Official Title: An Open-label, Multicenter, Biomarker Study to Explore the Mechanism of Action of Ocrelizumab and B-Cell Biology in Patients with Relapsing Multiple Sclerosis or Primary Progressive Multiple Sclerosis

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PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER, BIOMARKER STUDY TO EXPLORE THE MECHANISM OF ACTION OF OCRELIZUMAB AND B-CELL BIOLOGY IN PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS** ***OR PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS***
PROTOCOL NUMBER:	ML29966
VERSION NUMBER:	4 (Global)
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FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	21-Nov-2016 18:25:11

PROTOCOL AMENDMENT, VERSION 4 (GLOBAL): RATIONALE

This Version 4 amendment consolidates elements of the previous country-specific amendment and revises the study design to add physical examinations at every treatment visit. The rationale for previous amendment (i.e., Version 3 [Germany]) is listed for the convenience of sites that did not receive this version of the protocol.

RATIONALE FOR VERSION 3 (GERMANY)

Protocol ML29966 was amended to Version 3 to include physical examinations at every treatment visit. The schedule of activities (Appendix 1) was updated to address a deficiency letter from the Paul-Erlich-Institut (PEI) dated 13 October 2016. In this letter, the PEI asked that physical examinations be conducted at every treatment visit, prior to treatment, to rule out any conditions that may require withholding of study drug (e.g., signs of active infection). Thus, physical examinations were added at Week 3 and Week 48.

RATIONALE FOR VERSION 4 (GLOBAL)

Protocol ML29966 was amended to Version 4 to include pre-dose physical examinations at every treatment visit as in Version 3 (Germany) and to harmonize relevant regional feedback into a global amendment.

Additional changes to the protocol, along with a rationale for each change, are summarized below:

- The protocol has been expanded to include a primary progressive multiple sclerosis (PPMS) cohort and a relapsing multiple sclerosis (RMS) control arm. The RMS delayed time to start control arm (Arm 4) has been added to the study for RMS patients who are willing to delay the first treatment with ocrelizumab for 12 weeks after the first lumbar puncture (LP) in cerebrospinal fluid. Arm 4 will provide a control for Arm 1 of the RMS cohort. Due to the relapsing and remitting nature of RMS, some biomarkers may change due to disease course rather than based on influence of a drug treatment. Therefore, some biomarkers may “regress to the mean” across the disease course over time, and this change could then inaccurately be reported as a change due to drug treatment over time. Arm 4 will allow for an estimate of the natural variability of the disease when analyzing the other treated arms. The PPMS cohort has been added as an exploratory, hypothesis-generating part of the trial because less is known about PPMS biomarkers. Multiple sections have been revised to include the PPMS cohort and RMS control arm, including the following:
  - The Study Rationale and Benefit-Risk Assessment section (Section 1.3) has been updated to include information regarding the benefit-risk profile of PPMS, according to a pivotal Phase III study of ocrelizumab.
  - The study objectives and endpoints (Section 2), as well as the study analyses (Section 6.4), have been updated to pertain to the RMS cohort, including specific information regarding the RMS control arm, and to the PPMS cohort.

- The Description of the Study section (Section 3.1) has been updated to include information on the PPMS cohort, such as the different dosing regimen and timing of LPs; to include information on the RMS control arm, such as the delayed dosing regimen and timing of LPs; and to and clarify the overall study design.
- The End of Study and Length of Study section (Section 3.2) has been updated to account for the extended time period of the RMS control arm (Arm 4).
- The Rationale for Ocrelizumab Dose and Schedule section (Section 3.3.1) and the Dosage, Administration, and Compliance section (Section 4.3.2) have been updated to include the different dosing regimen for the PPMS cohort.
- The patient population has been updated to reflect the estimated number of patients to be included in the study with the addition of the RMS control arm and the PPMS cohort (Section 4.1).
- The inclusion and exclusion criteria (Sections 4.1.1 and 4.1.2, respectively) have been expanded to include information pertaining to the RMS cohort (including the RMS control arm) and the PPMS cohort and have been reorganized by general criteria, RMS-specific criteria, and PPMS-specific criteria.
- The Method of Randomization section (Section 4.2) has been renamed to Method of Determination of the Time of Lumbar Puncture to more accurately describe the section, which has been expanded to include details about randomization of the RMS cohort and to indicate that the singular PPMS cohort will not be randomized.
- The Study Assessments section (Section 4.5) has been revised to indicate that assessments apply to the RMS cohort as specified in Appendix 1 for Arms 1–3 and Appendix 2 for Arm 4, as well as to the PPMS cohort as specified in Appendix 3.
- The 25-foot walk test and 9-hole peg test have been added to the neurological examinations performed only for the PPMS cohort (Section 4.5.6 and Appendix 3).
- Section 5.3.5.8 (Deaths) has been updated to specify reporting requirements for deaths due to MS instead of RMS in order to account for the PPMS cohort.
- The Statistical Considerations and Analysis Plan (Section 6) has been updated to clarify analyses that pertain to the RMS cohort (including the RMS control arm) and to the PPMS cohort.
- Schedules of activities have been added for the RMS control arm (Appendix 2) and for the PPMS cohort (Appendix 3).

- The Post-Trial Access to Ocrelizumab section (Section 4.3.6) has been revised to allow for possible post-trial access to ocrelizumab under the Roche Global Policy on Continued Access to Investigational Medicinal Product.

- The Concomitant Therapy section (Section 4.4) has been updated to reflect that concomitant therapy is any medication used from 4 weeks prior to screening until study completion instead of 7 days prior to the initiation of study drug until study completion and to clarify that medications used after treatment discontinuation should be recorded during the Safety Follow-Up Period.
- The Permitted Therapy section (Section 4.4.1) has been revised to include IV or oral corticosteroids and to specify that patients who experience a relapse and are treated with IV or oral corticosteroids should not discontinue treatment with ocrelizumab solely based on the occurrence of a relapse, unless he or she meets withdrawal criteria.
- The Medical History and Demographic Data section (Section 4.5.2) has been revised to clarify that use of any previous medication for MS should be reported.
- Sections 4.5.4 (Vital Signs) and 4.5.8 (Laboratory, Biomarker, and Other Biological Samples) have been revised to align with the current ocrelizumab program. Section 4.5.9 (Electrocardiograms) has been deleted for program alignment.
- Section 4.6.1 (Criteria for Re-Treatment with Ocrelizumab) has been added to specify that treatment with ocrelizumab should be suspended prior to re-dosing until certain conditions are resolved.
- Section 4.6.3 (Study Treatment Discontinuation) has been revised to indicate that, although pregnancies will be followed after study treatment discontinuation, infants born to patients or their partners will not be followed until 1 year of age, as such follow-up is not planned for this study.
- The Risks Associated with Ocrelizumab section (Section 5.1.1) of the protocol has been revised to align with the Ocrelizumab Investigator's Brochure, Version 14.
- The Infusion-Related Reactions and Diagnosis versus Signs and Symptoms sections (Sections 5.3.5.1 and 5.3.5.2, respectively) have been updated to align with an administrative letter dated 7 April 2016.
- Contact information for the Medical Monitor has been updated (Section 5.4.1).
- Information for men in the study regarding their pregnant partners has been added back into the protocol for consistency with current safety recommendations (Section 5.4.3.2).
- The B-Cell Monitoring Schedule of Activities has been added for monitoring of patients with prolonged B-cell depletion after the Safety Follow-up Period (Appendix 8).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 4 (GLOBAL): SUMMARY OF CHANGES

This Version 4 amendment consolidates elements of the previous country-specific amendment and revises the study design to include pre-dose physical examinations at every treatment visit. The Summary of Changes for the previous amendment (i.e., Version 3 [Germany]) is listed in this section for the convenience of sites that did not receive this version of the protocol. However, only Version 4 revisions are presented as italicized text in the body of the protocol.

SUMMARY OF CHANGES: VERSION 3 (GERMANY)

APPENDIX 1: Schedule of Assessments

The schedule of assessments was revised to include pre-dose physical examinations at Week 3 and Week 48.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form was revised to reflect the changes to the protocol.

SUMMARY OF CHANGES: VERSION 4 (GLOBAL)

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This is an exploratory biomarker study designed to be hypothesis-generating in order to better understand the mechanism of action of ocrelizumab and B-cell biology in RMS *and PPMS*.

Data from the two pivotal Phase III ocrelizumab RMS studies (WA21092 and WA21093) confirmed the favorable benefit-risk of ocrelizumab seen in the Phase II study (WA21493)*, and a pivotal Phase III ocrelizumab PPMS study (WA25046) demonstrated favorable benefit-risk profile in PPMS* (see Section 1.2.1). Together, these data demonstrate that ocrelizumab 600 mg administered every 6 months is effective and well tolerated in patients with *PPMS or* relapsing forms of MS.

SECTION 2.1: PRIMARY OBJECTIVES

The primary objectives for *the RMS cohort in* this study are: …

SECTION 2.2: EXPLORATORY OBJECTIVES

The exploratory objectives for *the PPMS cohort in* this study are:

- *To understand the impact of ocrelizumab treatment on NfL as a biomarker of neuronal damage in CSF*
- *To assess the number of CD19+B cells in CSF (cell number/microliter) before and after treatment with ocrelizumab*

- *To assess the number of CD3+T cells in CSF (cell number/microliter) before and after treatment with ocrelizumab*

The exploratory objectives for both cohorts in this study are:

- To understand the impact of ocrelizumab treatment on NfL and other biomarkers of neurodegeneration in CSF as a reflection of activity in the CNS and compared with peripheral blood
- To measure the impact of ocrelizumab treatment on B cells/B-cell subsets, T cells/T-cell subsets, and other cell types (e.g., natural killer [NK] cells, monocytes, etc.), functional parameters of B/T/other cell types (activation, cell products), and other biomarkers of inflammation in CSF as a reflection of activity in the CNS and compared with peripheral blood
- To assess potential correlation between change in blood or CSF biomarkers of neurodegeneration or inflammation and change in MRI or efficacy outcome measures, such as reduction in Gd-positive lesions or EDSS score

Exploratory objectives for the RMS delayed time to start control arm (Arm 4) will include comparisons between Arm 1 of the RMS cohort (second LP at 12 weeks) and Arm 4 (second LP at 12 weeks before the first dose of study drug), and may include but not be limited to changes in CSF, blood, and MRI biomarkers or efficacy, as outlined above.

