsequently, urine β-hCG (sensitivity ≥25 mIU/mL) must be collected. On infusion visits, the urine pregnancy test should be performed prior to methylprednisolone infusion in all women of childbearing potential. If positive, ocrelizumab should be withheld. The FSH test is only applicable to confirm postmenopausal status in female patients.

[h] All patients must have negative HBsAg result and negative HepCAb screening tests prior to enrollment. If total HBcAb is positive at screening, HBV DNA measured by PCR must be negative in order for a patient to be eligible for the study. For enrolled patients with negative HBsAg and positive total HBcAb, HBV DNA (by PCR) must be repeated every 24 weeks.

[i] Lymphocytes subtypes samples should be collected prior to ocrelizumab infusion to screen for CD19+ and T-cell counts (CD4+, CD8+) at a local laboratory.

[j] Plasma samples for anti-JCV antibodies should be taken at baseline and repeated yearly and end of study for storage in a central laboratory. Samples will be analyzed upon request.

[k] Patients must have an EDSS score of 0.0 to 4.0 points, inclusive at screening to be eligible. EDSS needs to be confirmed after 24 weeks if EDSS changes from baseline to Week 96

[l] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. 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.

[m] All adverse events should be reported until 96 weeks after the last dose of study drug. 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 (see Sections 5.3.1 and 5.6).

[n] All patients must receive prophylactic treatment with 100 mg methylprednisolone, administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab.

[o] Ocrelizumab will be administered as two 300-mg IV infusions in 250 mL 0.9% sodium chloride each on Days 1 and 15 and one 600-mg infusion in 500 mL 0.9% sodium chloride every subsequent dose (i.e., every 24 weeks) for a maximum of 72 weeks. It is anticipated that the patient will need to stay at the hospital or clinic for a full day for the infusion visits.

[p] A structured telephone interview will be conducted by site personnel every 8 weeks (± 3 days) to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections. No telephone contact is needed in weeks where patient is performing on-site visits (week 24, 48, 72 and 96).

[q] If the subject discontinues treatment early, all efforts should be made to perform the Early study treatment discontinuation evaluation visit as soon as possible after discontinuation from treatment period. Otherwise, reasons for discontinuation will be captured via telephone call.

[r] All efforts should be made to obtain the brain MRI scans before the next ocrelizumab infusion and the scans should be reviewed locally for the presence of any non-MS pathology, including PML, before the next infusion is administered.

[s] In case of re-screening, MRI does not need to be repeated if the MRI scan obtained at first screening is not older than 3 months.[t] Since CVLT-II is not yet available in all the languages of the countries participating in this study, the patients will not be assessed with this portion of the BICAMS. The patients will only need to complete the two components of the BICAMS test battery (Symbol Digit Modalities Test and Brief Visuospatial Memory Test Revised).

Note: Lab samples can be taken up to 2 weeks prior to the scheduled study visit. Results should be available prior dosing, except for anti-JCV antibodies (plasma samples collected and stored centrally) which will be analyzed upon request, and CD8 and CD19 (no interference with re-treatment)

Appendix 3: Follow-up Schedule of Assessments (Including Additional B-Cell Monitoring, if required)

Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

	Follow Up	Prolonged B-Cell Monitoring [a]
Assessment	Visits Every 24 Weeks (± 14 days) [b]	Visits Every 24 Weeks (± 14 days)
Routine safety laboratory tests [c]	X	X
Lymphocytes subtypes [d]	X	X
Plasma anti-JCV antibodies sample [e]	X	X
Vital signs	X	X
EDSS score [f]	X	
Potential relapses recorded	X	X
Adverse events [g]	X	X
BICAMS assessment [h]	X	X
Concomitant medication	X	X
MRI [i]	X	X
Telephone contact every 8 weeks [j]	X	X

BICAMS= Brief International Cognitive Assessment for Multiple Sclerosis; EDSS = Expanded Disability Status Scale; JCV = John Cunningham virus; MRI = Magnetic resonance imaging; MS = Multiple sclerosis

[a] Patients whose B-cells have not been repleted after 96 weeks of Follow-up Period will continue with visits every 24 weeks (± 14 days) and telephone contacts every 8 weeks until B-cell repletion (Prolonged B-cell monitoring). If the patients are receiving other B-cell targeted therapies, then the Follow-up Period is only 96 weeks regardless of their B-cell count.

[b] Visits will be performed at 24-week intervals following the last infusion of ocrelizumab. (if discontinued early) or after the end of the Treatment Period

[c] Routine safety lab: hematology, chemistry and urinalysis.

[d] Lymphocytes subtypes samples for CD19+ and T-cell counts (CD4+, CD8+)

[e] Plasma sampling for anti-JCV antibodies will be repeated yearly. Samples will be analyzed upon request.

[f] EDSS assessment needs to be performed only once, at the first follow-up visit

[g] Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Unrelated SAEs must be collected and reported during the study through the end of the Safety Follow-Up Period, which is at least 96 weeks after the last infusion, but may be extended in patients whose B-cells take longer to replete. Non-serious adverse events have to be reported until the end of SFU (see Sections 5.3.1 and 5.6).

[h] BICAMS will be assessed yearly. Since CVLT-II is not yet available in all the languages of the countries participating in this study, the patients will not be assessed with this portion of the BICAMS. The patients will only need to complete the other two components of the BICAMS test battery (Symbol Digit Modalities Test and Brief Visuospatial Memory Test Revised).

[l] MRIs will be performed yearly

[j] A structured telephone interview will be conducted by site personnel every 8 weeks (± 3 days) to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections. No telephone contact is needed in weeks where patient is performing on-site visits.

Patients who receive alternative MS therapies that may decrease B-cell levels will not be entered into the prolonged B-cell Monitoring period thereafter.

A dedicated (scheduled or unscheduled) follow-up visit directly prior to the start of an alternative MS treatment is required for patients who begin an alternative treatment for MS while in follow-up in order to assess the patient's clinical status and safety parameters (assessments to be performed as per schedule of assessments: follow-up or prolonged B-cell monitoring visits, depending on the study period in which