SECTION 3.1: DESCRIPTION OF THE STUDY

This is an open-label, multicenter, biomarker study conducted at centers in multiple countries in which all eligible patients will be enrolled to a single treatment arm of ocrelizumab. *The study will include an RMS cohort and a PPMS cohort (see Table 1). The RMS cohort is the main cohort and will include the majority of study participants. The RMS cohort will be comprised of four arms, three of which will have patients randomized into one of three arms (Arms 1–3) depending on the time of their second lumbar puncture (LP). In Arm 4, treatment with ocrelizumab will be delayed for 12 weeks after the first LP. The PPMS cohort will comprise a smaller, hypothesis-generating portion of the trial, as less is known about PPMS biomarkers.*

Arm 4 will provide a control for Arm 1 of the RMS cohort. Due to the relapsing and remitting nature of RMS, some biomarkers may change due to disease course rather than based on influence of a drug treatment. Therefore, some biomarkers may "regress to the mean" across the disease course over time, and this change could then inaccurately be reported as a change due to drug treatment over time. Arm 4 will allow for an estimate of the natural variability of the disease when analyzing the other treated arms.

Male and female patients age 18–55 years with a diagnosis of RMS *or PPMS* in accordance with the 2010 revised McDonald criteria (Polman et al. 2011; Appendix 6) and an EDSS score of 0–5.5 points *for RMS patients, or an EDSS score of 3.0–6.5 for*

PPMS patients, at screening will be eligible. Screening will occur over a 4-week period, after which eligible patients may begin treatment with ocrelizumab.

~~Treatment with ocrelizumab will continue for 1 year after the first infusion, after which time patients may be eligible to enter an OLE phase and continue to receive treatment with ocrelizumab or to enter safety follow-up. Alternatively, treatment may be stopped at any time due to lack of clinical benefit, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, or if the Sponsor decides to close the trial, whichever occurs first.~~

For patients in the RMS cohort (Arms 1–3), ~~O~~ocrelizumab will be administered at Week 1, Week 3, Week 24, and Week 48. The first dose will be administered as two infusions of 300 mg given on Day 1 (Week 1) and Day 15 (Week 3). The subsequent doses will be given as single 600-mg infusions. ~~Patients will be evaluated for safety throughout the study.~~

For patients in the RMS cohort (Arm 4), after receiving two LPs at Week –12 and Week 1, the first dose of ocrelizumab will be administered as two 300-mg infusions on Week 1 (Day 1) and Week 3 (Day 15), with subsequent doses given as single 600-mg infusions at Weeks 24 and 48. The timeline for Arm 4 will continue for an extra 12 weeks to accommodate the same one-year dosing regimen.

For patients in the PPMS cohort, ocrelizumab 600 mg will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks (see Appendix 3).

Treatment with ocrelizumab will continue for approximately 1 year after the first infusion; however, treatment may be stopped at any time due to lack of clinical benefit, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, or if the Sponsor decides to close the trial, whichever occurs first. Patients may be eligible to continue to receive treatment if ocrelizumab is not commercially available in the patient's country or is not reasonably accessible to the patient (see Section 4.3.6), and these patients will continue to be followed.

~~Ocrelizumab p~~*P*atients who complete the 52-week ~~period of the~~ study *(64 weeks for patients in Arm 4)* and choose not to continue ~~with an OLE~~*on ocrelizumab treatment*, or ~~ocrelizumab patients~~ who discontinue from treatment early, should enter the Safety Follow-up Period and be assessed every 24 weeks for 48 weeks counting from the date of the last infusion of the ocrelizumab ~~or until B cells return to baseline level or the lower limit of normal, whichever occurs first~~. ~~At the end of this period~~*After 48 weeks*, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is ~~the~~ lower *(see Appendix 8).*

~~Patients who choose to receive commercially available ocrelizumab will not be followed for safety.~~

Biomarkers will be monitored in a longitudinal fashion before and after treatment with ocrelizumab in order to assess dynamic changes in biomarkers as they relate to drug exposure, length of time on drug, response to drug, and MS disease pathogenesis. Biomarkers will be assessed via blood draws throughout the study and via *LP in* CSF ~~from LP~~ at baseline before the first dose of ocrelizumab and at one other timepoint.

Two LPs will be drawn from each patient during the study. …

~~All p~~*P*atients *in the RMS cohort (Arms 1–3)* will receive an LP before the start of dosing with ocrelizumab. Subsequently, *these* patients will be randomized into one of three ~~groups~~ *arms* for timing of the second LP, either Week 12, 24, or 52 following the first dose of ocrelizumab. ~~Any additional LPs will be optional.~~

Patients in Arm 4 will receive two LPs, separated by a 12-week interval, before administration of the first dose of ocrelizumab. Patients in this arm will be asked if they are willing to give an optional CSF sample via LP 12 weeks after the ocrelizumab dose.

Patients in the PPMS cohort will receive an LP at the start of the study before dosing with ocrelizumab. Subsequently, they will receive a second LP at Week 52 following the first dose of ocrelizumab.

In the case of MS relapse *or worsening (for PPMS patients)* during the study, the patient should have an unscheduled visit and will be asked to receive an optional LP at the time of relapse *or worsening (for PPMS patients)*. The patient will have another LP at the originally scheduled time based on their randomization, or if a relapse occurs after they have already given the second LP, the relapse LP will remain optional.

All p~~P~~atients will be evaluated for safety throughout the study.

…

A ~~schedule of activities~~*study schema the RMS cohort Arms 1–3* is provided in Figure 1*, for the RMS cohort Arm 4 is provided in Figure 2, and for the PPMS cohort is provided in Figure 3. Organization of study cohorts and overall study design is provided in Table 1.*

FIGURE 1: Study Schema*: RMS Cohort Arms 1–3*

Figure 1 has been revised to pertain only to the RMS cohort.

FIGURE 2: *Study Schema: RMS Cohort Arm 4*

Figure 2 has been added to include information about the newly added RMS control arm (Arm 4).

FIGURE 3: *Study Schema: PPMS Cohort*

Figure 2 has been added to include information about the newly added PPMS cohort.

TABLE 1: *Study Cohorts and Overall Design*

Table 1 has been added to clarify the study design, which includes the RMS control arm (Arm 4) and the PPMS cohort. Subsequent tables have been renumbered accordingly.

SECTION 3.2: END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. ~~LPLV is expected to occur approximately 52 weeks after the last patient is enrolled, excluding any follow-up.~~

The total length of the study is expected to be approximately ~~2.5~~*3.5* years from the first patient enrolled to LPLV~~, excluding any follow-up~~. ~~Patients may be consented for participation in an OLE phase if, in the opinion of the investigator, they may benefit from treatment with ocrelizumab. The OLE phase would continue until the Sponsor decides to terminate the ocrelizumab program.~~

SECTION 3.3.1: Rationale for Ocrelizumab Dose and Schedule

The dose level of ocrelizumab administered in this study is 600 mg. The first dose will be administered as two 300-mg IV infusions separated by 14 days in order to lower amount of ocrelizumab administered upon first exposure. *For the RMS cohort, t*~~T~~he remaining doses will be administered as single 600-mg doses every 24 weeks. *For the PPMS cohort, ocrelizumab will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks during the treatment period.*

This dosing regimen is anticipated to be well tolerated and is consistent with the dosing regimen used in Study WA21092 and WA21093 in patients with RMS *and in Study WA25046 in patients with PPMS* (see Section 1.2.1).

SECTION 4.1: PATIENTS

Approximately 104 patients will be enrolled in this study; 88 patients with RMS and 16 patients with PPMS.~~Approximately 99 patients with RMS will be enrolled in this study.~~

SECTION 4.1.1: Inclusion Criteria

General Inclusion Criteria

Patients must meet the following criteria for study entry: …

Inclusion Criteria Specific to RMS Patients…

Inclusion Criteria Specific to RMS Cohort Arm 4 Patients

- *Must meet inclusion criteria for the RMS cohort*
- *Separate signed Informed Consent Form for the RMS Delayed Time to Start Control Arm (Arm 4)*
- *Must be willing to remain on the same dose and regimen of current standard of care, or no treatment if treatment-naïve, for 12 weeks after study enrollment*
  - *The treating and/or study physician must agree that the patient is eligible to remain on the same dose and regimen of their current standard of care at screening, or to receive no treatment if the patient is treatment-naïve, for 12 weeks after study enrollment.*

Inclusion Criteria Specific to PPMS Patients

- *Diagnosis of PPMS in accordance with the 2010 revised McDonald criteria (Pollman et al. 2011; Appendix 7)*
- *EDSS score of 3.0 – 6.5 points, inclusive, at screening*
- *Disease duration from the onset of MS symptoms:*
  - *Less than 10 years in patients with an EDSS at screening ≤5.0*
- *Documented history of at least one of the following laboratory findings in CSF:*
  - *Elevated IgG Index*
  - *One or more IgG OCBs detected by isoelectric focusing*

SECTION 4.1.2: Exclusion Criteria

General Exclusion Criteria

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

- Diagnosis of secondary progressive MS ~~(~~without relapses for at least 1 year~~)~~
- Certain laboratory abnormalities or findings at screening, including the following:
  - ~~Serum IgG 18% below the lower limit of normal (LLN)~~
  - ~~Serum IgM 8% below the LLN~~
  - ~~Positive rapid plasma reagin (RPR), confirmed by microhemagglutination assay (MHA-TP) or fluorescent treponemal antibody absorption (FTA-ABS) test~~
  - ~~Serum creatinine > 1.4 mg/dL (> 124 µmol/L) for women or > 1.6 mg/dL (> 141 µmol/L) for men~~
  - ~~Hemoglobin < 8.5 g/dL (< 5.15 mmol/L)~~
  - Abnormal lymphocyte count *(below LLN)*

    Re-testing before baseline: in rare cases in which the screening laboratory samples are rejected by the laboratory (e.g., hemolyzed sample) or the results are not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated ~~within 4 weeks~~. 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 randomization must

meet study criteria. In such circumstances, the screening period may need to be prolonged but should not exceed 8 weeks.

Exclusion Criteria Specific to RMS Patients

- *Diagnosis of PPMS or SPMS without relapses*

SECTION 4.2: ~~METHOD OF RANDOMIZATION FOR LUMBAR PUNCTURE~~*METHOD OF DETERMINATION OF THE TIME OF LUMBAR PUNCTURE*

Patients *in Arms 1 –3 of the RMS cohort* will be randomized into *each of the* three ~~groups~~ *arms* at 1:1:1 ratio according to the timing of the second LP at Week 12, 24, or 52 following the first dose of ocrelizumab *(see Table 1)*. An independent interactive voice/web response system (IxRS) provider will conduct randomization and maintain the treatment assignment code. Enrolled patients will be stratified by the previous disease-modifying therapy (DMT) treatment status (DMT-naïve vs. DMT-experienced). Therefore, the proportion of DMT-naïve patients will be approximately equal in each of three ~~groups~~*arms*.

A fourth RMS arm with delayed treatment start (Arm 4) will not be a part of the randomization and will be recruited separately.

All patients in the PPMS cohort will receive the second LP at 52 weeks and therefore will not be randomized.

Enrollment of the PPMS cohort and/or the RMS control arm (Arm 4) is open to all sites choosing to participate.

SECTION 4.3.2.1: Ocrelizumab

For the RMS cohort, d~~D~~ose 1 of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) separated by 14 days (i.e., Day 1 [Week 1] and Day 15 [Week 3]). Subsequent doses will be administered as one 600-mg IV infusion every 24 weeks for a maximum of 3 doses *(see Table 2)*.

For the PPMS cohort, ocrelizumab 600 mg will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks (see Table 3).

Although ocrelizumab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Ocrelizumab infusions should always be administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member. *It is anticipated that the patient will need to stay at the hospital or clinic for a full day for the infusion visits.*

An overview of the ocrelizumab dosing is presented in Table 2 *and Table 3*. ~~The ocrelizumab infusions will be administered per the instructions outlined in Table 4 and Table 5.~~

TABLE 2: Overview of Ocrelizumab Dosing: ***RMS Cohort***

Table 2 has been revised to pertain only to the RMS cohort.

TABLE 3: ***Overview of Ocrelizumab Dosing: PPMS Cohort***

Table 3 has been added to include information about the PPMS cohort.

TABLE 4: ~~Infusion Rates for 300-mg and 600-mg Ocrelizumab Infusions: RMS Cohort~~

Table 4 has been deleted, as information was outdated.

TABLE 5: ~~Infusion Rates for 300-mg Ocrelizumab Infusions: PPMS Cohort~~

Table 5 has been deleted, as information was outdated.

SECTION 4.3.6: <u>Post-Trial Access to Ocrelizumab</u>

The Sponsor (Genentech, a member of the Roche Group) will offer post-trial access to the study drug (ocrelizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if <u>all</u> of the following conditions are met:

- *The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being*
- *There are no appropriate alternative treatments available to the patient*
- *The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will <u>not</u> be eligible to receive study drug after completing the study if <u>any</u> of the following conditions are met:

- *The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- *The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for MS*
- *The Sponsor has reasonable safety concerns regarding the study drug as treatment for MS*
- *Provision of study drug is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

~~Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide ocrelizumab or any other study treatments or interventions to patients who have completed the study in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:~~

~~http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf~~

SECTION 4.4: CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from ~~7 days~~*4 weeks* prior to ~~initiation of study drug~~*screening* to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Medications used after treatment discontinuation should be recorded during the Safety Follow-up Period.

SECTION 4.4.1: Permitted Therapy

- *IV or oral corticosteroids*
  - *Patients who experience a relapse may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. Such patients should not discontinue treatment solely based on the occurrence of a relapse, unless the patient or investigator feels he or she has met the criteria for withdrawal (Section 4.6.3).*

SECTION 4.5: STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities ~~performed during the study~~*for the RMS cohort Arms 1–3, Appendix 2 for the schedule of activities for the RMS cohort Arm 4, and Appendix 3 for the schedule of activities for the PPMS cohort.*

SECTION 4.5.2: Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the screening visit. *In addition, use of any previous MS medication should be recorded.*

SECTION 4.5.4: Vital Signs

Vital signs should be performed at all visits. Vital signs will include the measurements of ~~respiratory rate,~~ heart rate, systolic and diastolic blood pressure, 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.

SECTION 4.5.5: Assessment of Disability

Disability in MS will be measured by the EDSS, which will be assessed by a certified ~~independent~~ assessor *at timepoints according to the appropriate schedule of activities* ~~at screening; baseline; Weeks 12, 24, 48, 52; in the case of relapse or early termination; and during safety follow-up~~.

SECTION 4.5.6: Neurological Examinations

Neurological examinations will be performed *at timepoints according to the appropriate schedule of activities*~~at screening; baseline; Weeks 12, 24, 48, 52;~~ and in the case of relapse or early termination so that the investigator can assess whether the patient is experiencing a relapse of MS or another neurological (non-MS) disorder.

For patients in the PPMS cohort, disease worsening or improvement over the treatment period will also be assessed and is defined as a 20% change in timed 25-foot walk test or a 20% change in 9-hole peg test time (see Appendix 3).

SECTION 4.5.7: Brain Magnetic Resonance Imaging

MRI scans will be read by a centralized reading center for both efficacy and safety endpoints. Further details on scanning acquisition sequences, methods, handling, transmission of the scans, and certification of site MRI ~~radiologist/technicians~~*scanner* are described in a separate MRI technical manual.

SECTION 4.5.8: Laboratory, Biomarker, and Other Biological Samples

Pre-infusion laboratory samples ~~should~~ *may* be drawn up to 14 days before the start of infusion so that routine laboratory test results are available for review before the infusion, unless otherwise specified.

- ~~Urinalysis~~ *Urine dipstick* (standard to assess kidney function)
- Viral serology
  - ~~RPR assessment (must be negative for syphilis)~~

In the case of suspected PML, serum or plasma biomarker, PK, or ADA samples may be used to assess status of JC virus (JCV) antibodies.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. *Fluoroscopy can be used, if required, for the LP to draw the CSF.*

SECTION 4.5.9: ~~Electrocardiograms~~

~~Twelve-lead electrocardiogram (ECG) measurements must be obtained at screening and when clinically indicated. ECG recordings must be performed after the patient has~~

~~been resting in a supine position for at least 10 minutes and obtained from the same machine whenever possible. All ECG tracings should be printed and kept with the patient's record. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings.~~

SECTION 4.6.1: *Criteria for Re-Treatment with Ocrelizumab*

Prior to re-treatment with ocrelizumab, patients will be evaluated for the following conditions and laboratory abnormalities. If any of these are present prior to re-dosing, further administration of ocrelizumab should be suspended until these are resolved or held indefinitely:

- *Life-threatening (Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion*
- *Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality*
- *Active infection*
- *Ongoing pregnancy*

In addition to the criteria above, patients with PPMS will also be evaluated for:

- *ANC $<1.5 \times 10^3/\mu L$*

SECTION 4.6.3: Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Ongoing pregnancy: Please note that the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications. ~~The health status of any infant born to patients or their partners may be followed until the child is 1 year of age.~~

SECTION 5.1: SAFETY PLAN

Safety assessments will include the incidence, nature, and severity of (serious) adverse events graded per the NCI CTCAE v4.0. Safety assessments will be conducted *for the RMS cohort Arms 1–3* per the schedule of activities in Appendix 1*, for the RMS cohort Arm 4 per the schedule of activities in Appendix 2, and for patients in the PPMS cohort per the schedule of activities in Appendix 3*.

SECTION 5.1.1: Risks Associated with Ocrelizumab

~~**5.1.1.1 Selected Adverse Events**~~

~~**5.1.1.1.1 Infusion-Related Reactions**~~

~~**Studies WA21092 and WA21093**~~

~~IRRs were the most common adverse event in patients treated with ocrelizumab 600 mg, and the proportion of patients experiencing IRRs was higher in the ocrelizumab 600 mg group (34.3%) compared with IFN β 1a treatment group (9.7%). The rate of IRRs was~~

highest during the first infusion of Dose 1 (27.5%) and decreased over time (13.7%, 9.6%, and 7.8% during Dose 2, 3, and 4, respectively).

The majority of IRRs in both treatment groups were of Grade 1 or 2. One patient in the IFN β-1a group had an IRR of Grade 3 (associated with first infusion). There were 20 patients in the ocrelizumab group who experienced a Grade 3 IRR (14 associated with first infusion of the first dose, although Grade 3 events occurred with the second and third doses).

Two serious IRRs were reported. One patient in the IFN β-1a group had a Grade 3 IRR in association with the initial infusion of ocrelizumab placebo. Symptoms in this patient included balance disorder, dizziness, flushing, and hypoaesthesia. The second serious IRR (Grade 4) was reported in association with the initial ocrelizumab infusion. Bronchospasm was reported as the IRR symptom. This event was the only serious IRR associated with ocrelizumab infusion reported in studies WA21092 and WA21093.

During the controlled treatment period, all patients received methylprednisolone (or equivalent) as pre-treatment prior to all ocrelizumab/placebo infusions. The majority of infusions were also preceded by analgesic/antipyretic and oral antihistamine treatments, as recommended. In patients receiving ocrelizumab, the addition of oral antihistamine to methylprednisolone pretreatment for each infusion further decreased the rate of IRRs compared to pretreatment with methylprednisolone alone.

Study WA25046

IRRs were the most frequently reported adverse events in patients treated with ocrelizumab. The proportion of patients who reported an IRR was higher in the ocrelizumab group (39.9%) compared with placebo (25.5%). The proportion of patients who experienced an IRR was highest after the first infusion, with 1 patient withdrawing from ocrelizumab treatment at this time. The proportion of patients experiencing an IRR was lower at subsequent infusions. Overall, 5 patients (1.0%) experienced a serious IRR in the ocrelizumab group.

Study WA21493

The proportion of patients reporting IRRs was higher in ocrelizumab-treated patients after the first infusion on Day 1 of the study (9.3% in placebo arm, 34.5% in the 300 mg×2 arm, and 43.6% in the 1000 mg×2 arm). The percentage of patients experiencing IRRs was lower after the second infusion on Day 15 compared with the first infusion in the ocrelizumab arms only (11.1% in placebo arm, 3.8% in the 300 mg×2 arm, and 9.4% in the 1000 mg×2 arms). Most IRRs (>90%) were of mild to moderate intensity (Grades 1 and 2).

5.1.1.1.2 Infections

Studies WA21092 and WA21093

All Infections

The percentage of patients experiencing an infection was higher in the pooled ocrelizumab treatment group (58.4%) compared with the pooled IFN β 1a treatment group (52.4%). The number of infections reported was also higher in the ocrelizumab treatment group (1224 events) than in the IFN β 1a treatment group (948 events). This difference was primarily driven by more patients with upper respiratory tract infections, as well as bronchitis, in the ocrelizumab group. In addition, the rate of herpes virus-associated infections was also higher in the ocrelizumab treatment group, although the overall rate was low.

The majority of infections were classified by the investigators as Grade 1 or 2 in intensity. Thirty one patients in the IFN β 1a group (3.89%) and 24 patients in the ocrelizumab group (2.9%) experienced a Grade 3 infection. Two patients in the ocrelizumab group (0.2%) reported an infection of Grade 4 intensity, "biliary sepsis" and "appendicitis." No fatal infections (Grade 5) were reported during the controlled treatment period.

No opportunistic infections were reported during the controlled treatment period, despite a broad screening that mostly retrieved herpes virus related infections that did not present any particular pattern.

Serious Infections

The proportion of patients with serious infections was overall low, and was lower in the ocrelizumab group (1.3%) than in the IFN β 1a group (2.9%).

The serious infection profile observed with increased exposure to ocrelizumab was similar to that in the treatment controlled period with regard to incidence, type, and severity.

Study WA25046

The proportion of patients with adverse events or serious adverse events of infection was similar in both the placebo and ocrelizumab groups. The proportion of patients who experienced an infection was 69.8% in the ocrelizumab group compared with 67.8% in the placebo group. The most frequently reported adverse events of infection were nasopharyngitis and urinary tract infection. The proportion of patients who experienced a serious infection was 6.2% in the ocrelizumab group compared with 5.9% in the placebo group.

Study WA21493

On review of the double blinded, 24 week safety data in Study WA21493, no imbalance in the overall number of infections or serious infections between placebo and active ocrelizumab arms was observed. The rate of infections remained consistent throughout

the study, including the treatment period (up to Week 96) and the treatment free period (up to Week 144).

5.1.1.1.3 Malignancies

In the MS program (studies WA21493, WA21092, WA21093, and WA25046) there were 20 malignancies in 18 patients receiving ocrelizumab (Table 6).

Table 6 Summary of Malignancies in the Multiple Sclerosis Studies

	Placebo	IFN	OCR 600 mg	OCR Total Events
Study WA21493				
n	—	—	220	
Total number of events	—	—	1	1
Total number of patients	—	—	1 [a]	
Studies WA21092 and WA21093 [b]				
n	—	826	825	
Total number of events	—	2	6	6
Total number of patients	—	2	6	
Study WA25046				
n	239	—	486	
Total number of events	2	—	13	13
Total number of patients	2	—	11	
Overall number of events in ocrelizumab patients in studies WA21493, WA21092, WA21093, and WA25046				20

IFN=interferon; OCR=ocrelizumab; OLE=open label extension.

[a] Patient received 1000 mg of ocrelizumab.

[b] Includes controlled treatment period and OLE up to the clinical cutoff dates. As of 31 October 2015, an additional malignancy (malignant melanoma) was reported in an ocrelizumab patient in Study WA21092 after the clinical cutoff date for this study.

Studies WA21092 and WA21093

During the 96 week controlled treatment period, a total of 6 malignancies were reported; 2 events (1 mantle cell lymphoma and 1 squamous cell carcinoma) occurred in 2 patients (0.2%) in the IFN β 1a treatment group and 4 events (2 invasive ductal breast carcinoma, 1 renal cancer, and 1 malignant melanoma) occurred in 4 patients (0.5%) in the ocrelizumab treatment group.

There were 2 additional malignancies in Study WA21092 during the open label extension (1 adenocarcinoma of the colon in a patient initially in the IFN β 1a group and 1 thyroid cancer in a patient initially in the ocrelizumab group).

Study WA25046

A total of 15 malignancies in 13 patients were reported (Table 7): 2 events (basal cell carcinoma and adenocarcinoma of the cervix) occurred in 2 patients (0.8%) in the placebo group and 13 events (5 basal cell carcinoma, 2 invasive ductal breast carcinoma, 1 anaplastic large cell lymphoma, 1 breast cancer, 1 endometrial cancer, 1 invasive breast carcinoma, 1 malignant fibrous histiocytoma, 1 pancreatic carcinoma metastatic) occurred in 11 patients (2.3%) in the ocrelizumab group.

Table 7 Malignancies by Body System Class and Preferred Term. Controlled Treatment Period, Safety-Evaluable Population

MedDRA System Organ Class MedDRA Preferred Term	Placebo N=239	OCR 600 mg N=486
Total number of patients with at least one adverse event	2 (0.8%)	11 (2.3%)
Overall total number of events	2	13
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)		
Total number of patients with at least one adverse event	2 (0.8%)	11 (2.3%)
Overall total number of events	2	13
Basal cell carcinoma	1	5
Invasive ductal breast carcinoma	0	2
Adenocarcinoma of the cervix	1	0
Anaplastic large cell lymphoma	0	1
Breast cancer	0	1
Endometrial cancer	0	1
Invasive breast carcinoma	0	1
Malignant fibrous histiocytoma	0	1
Pancreatic carcinoma metastatic	0	1

MedDRA=Medical Dictionary for Regulatory Activities; OCR=ocrelizumab.

Note: Multiple occurrences of the same adverse event in one patient are counted multiple times. Malignancies are identified using adverse events falling into the MedDRA System Organ Class "Malignant Tumours (narrow)."

Study WA21493

There was one malignancy (breast cancer) reported in Study WA21493 in the ocrelizumab group. An additional malignancy of squamous cell carcinoma occurred 2 days prior to the patient receiving ocrelizumab.

5.1.1.2 Identified Risks and Adverse Drug Reactions

This section refers to adverse events considered, after routine/ongoing medical evaluation, to be adverse drug reactions (ADRs) to the medical product at the present stage of development. A summary of identified risks in MS is presented in Table 8, and serious ADRs to ocrelizumab in MS are presented in Table 9.

Table 8 Summary of Identified Risks in Multiple Sclerosis

Risk	Description of Risk
Infusion related reactions	In the ocrelizumab group, the most frequently reported AE was IRR, and as expected, the percentage of patients experiencing IRRs was higher in the ocrelizumab group (RMS: 34.3%; PPMS: 39.9%) compared with the active control group who received placebo infusions (RMS: 9.7%; PPMS: 25.5%). These IRRs were reported more frequently with the first infusion of Dose 1 (approx. 27.5% in both RMS and PPMS), and were primarily mild to moderate in severity (NCI CTCAE Grades 1 and 2). Serious IRR occurred in 0.1% and 1.0% of patients, respectively, with RMS and PPMS and treated with ocrelizumab. IRRs are manageable through premedication before each infusion (100 mg of IV methylprednisolone or equivalent is mandatory, anti histaminics are recommended, and analgesics/antipyretics considered), as well as by infusion adjustments (slowing or interrupting) and symptomatic treatment (e.g., acetaminophen/paracetamol, intramuscular or slow IV antihistamine administration, bronchodilators).
Infections	In the pooled dataset of the pivotal Phase III trials in RMS population, the percentage of patients experiencing an infection was higher in the pooled ocrelizumab treatment group (58.4%) compared with the pooled IFN β 1a treatment group (52.4%). This difference was primarily driven by more patients with upper respiratory tract infections in the ocrelizumab group, as well as bronchitis and herpes virus associated infections. The majority of infections were classified by the investigators as Grade 1 or 2 in intensity. The proportion of patients with serious infections was overall low, and was lower in the ocrelizumab group (1.3%) than in the IFN β 1a group (2.9%). The serious infection profile observed with increased exposure to ocrelizumab was similar to that in the treatment controlled period with regard to incidence, type, and severity. In the PPMS population, the proportion of patients with AEs or SAEs of infection was similar in both the placebo and ocrelizumab groups. The proportion of patients who experienced an infection was 69.8% in the ocrelizumab group compared with 67.8% in the placebo group. The most frequently reported AEs of infection were nasopharyngitis and urinary tract infection. The proportion of patients who experienced a serious infection was 6.2% in the ocrelizumab group compared with 5.9% in the placebo group. All individual SAEs of infection were reported in fewer than 1% of patients in any group, with the exception of pneumonia (placebo 0.8% vs. OCR 1.2%) and urosepsis (placebo 1.3% vs. OCR 0.4%).

Risk	Description of Risk
Decrease in immunoglobulins	Treatment with ocrelizumab resulted in a decrease in total immunoglobulins over 2 years, mainly driven by reduction in IgM, with no apparent association with serious infections. The proportion of patients treated with ocrelizumab in the RMS program with immunoglobulins levels below the LLN was 2.4% for IgA, 1.5% for IgG, and 16.5% for IgM. The proportion of patients with decrease in immunoglobulins below LLN increased over time and successive dosing. The proportion of patients treated with ocrelizumab in the PPMS study with immunoglobulin levels below the LLN was 0.5% for IgA, 1.1% for IgG, and 15.5% for IgM.
Delayed return of peripheral B cells	Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post treatment (first timepoint of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B cells was 72 weeks (range 27 – 175 weeks).

AE = adverse event; IFN = interferon; IRR = infusion related reaction; IV = intravenous; LLN = lower limit of normal; PPMS = primary progressive multiple sclerosis; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RMS = relapsing forms of multiple sclerosis; SAE = serious adverse event.

Table 9 Serious Adverse Drug Reactions to Ocrelizumab in Multiple Sclerosis

Risk	Notes/Exclusions
IRRs	excluding fatal outcome
Infections [a]	excluding fatal outcome

IRR = infusion related reaction.

Note: Any term covered by the medical concepts presented in this list is considered "expected" for both non serious and serious reports of suspected unexpected adverse drug reactions to health authorities, excluding events with fatal outcome unless detailed otherwise in the table.

[a] Data not supportive of increased risk compared to placebo/IFN β 1a across all indications. Classification for reporting purposes only.

5.1.1.2.1 Serious Infections

Serious infections are not considered preliminary ADRs to date since no increase in individual serious infections was observed in the ocrelizumab treatment group in the MS population. However, for regulatory purposes only, serious infections will be considered as expected ADRs.

Prolonged peripheral B-cell depletion is the expected outcome of ocrelizumab treatment. Infection is a potentially serious complication of B-cell depleting therapy and thus

requires vigilant attention and prompt investigation and treatment in patients that exhibit signs of infection at any time following anti-CD20 antibody therapy.

Based on the available data from the completed controlled and ongoing open-label extension periods of the MS clinical program, the rate of serious infections in patients treated with ocrelizumab was low (2.32 per 100 patient years [PY]). In RMS patients, the rate of serious infections in the IFN group was higher (2.43 per 100 PY) than in the OCR group (1.24 per 100 PY). The rate of serious infections in PPMS patients was balanced between the placebo (4.24 per 100 PY) and OCR (3.74 per 100 PY) groups (see the Ocrelizumab Investigator's Brochure for further details).

Serious, opportunistic and fatal infections have occurred in patients with lupus and RA treated with ocrelizumab in Phase III clinical trials. Data from completed studies regarding infection risks with ocrelizumab treatment in these patient populations are provided in the Ocrelizumab Investigator's Brochure.

No opportunistic infections were reported by any MS patient treated with ocrelizumab (see the Ocrelizumab Investigator's Brochure for further details).

There were no reports of hepatitis B reactivation for screening and monitoring of hepatitis) in MS patients treated with ocrelizumab, but it was reported in RA (see the Ocrelizumab Investigator's Brochure for further details).

There were no reports of PML in MS patients treated with ocrelizumab. Among patients treated with rituximab, cases of PML have been observed. Most, but not all, patients who developed PML received rituximab in combination with chemotherapy or following a bone marrow transplant in order to treat cancer. The remaining patients who developed PML had other severe autoimmune diseases, such as RA or granulomatosis with polyangiitis (GPA/Wegener's), and all, including the patients who received rituximab for MS, had previously received or were receiving other drugs that suppressed their immune system at the same time (see the Ocrelizumab Investigator's Brochure for further details).

JC virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies and associated with risk factors (e.g., patient population, polytherapy with immunosuppressants). However, a risk of PML cannot be ruled out. Healthcare professionals should be alert to the early signs and symptoms of PML, which can include any new onset or worsening of neurological signs or symptoms as these can be similar to an MS relapse. Guidance for diagnosis is given in Appendix 5.

Delay ocrelizumab administration in patients with an active infection until the infection is resolved.

5.1.1.3 Potential Risks

5.1.1.3.1 Impaired Response to Vaccination

The degree of impairment of B-cell dependent humoral response to neo-antigens and polysaccharide antigens and its clinical relevance are currently unknown in patients with MS.

5.1.1.3.2 Malignancies

Malignancies are considered a potential risk with ocrelizumab due to the potential decreased immune surveillance associated with B-cell depletion in the context of treatments that are used long-term to treat chronic diseases.

The overall incidence rate per patient for malignancies in MS (RMS and PPMS combined) for ocrelizumab (Table 10) was 0.42 per 100 patient years (100 PY) (95% CI: 0.26, 0.66) compared with an incidence rate per patient for the control group (placebo/IFN) of 0.19 per 100 PY (95% CI: 0.05, 0.50). Although the incidence rate of malignancies in the ocrelizumab treatment groups across the MS program is higher than IFN or placebo groups, the overlapping CIs do not allow a firm conclusion regarding a higher risk.

The only cluster identified was for breast cancer (7 patients in the ocrelizumab groups across all MS trials compared with none in the comparator groups), and this was reflected in an increased incidence rate in female patients treated with ocrelizumab when compared with female placebo/interferon controls, albeit with overlapping CIs (female placebo/IFN: 0 patients, 0 per 100 PY [95% CI: 0,0.29]; female ocrelizumab: 7 patients, 0.26 per 100 PY [95% CI: 0.10, 0.54]).

No firm conclusion can be made to date concerning the risk due to the low number and the limited follow-up; hence, the risk remains potential to date.

5.1.1.3.3 Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. During clinical trials, no hypersensitivity reactions were reported in patients treated with ocrelizumab. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

5.1.1.3.4 Neutropenia

In MS patients (12% 15%), treatment with ocrelizumab resulted in a decrease in neutrophils of mild to moderate severity, which was not sustained. It did not necessitate treatment with granulocyte-colony stimulating factor and was not temporally associated with an infection.

A summary of potential risks is presented in Table 10.

Table 10 Summary of Potential Risks in Multiple Sclerosis

Risk	Description of Risk
Impaired immunization response	Over 2 years of treatment, the proportion of patients with positive antibody titers against *S. pneumoniae*, mumps, rubella, and varicella were generally similar to the proportions at baseline.
Malignancies	Across all MS trials, 23 patients reported a malignancy (19 [a] in the ocrelizumab group and 4 in the comparators groups). This imbalance is reflected in the overall incidence rate as described above, and the only cluster identified was for breast cancer. No firm conclusion can be made to date concerning the risk due to the low number and the limited follow up.
Neutropenia	The proportions of patients treated with ocrelizumab and reporting any single event of neutropenia defined by an absolute count of neutrophils below LLN were: 13.9% in Study WA21093, 15.6% in Study WA21092, and 12.1% in Study WA25046 compared with 9.6% of the patients in the placebo group in Study WA25046. Overall, approximately 1% of the patients in the ocrelizumab group had Grades 3 or 4 neutropenia (which did not necessitate treatment with G-CSF) and was not temporally associated with a serious infection.
Hypersensitivity	No hypersensitivity reactions to ocrelizumab were reported in the controlled clinical trials. Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms (see the Ocrelizumab Investigator's Brochure for further details).

G-CSF=granulocyte-colony stimulating factor; IRR=infusion-related reaction; LLN=lower limit of normal; MS=multiple sclerosis.

[a] As of 31 October 2015; includes one malignancy (malignant melanoma) in an ocrelizumab patient in Study WA21092 reported after the clinical cutoff date.

SECTION 5.1.1.1: *Identified Risks and Adverse Drug Reactions*

5.1.1.1.1 Infusion-Related Reactions

All CD20-depleting agents administered via the intravenous route, including ocrelizumab, have been associated with acute IRRs. Symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia.

Patients should be observed for at least one hour after the completion of the infusion for any symptom of IRR. They will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Hypotension, as a symptom of IRR, may occur during ocrelizumab infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

5.1.1.1.2 Infections

Infection is an identified risk associated with ocrelizumab treatment, predominantly involving mild to moderate respiratory tract infections. Non-disseminated herpes virus-associated infections, mostly mild to moderate, were also reported more frequently with ocrelizumab (approximately 5% to 6%, simplex and zoster) than with comparators (approximately 3%).

During the controlled period of the pivotal trials, the proportion of patients with serious infections was lower in RMS in the ocrelizumab group (1.3%) than in the interferon beta-1a group (2.9%); in PPMS, the proportion of patients with serious infections was similar in both groups: 6.7% in the placebo group compared with 6.2% in the ocrelizumab group.

Serious, opportunistic, and fatal infections have occurred in patients with lupus and rheumatoid arthritis (RA) treated with ocrelizumab in Phase III clinical trials. Data from completed studies regarding infection risks with ocrelizumab treatment in these patient populations are provided in the Ocrelizumab Investigator's Brochure.

No opportunistic infections were reported by any MS patient treated with ocrelizumab.

There were no reports of hepatitis B reactivation in MS patients treated with ocrelizumab, but it had been reported in one RA patient treated with ocrelizumab. HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active hepatitis B virus should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before the start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

There were no reports of PML in patients treated with ocrelizumab. JC virus (JCV) infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies and associated with risk factors (e.g., patient population, polytherapy with immunosuppressants). However, a risk of PML cannot be ruled out. Healthcare professionals should be alerted to the early signs and symptoms of PML, which can include any new onset or worsening of neurological signs or symptoms as these can be similar to an MS relapse. Please refer to Appendix 5 for guidance for diagnosis of PML.

Delay ocrelizumab administration in patients with an active infection until the infection is resolved.

5.1.1.1.3 Decrease in Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total immunoglobulins (Igs) over 2 years, mainly driven by reduction in IgM, with no observed association with serious infections. The proportion of patients with decrease in Igs below the LLN increased over time and with successive dosing.

5.1.1.1.4 Delayed Return of Peripheral B Cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post-treatment (first timepoint of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B cells was 72 weeks (range: 27–175 weeks). Patients with prolonged B-cell depletion should be monitored until their B cells have repleted.

SECTION 5.1.1.2: *Potential Risks*

5.1.1.2.1 Hypersensitivity Reactions

No hypersensitivity reactions to ocrelizumab were reported in the controlled clinical trials.

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

5.1.1.2.2 Impaired Response to Vaccination

The degree of impairment of B cell-dependent humoral response to neoantigens and polysaccharide antigens and its clinical relevance are currently unknown in patients with MS.

After treatment with ocrelizumab over 2 years, the proportion of patients with positive antibody titers against Streptococcus pneumoniae, mumps, rubella, and varicella were generally similar to the proportions at baseline.

No data are available on the effects of vaccination in patients receiving ocrelizumab. Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab.

The safety of immunization with live or live-attenuated viral vaccines following ocrelizumab therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended while B cells are depleted.

5.1.1.2.3 Malignancies including Breast Cancer

Malignancies are considered a potential risk with ocrelizumab due to the potential decreased immune surveillance associated with B-cell depletion in the context of treatments that are used long-term to treat chronic diseases. During the controlled treatment period, the incidence rate of malignancies in the ocrelizumab treatment groups across the MS program was higher than IFN or placebo groups with overlapping confidence intervals. The incidence rates were within the expected ranges for the MS population from epidemiology sources. The only cluster identified was for breast cancer. No firm conclusion can be made to date concerning the risk due to the low number and the limited follow-up; hence, the risk remains potential to date.

5.1.1.2.4 Neutropenia

In the controlled treatment period, decreased neutrophils were observed in 12% and 15% of MS patients treated with ocrelizumab in PPMS and RMS, respectively. Most were mild to moderate in severity, and approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified.

Detailed information for all risks can be found in the current Ocrelizumab Investigator's Brochure.

SECTION 5.3.5.1: Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration *and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.*~~should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).~~

~~All CD20-depleting agents, including ocrelizumab, have been associated with acute infusion-related reactions. Symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. IRRs can occur within 24 hours of the infusion. These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia.~~

SECTION 5.3.5.2: Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or

hepatitis rather than jaundice, asterixis, and elevated transaminases). ~~For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases).~~ …

SECTION 5.3.5.8: Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of ~~RMS~~*MS*.

If the death is attributed to progression of ~~RMS~~*MS*, "~~R~~MS progression" should be recorded on the Adverse Event eCRF.

SECTION 5.4.1: Emergency Medical Contacts
Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D. ~~(Primary)~~

Telephone No.: [redacted]

SECTION 5.4.3.2 *Pregnancies in Female Partners of Male Patients*

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This study is designed to assess levels of NfL, levels of lymphocyte populations in CSF, and to generate hypotheses about biomarkers of ocrelizumab treatment in patients with RMS *and PPMS*. Levels of NfL in CSF and levels of lymphocyte populations in CSF will be compared to baseline levels. *In addition, Arm 1 of the RMS cohort (second LP at 12 weeks) will be compared to Arm 4 (second LP at 12 weeks before the first dose of study drug).*

In this exploratory biomarker study, the analyses will be mostly descriptive and hypothesis-generating. ~~Inferential statistical methods, if applied, will be employed to highlight the data aspect of interest.~~ Unless otherwise specified, statistical tests will be two sided and the statistical significance level will be 5%. Corresponding 95% confidence intervals will be presented as appropriate. No corrections for multiple testing will be applied to the primary endpoint analyses, exploratory endpoint analyses, or interim analysis.

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

The ~~main objective of the~~*sample size calculations for this* study ~~is to generate hypotheses about biomarkers of ocrelizumab treatment. The NfL parameter,~~ *are* based on the ~~remitting patients, is used for sample size calculation~~ *assumed reduction from baseline in NfL* (Gunnarsson et al. 2011~~), and other~~*) at Weeks 24 and 52 combined (Arms 2 and 3) in the RMS cohort. Other* biomarker measures are not considered for power *determination*.

Assuming (a) a 30% reduction from ~~baseline~~ *pre-treatment* NfL (mean [SD]=860 *pg/mL* [780 *pg/mL*]) to post-treatment ~~(Week 24 and Week 52 combined;~~ *NfL (*mean [SD]=602 *pg/mL* [310~~])~~ *pg/mL])* and a correlation coefficient of ~~r~~=0.6*,* ~~(~~resulting in an SD of 643 *pg/mL* for *the* change~~) before and after~~ *from pre- to post-*treatment*,* and (b) a *desired* power of 80% with a *T*~~t~~ype 1 error of 5%, ~~the~~*a* sample size ~~will be n=~~*of* 51 ~~for Groups 2 and 3 combined (e.g., n=~~*patients is required, with approximately* 25 *patients* in ~~Group~~ *Arm* 2 and ~~n=~~26 *patients* in ~~Group~~ *Arm* 3~~). A total of 25 patients will be included in Group 1 to explore the possible reduction in NfL at an earlier timepoint. Therefore, the total sample size for data analysis from three groups will be N=76~~.

This is the first study to explore the impact of ocrelizumab on CSF B-cell count. In a study by Piccio et al. (2010), the rate of undetectable B cells in CSF was 74% (21/26) after 24–30 weeks of rituximab ~~treatment~~ as an add-on ~~therapy in addition~~ to immunomodulatory therapy. Based on this information~~, we would expect that the~~ *and a sample size of 51 patients (Arm 2 and 3 combined), the expected* 95% CI for the CSF B-cell undetectable rate will be: (0.61, 0.85~~) with the proposed sample size of n=51 for Groups 2 and 3 combined.~~*)*.

~~To~~*In the RMS cohort, 15 patients will be included in Arm 1 to explore the possible reduction in NfL at Week 12 post-treatment and 15 patients will be assigned to the delayed start RMS control arm (Arm 4). Fifteen patients will be recruited to the PPMS cohort. The above sample sizes are not based on statistical considerations and are meant to help explore the changes in biomarkers and generate hypotheses for future studies.*

Based on the above, the total sample size for this study will be 96 patients. The sample size will be increased by approximately 10% in order to account for ~~early dropouts without providing any~~*potential missing* post-treatment CSF ~~data~~*information*; *therefore*,

the ~~total~~ number of patients *to be* enrolled ~~will be increased by 30%. Therefore, the number of patients to be enrolled~~*in the RMS cohort* will be N = ~~99 (33 patients from each of three groups).~~*88 (Arm 1: 16 patients, Arm 2: 28 patients, Arm 3: 28 patients, and Arm 4: 16 patients), and N =16 in the PPMS cohort. Therefore, the total number of patients to be enrolled is 104.*

SECTION 6.3: SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographics, medical history, and neurological examination will be summarized. MS disease history (duration since MS first symptom, duration since MS diagnosis), MS disease status (MS treatment naïve or experienced), and MS prior treatment (for those being treated) will be summarized. Also, the baseline measures of key CSF biomarkers, MRI, EDSS, or other important endpoints will be summarized. *It should be noted that two baseline measures for the RMS control arm (Arm 4) will be obtained: the first at the Week –12 visit, which is 12 weeks before the first infusion of ocrelizumab, and the second at the first treatment visit pre-infusion.*

SECTION 6.4: ANALYSES

Statistical analyses will be performed on the analysis population, defined as all enrolled patients who *(a)* received at least one infusion of ocrelizumab, even if the infusion was incomplete *or (b) received at least one LP*.

SECTION 6.4.1: Primary Endpoints

Primary endpoints *for the RMS cohort (Arms 1–3)* include:

- Change in levels of NfL in CSF from *treatment* baseline to post-treatment with ocrelizumab
- Change in number of CD19+ B cells in CSF from *treatment* baseline to post-treatment with ocrelizumab
- Change in number of CD3+ T cells in CSF from *treatment* baseline to post-treatment with ocrelizumab

SECTION 6.4.2: Exploratory Endpoints

Exploratory endpoints for the PPMS cohort include:

- *Change in levels of NfL in CSF from treatment baseline to post-treatment with ocrelizumab*
- *Change in number of CD19+ B cells in CSF from treatment baseline to post-treatment with ocrelizumab*
- *Change in number of CD3+ T cells in CSF from treatment baseline to post-treatment with ocrelizumab*

CSF biomarker endpoints *for both cohorts* may include, but may not be limited to:

- Activation markers, functional attributes, activity, and/or molecular status of cells (e.g., proteins, non-heritable RNA levels, etc.) at ~~Weeks 1, 12, 24, and 52 (and~~

~~optional sample in case of relapse)~~*all collected timepoints* before and after treatment with ocrelizumab*, including optional samples*

- Levels of soluble neurodegeneration markers and/or inflammatory markers at ~~Weeks 1, 12, 24, and 52 (and optional sample in case of relapse)~~ *all collected timepoints* before and after treatment with ocrelizumab*, including optional samples*

Blood biomarker endpoints *for both cohorts* may include, but may not be limited to:

- Change in number of CD19+ B and CD3+ T cells in blood *at all collected timepoints before and after* ~~from baseline to post-~~treatment with ocrelizumab, *including optional samples*
- Activation markers, functional attributes, activity, and/or molecular status of PBMCs or cell products (e.g., proteins, non-heritable RNA levels) ~~at Weeks 1, 3, 12, 24, 36, 48, and 52~~ *at all collected timepoints* before and after treatment with ocrelizumab*, including at unscheduled visits*
- Levels of NfL, levels of soluble neurodegeneration markers, and/or inflammatory markers in the peripheral blood serum or plasma ~~at Weeks 1, 3, 12, 24, 36, 48, and 52~~ *at all collected timepoints* before and after treatment with ocrelizumab*, including at unscheduled visits*

MRI biomarker endpoints *for both cohorts* may include, but may not be limited to:

- Total number of T1 Gd-enhanced lesions at *at all collected timepoints before and after treatment with ocrelizumab*~~Weeks 12, 24, and 52~~*, including at unscheduled visits*
- Change in total T2 lesion volume *at all collected timepoints before and after treatment with ocrelizumab*~~from baseline to Weeks 12, 24, and 52~~*, including at unscheduled visits*
- Total number of new and/or enlarging T2 lesions *at all collected timepoints before and after treatment with ocrelizumab*~~at Weeks 12, 24, and 52~~*, including at unscheduled visits*
- Changes in regional or total brain volume *at all collected timepoints before and after treatment with ocrelizumab*~~from baseline or Week 12 to Weeks 24 and 52~~*, including at unscheduled visits*
- *Total number of leptomeningeal-enhancing regions at all collected points before and after treatment with ocrelizumab, including at unscheduled visits*

Efficacy endpoints *for both cohorts* may include, but may not be limited to:

- Change in EDSS score from baseline

Other analyses may include evaluation of the possible associations between the changes in biomarkers of neurodegeneration or inflammation and change in MRI or efficacy outcome measures, such as reduction in Gd-positive lesions or *time to worsening as measured by the* EDSS score *(RMS and PPMS cohort), or the 25-foot timed walk or the 9-hole peg test (PPMS cohort only).*

Endpoints for the RMS control arm (Arm 4) will include comparisons between Arm 1 of the RMS cohort (treatment baseline to second LP at 12 weeks) and Arm 4 (pre-treatment baseline to treatment baseline, second LP at 12 weeks before the first dose of study drug), and may include, but may not be limited to, changes in CSF at all collected timepoints including optional samples, blood, and MRI biomarkers or efficacy, as outlined above.

SECTION 6.4.3: Pharmacokinetic and Immunogenicity Endpoints

Pharmacokinetics and immunogenicity may be explored in relation to the pharmacodynamics of blood and/or CSF biomarkers *in both cohorts*. Serum concentration of ocrelizumab may be measured at Weeks 12, 24, 48, and 52; in the case of early termination; and at safety follow-up. The level of ocrelizumab may be measured in the CSF at Weeks 12, 24, and*/or* 52 *and at Week 52 for the PPMS cohort*; and/or in a CSF sample taken at an unscheduled visit *or from an optional sample*.

SECTION 6.6: INTERIM ANALYSIS

An interim analysis may be performed when *approximately* 50% of patients have had their second LP.

SECTION 7.5: RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results *(including flow cytometry data)*, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

APPENDIX 1: Schedule of Activities *for the RMS Cohort Arms 1-3*

The schedule of activities has been revised to include and clarify assessments for the RMS cohort.

APPENDIX 2: *Schedule of Activities for the RMS Cohort Arm 4*

Appendix 2 has been added to include assessments for the PPMS cohort. Subsequent appendices have been renumbered accordingly.

APPENDIX 3: *Schedule of Activities for the PPMS Cohort*

Appendix 3 has been added to include assessments for the PPMS cohort.

APPENDIX 8: *B-Cell Monitoring Schedule of Activities*

Appendix 8 has been added to include assessments for B-cell monitoring.

SAMPLE INFORMED CONSENT FORMS

The sample Informed Consent Form has been revised to reflect the changes to the protocol and pertains only to patients in the RMS cohort Arms 1–3. In addition, separate sample Informed Consent Forms have been created for patients in the RMS delayed time to start control arm (Arm 4) and for patients in the PPMS cohort.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, MULTICENTER, BIOMARKER STUDY TO EXPLORE THE MECHANISM OF ACTION OF OCRELIZUMAB AND B-CELL BIOLOGY IN PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS** ***OR PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS***
PROTOCOL NUMBER:	ML29966
VERSION NUMBER:	4 (Global)
EUDRACT NUMBER:	2015-004616-37
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, MULTICENTER, BIOMARKER STUDY TO EXPLORE THE MECHANISM OF ACTION OF OCRELIZUMAB AND B-CELL BIOLOGY IN PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS** *OR PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS*
PROTOCOL NUMBER:	ML29966
VERSION NUMBER:	4 (Global)
EUDRACT NUMBER:	2015-004616-37
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	IIIb
INDICATION:	Relapsing multiple sclerosis *and primary progressive multiple sclerosis*
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This is an exploratory biomarker study designed to be hypothesis-generating in order to better understand the mechanism of action of ocrelizumab and B-cell biology in relapsing multiple sclerosis (RMS) *and primary progressive multiple sclerosis (PPMS).*

Primary Objectives

The primary objectives for *the RMS cohort in* this study are:

- To understand the impact of ocrelizumab treatment on neurofilament light (NfL) as a biomarker of neuronal damage in cerebrospinal fluid (CSF)
- To assess the number of CD19+ B cells in CSF (cell number/microliter) before and after treatment with ocrelizumab
- To assess the number of CD3+ T cells in CSF (cell number/microliter) before and after treatment with ocrelizumab

Exploratory Objectives

The exploratory objectives for *the PPMS cohort in* this study are:

- *To understand the impact of ocrelizumab treatment on NfL as a biomarker of neuronal damage in CSF*
- *To assess the number of CD19+ B cells in CSF (cell number/microliter) before and after treatment with ocrelizumab*
- *To assess the number of CD3+ T cells in CSF (cell number/microliter) before and after treatment with ocrelizumab*

The exploratory objectives for both cohorts in this study are:

- To understand the impact of ocrelizumab treatment on NfL and other biomarkers of neurodegeneration in CSF as a reflection of activity in the central nervous system (CNS) and compared with peripheral blood

- To measure the impact of ocrelizumab treatment on B cells/B-cell subsets, T cells/T-cell subsets, and other cell types (e.g., natural killer cells, monocytes, etc.), functional parameters of B/T/other cell types (activation, cell products), and other biomarkers of inflammation in CSF as a reflection of activity in the CNS and compared with peripheral blood
- To assess potential correlation between change in blood or CSF biomarkers of neurodegeneration or inflammation and change in magnetic resonance imaging (MRI) or efficacy outcome measures, such as reduction in gadolinium (Gd)-positive lesions or Expanded Disability Status Scale (EDSS) score

Exploratory objectives for the RMS delayed time to start control arm (Arm 4) will include comparisons between Arm 1 of the RMS cohort (second lumbar puncture [LP] at 12 weeks) and Arm 4 (second LP at 12 weeks before the first dose of study drug), and may include but not be limited to changes in CSF, blood, and MRI biomarkers or efficacy, as outlined above.

Pharmacokinetic Objective

The pharmacokinetic objective for this study is:

- To assess pharmacokinetics of ocrelizumab in CSF compared with serum concentration

Immunogenicity Objective

The immunogenicity objective for this study is:

- To assess the incidence of anti-drug antibodies to ocrelizumab

Safety Objectives

The safety objective for this study is to evaluate the safety of ocrelizumab on the basis of the following endpoints:

- Nature, frequency, severity, and timing of adverse events
- Changes in vital signs, physical findings, and clinical laboratory results during and following ocrelizumab administration
- Adverse events related to biomarker sample collection

Study Design

Description of Study

This is an open-label, multicenter, biomarker study conducted at centers in multiple countries in which all eligible patients will be enrolled to a single treatment arm of ocrelizumab. *The study will include an RMS cohort and a PPMS cohort (see Table 1). The RMS cohort is the main cohort and will include the majority of study participants. The RMS cohort will be comprised of four arms, three of which will have patients randomized into one of three arms (Arms 1–3) depending on the time of their second LP. In Arm 4, treatment with ocrelizumab will be delayed for 12 weeks after the first LP. The PPMS cohort will comprise a smaller, hypothesis-generating portion of the trial, as less is known about PPMS biomarkers.*

Arm 4 will provide a control for Arm 1 of the RMS cohort. Due to the relapsing and remitting nature of RMS, some biomarkers may change due to disease course rather than based on influence of a drug treatment. Therefore, some biomarkers may "regress to the mean" across the disease course over time, and this change could then inaccurately be reported as a change due to drug treatment over time. Arm 4 will allow for an estimate of the natural variability of the disease when analyzing the other treated arms.

Male and female patients age 18–55 years with a diagnosis of RMS *or PPMS* in accordance with the 2010 revised McDonald criteria (Polman et al. 2011; Appendix 7) and an EDSS score of 0–5.5 points *for RMS patients, or an EDSS score of 3.0–6.5 for PPMS patients,* at screening will be eligible. Screening will occur over a 4-week period, after which eligible patients may begin treatment with ocrelizumab.

*For patients in the RMS cohort (Arms 1–3), o*crelizumab will be administered at Week 1, Week 3, Week 24, and Week 48. The first dose will be administered as two infusions of 300 mg given on Day 1 and Day 15. The subsequent doses will be given as single 600-mg infusions.

For patients in the RMS cohort (Arm 4), after receiving two LPs at Week –12 and Week 1, the first dose of ocrelizumab will be administered as two 300-mg infusions on Week 1 (Day 1) and

Week 3 (Day 15), with subsequent doses given as single 600-mg infusions at Weeks 24 and 48. The timeline for Arm 4 will continue for an extra 12 weeks to accommodate the same one-year dosing regimen.

For patients in the PPMS cohort, ocrelizumab 600 mg will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks (see Appendix 3).

Treatment with ocrelizumab will continue for approximately 1 year after the first infusion; however, treatment may be stopped at any time due to lack of clinical benefit, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, or if the Sponsor decides to close the trial, whichever occurs first. Patients may be eligible to continue to receive treatment if ocrelizumab is not commercially available in the patient's country or is not reasonably accessible to the patient (see Section 4.3.6), and these patients will continue to be followed.

*P*atients who complete the 52-week study *(64 weeks for patients in Arm 4)* and choose not to continue *on ocrelizumab treatment*, or who discontinue from treatment early, should enter the Safety Follow-up Period and be assessed every 24 weeks for 48 weeks counting from the date of the last infusion of ocrelizumab. *After 48 weeks*, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is lower *(see Appendix 8*).

Biomarkers will be monitored in a longitudinal fashion before and after treatment with ocrelizumab in order to assess dynamic changes in biomarkers as they relate to drug exposure, length of time on drug, response to drug, and MS disease pathogenesis. Biomarkers will be assessed via blood draws throughout the study and via *LP in* CSF at baseline before the first dose of ocrelizumab and at one other timepoint.

Two LPs will be drawn from each patient during the study. The two LPs will allow for assessment of biomarkers in CSF that are indicative of response to drug, pharmacokinetic/pharmacodynamic relationships, and/or disease pathogenesis in the CNS.

*P*atients *in the RMS cohort (Arms 1–3)* will receive an LP before the start of dosing with ocrelizumab. Subsequently, *these* patients will be randomized into one of three *arms* for timing of the second LP, either Week 12, 24, or 52 following the first dose of ocrelizumab.

Patients in Arm 4 will receive two LPs, separated by a 12-week interval, before administration of the first dose of ocrelizumab. Patients in this arm will be asked if they are willing to give an optional CSF sample via LP 12 weeks after the ocrelizumab dose.

Patients in the PPMS cohort will receive an LP at the start of the study before dosing with ocrelizumab. Subsequently, they will receive a second LP at Week 52 following the first dose of ocrelizumab.

In the case of MS relapse *or worsening (for PPMS patients)* during the study, the patient should have an unscheduled visit and will be asked to receive an optional LP at the time of relapse *or worsening (for PPMS patients)*. The patient will have another LP at the originally scheduled time based on their randomization, or if a relapse occurs after they have already given the second LP, the relapse LP will remain optional.

*All p*atients will be evaluated for safety throughout the study.

In the case of early termination, the patient will be asked to have an early termination visit.

Number of Patients

Approximately 104 patients will be enrolled in this study; 88 patients with RMS and 16 patients with PPMS.

Target Population

Inclusion Criteria

General Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with the protocol, in the investigator's judgment
- Age 18–55 years, inclusive

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 24 weeks after the last dose of study treatment or until their B cells have repleted, whichever is longer
  - 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).
  - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Inclusion Criteria Specific to RMS Patients

- Diagnosis of RMS in accordance with the 2010 revised McDonald criteria (Polman et al. 2011; Appendix 7)
- EDSS score of 0–5.5 points, inclusive, at screening
- Disease duration from the onset of MS symptoms:
  - Less than 15 years in patients with an EDSS >5.0 at screening
- Either treatment-naïve or receiving treatment with disease-modifying therapies, including prior use of interferon (IFN)-β-1a (Avonex®, Rebif®), IFN-β-1b (Betaseron®/Betaferon), or glatiramer acetate (Copaxone®)
- At least one clinically documented relapse in the past year and/or at least one T1-weighted Gd-enhancing lesion in the past year and/or at least one new T2 lesion in the past year at the time of enrollment

Inclusion Criteria Specific to RMS Cohort Arm 4

- *Must meet inclusion criteria for the RMS cohort*
- *Separate signed Informed Consent Form for the RMS Delayed Time to Start Control Arm (Arm 4)*
- *Must be willing to remain on the same dose and regimen of current standard of care, or no treatment if treatment-naïve, for 12 weeks after study enrollment*
  - *The treating and/or study physician must agree that the patient is eligible to remain on the same dose and regimen of their current standard of care at screening, or to receive no treatment if the patient is treatment-naïve, for 12 weeks after study enrollment.*

Inclusion Criteria Specific to PPMS Patients

- *Diagnosis of PPMS in accordance with the 2010 revised McDonald criteria (Polman et al. 2011; Appendix 7)*
- *EDSS score of 3.0–6.5 points, inclusive, at screening*
- *Disease duration from the onset of MS symptoms:*
  - *Less than 10 years in patients with an EDSS at screening ≤5.0*
- *Documented history of at least one of the following laboratory findings in CSF:*
  - *Elevated IgG Index*
  - *One or more IgG oligoclonal bands detected by isoelectric focusing*

Exclusion Criteria

General Inclusion Criteria

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

- Diagnosis of secondary progressive MS without relapses for at least 1 year

- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, tuberculosis)
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- History of cancer, including solid tumors and hematological malignancies (except basal cell, in situ squamous cell carcinomas of the skin, and in situ carcinoma of the cervix or the uterus that have been excised and resolved with documented clean margins on pathology)
- History of or currently active primary or secondary immunodeficiency
- History of coagulation disorders
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of alcohol or other drug abuse within 24 weeks prior to enrollment
- Known presence or history of other neurologic disorders, including but not limited to, the following:
  - *History or known presence of progressive multifocal leukoencephalopathy*
  - *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, HTLV-1, herpes zoster myelopathy)*
  - *History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS])*
  - *History or known presence of systemic autoimmune disorders, potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren's syndrome, Behçet's disease)*
  - *History or known presence of sarcoidosis*
  - *Neuromyelitis optica*
  - *Ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord*
  - *Severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)*
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including chronic obstructive pulmonary disease), renal, hepatic, endocrine, gastrointestinal, or any other significant disease
- Congestive heart failure (according to New York Heart Association III or IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis or atypical mycobacterial disease, but excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- Contraindications for, or intolerance to, oral or IV corticosteroids, including IV methylprednisolone, according to the country label, including:
  - *Psychosis not yet controlled by a treatment*
  - *Hypersensitivity to any of the treatment drug constituents*
- Contraindication for LP
- Previous treatment with B cell-targeted therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)

- Previous treatment with natalizumab (Tysabri®), alemtuzumab, anti-CD4 agents, cladribine, teriflunomide, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation
- Treatment with fingolimod (Gilenya®), dimethyl fumarate (Tecfidera®), or similar treatment within 6 months prior to enrollment
- Receipt of a live vaccine within 6 weeks prior to enrollment
  - *Vaccinations before baseline: In rare cases where a live vaccine must be administered by the patient's physician, the screening period may need to be prolonged but cannot exceed 12 weeks.*
- Systemic corticosteroid therapy within 4 weeks prior to baseline
  - *The screening period may be extended (but cannot exceed 8 weeks) for patients who have used systemic corticosteroids for their MS before screening.*
- Previous or concurrent treatment with any investigational agent or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Certain laboratory abnormalities or findings at screening, including the following:
  - *Positive serum β-hCG*
  - *Positive for hepatitis B (hepatitis B surface antigen [HBsAg] positive or hepatitis B core antibody [total HBcAb] confirmed by positive viral DNA polymerase chain reaction [PCR]) or hepatitis C (HepCAb)*
  - *AST or ALT ≥2.0 upper limit of normal*
  - *Platelet count <100,000/μL (<100 ×109/L)*
  - *ANC <1.5 ×103/μL*
  - *Abnormal lymphocyte count (below lower level of normal)*

    Re-testing before baseline: in rare cases in which the screening laboratory samples are rejected by the laboratory (e.g., hemolyzed sample) or the results are not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated. 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 randomization must meet study criteria. In such circumstances, the screening period may need to be prolonged but should not exceed 8 weeks.
- Inability to complete an MRI (contraindications for MRI include but are not restricted to weight ≥ 140 kg, pacemaker, cochlear implants, 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, contraindication to gadolinium, etc.)
- Lack of peripheral venous access
- Pregnant or lactating, or intending to become pregnant during the study
  - *Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.*

Exclusion Criteria Specific to RMS Patients

- *Diagnosis of PPMS or secondary progressive multiple sclerosis without relapses*

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

Length of Study

The total length of the study is expected to be approximately *3.5* years from the first patient enrolled to LPLV.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product for this study is ocrelizumab.

Non-Investigational Medicinal Products

Premedicate with 100 mg of methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion to reduce the frequency and severity of infusion-related reactions (IRRs).

Additional premedication with an antihistaminic drug (e.g., diphenhydramine) is recommended approximately 30–60 minutes before each infusion of ocrelizumab to further reduce the frequency and severity of IRRs. The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered.

Statistical Methods

Statistical analyses will be performed on the analysis population, defined as all enrolled patients who received at least one infusion of ocrelizumab, even if the infusion was incomplete.

Primary Endpoints

Primary endpoints for the RMS cohort include:

- Change in levels of NfL in CSF from treatment baseline to post-treatment with ocrelizumab
- Change in number of CD19+ B cells in CSF from treatment baseline to post-treatment with ocrelizumab
- Change in number of CD3+ T cells in CSF from treatment baseline to post-treatment with ocrelizumab

Determination of Sample Size

The sample size calculations for this study are based on the assumed reduction from baseline in NfL (Gunnarsson et al. 2011) at Weeks 24 and 52 combined (Arms 2 and 3) in the RMS cohort. Other biomarker measures are not considered for power determination.

Assuming (a) a 30% reduction from pre-treatment NfL (mean [SD] = 860 pg/mL [780 pg/mL]) to post-treatment NfL (mean [SD] = 602 pg/mL [310 pg/mL]) and a correlation coefficient of 0.6, resulting in an SD of 643 pg/mL for the change from pre- to post-treatment, and (b) a desired power of 80% with a Type 1 error of 5%, a sample size of 51 patients is required, with approximately 25 patients in Arm 2 and 26 patients in Arm 3.

This is the first study to explore the impact of ocrelizumab on CSF B-cell count. In a study by Piccio et al. (2010), the rate of undetectable B cells in CSF was 74% (21/26) after 24–30 weeks of rituximab as an add-on to immunomodulatory therapy. Based on this information and a sample size of 51 patients (Arm 2 and 3 combined), the expected 95% CI for the CSF B-cell undetectable rate will be: (0.61, 0.85).

In the RMS cohort, 15 patients will be included in Arm 1 to explore the possible reduction in NfL at Week 12 post-treatment and 15 patients will be assigned to the delayed start RMS control arm (Arm 4). Fifteen patients will be recruited to the PPMS cohort. The above sample sizes are not based on statistical considerations and are meant to help explore the changes in biomarkers and generate hypotheses for future studies.

Based on the above, the total sample size for this study will be 96 patients. The sample size will be increased by approximately 10% in order to account for potential missing post-treatment CSF information; therefore, the number of patients to be enrolled in the RMS cohort will be N = 88 (Arm 1: 16 patients, Arm 2: 28 patients, Arm 3: 28 patients, and Arm 4: 16 patients), and N = 16 in the PPMS cohort. Therefore, the total number of patients to be enrolled is 104.

Interim Analyses

An interim analysis may be performed when approximately 50% of patients have had their second LP.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ARR	annualized relapse rate
β-hCG	beta subunit human chorionic gonadotropin
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DMT	disease-modifying therapy
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
FDA	U.S. Food and Drug Administration
Gd	gadolinium
FS	Functional Systems
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HepCAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IFN-β	interferon beta
Ig	immunoglobulin
IMP	investigational medicinal product
IRR	infusion-related reaction
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
IxRS	interactive voice/web response system
LLN	lower limit of normal
LPLV	last patient, last visit
LP	lumbar puncture
MRI	magnetic resonance image
MS	multiple sclerosis
NCI	National Cancer Institute
NfL	neurofilament light (chain)

OCB	oligoclonal bands
NK	natural killer (cells)
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PY	patient years
RA	rheumatoid arthritis
RCR	Roche Clinical Repository
RMS	relapsing multiple sclerosis
RR	relative reduction
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary progressive multiple sclerosis
ULN	upper limit of normal
U.S.	United States

1. BACKGROUND

1.1 BACKGROUND ON BIOMARKERS IN MULTIPLE SCLEROSIS

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 2.5 million worldwide (Tullman et al. 2013). MS primarily affects young adults, with 70%–80% of patients having an age of onset (i.e., initial clinical presentation to a physician) between 20 and 40 years (Anderson et al. 1992; Noonan et al. 2002), and has a strong gender bias, with approximately 64%–70% of diagnosed patients being women (Goodin 2014). MS is subcategorized into three phenotypic disease patterns including relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). The term "RMS" (i.e., relapsing multiple sclerosis) applies to those patients with either RRMS or SPMS who continue to suffer relapses. Patients with RMS, whether or not they suffer from neurologic progression in the absence of relapses, have a common inflammatory pathophysiology that therefore constitutes a common target for treatment.

Although the etiology of MS remains largely unknown, it is well accepted that aberrant functioning of both the adaptive and innate immune system, including the dysregulation of B and T cells, occurs in the majority of patients. Despite advances in our understanding of the pathophysiology of disease and recent regulatory approval of a significant number of MS therapies, many patients continue to experience disease activity. Thus, there remains an unmet medical need to develop more effective and well-tolerated therapies for the treatment of MS.

To meet this need, the identification of MS disease biomarkers represents a critical opportunity to potentially understand disease pathogenesis, disease progression, and the mechanism of action of a therapeutic treatment. Biomarker identification can ultimately guide clinical decision-making, leading to patient stratification for therapeutic interventions that maximize clinical benefit while minimizing patient harm. In the context of MS, biomarkers from the cerebrospinal fluid (CSF) are utilized as a surrogate for the CNS tissue (Comabella and Montalban 2014) and brain magnetic resonance imaging (MRI) is utilized as a non-invasive surrogate marker of disease activity (e.g., contrast-enhancing lesions; new and unequivocally enlarging T2-weighted lesions). Biomarkers of neuroinflammation in CSF, such as neurofilament light (NfL) chain, an acute neuronal injury marker, have been correlated with gadolinium (Gd)-enhancing MRI lesions and clinical relapses (Burman et al. 2014) and with response to drug treatment in PPMS and RMS (Gunnarsson et al. 2011; Axelsson et al. 2014). Key sensitive CSF biomarkers of disease include the presence of oligoclonal bands (OCBs), or antibodies produced in the CSF (Link and Huang 2006), as well as the presence of intrathecal memory B-cell plasmablasts (Cepok et al. 2005). These biomarkers suggest a link between B-cell activity and MS pathology.

To better understand the mechanism of action of ocrelizumab in MS, this study will assess known biomarkers (OCBs, NfL, B cells, MRI as a surrogate marker, etc.) and explore new potential biomarkers associated with response to ocrelizumab in CSF and peripheral blood. In the context of B cell-depleting therapies, B and T cells trafficking between the CNS and periphery, and the chemokine CXCL13, can act as biomarkers of inflammation (Piccio et al. 2010; Bankoti et al. 2014; Palanichamy et al. 2014; Stern et al. 2014). This study will explore disease mechanism further in a larger patient sample size by examining additional biomarkers in CSF, cells, and peripheral blood. Several additional biomarkers, such cytokines, chemokines, and antigen-specific B or T cells, may also provide insight into disease mechanisms (Piccio et al. 2010; Barun and Bar-Or 2012; Alvermann et al. 2014; Hohmann et al. 2014).

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized anti-human monoclonal antibody that selectively targets CD20-expressing B cells (Klein et al. 2013).

CD20 is a cell surface antigen found on pre-B cells, mature B cells, and memory B cells but is not expressed on lymphoid stem cells and plasma cells (Stashenko et al. 1980; Loken et al. 1987; Tedder and Engel 1994). While ocrelizumab selectively depletes CD20-expressing B cells (Kappos et al. 2011), the capacity of B-cell reconstitution and pre-existing humoral immunity are preserved (Martin and Chan 2006; DiLillo et al. 2008). In addition, innate immunity and peripheral T-cell numbers are not affected (Clinical Study Report for WA21493).

See the Ocrelizumab Investigator's Brochure for additional details on nonclinical and clinical studies.

1.2.1 Summary of Clinical Studies of Ocrelizumab in Multiple Sclerosis

Current studies of ocrelizumab include four ongoing controlled clinical trials in patients with MS: three Phase III studies (pivotal studies WA21092 and WA21093 and Study WA25046) and one Phase II study (Study WA21493).

Studies WA21092 and WA21093 are multicenter, randomized, parallel-group, double-blind, double-dummy, active-comparator studies of ocrelizumab in patients with RMS. Patients receive 600 mg intravenous (IV) ocrelizumab every 24 weeks or interferon beta-1a (IFN-β-1a) 44 μg subcutaneous three times per week. The primary endpoint is the annualized protocol-defined relapse rate by 2 years (96 weeks).

Study WA25046 is a multicenter, randomized, parallel-group, placebo-controlled study in patients with PPMS. Patients receive 600 mg IV ocrelizumab every 24 weeks as two 300-mg infusions two weeks apart or placebo. The primary objective of this study is to evaluate the efficacy and safety of ocrelizumab compared with placebo. The primary endpoint in this study is the time to onset of confirmed disability progression as

measured by a pre-specified increase in Expanded Disability Status Scale (EDSS; see Appendix 4) score, sustained for at least 12 weeks.

The Phase II study (Study WA21493) is a multicenter, randomized, parallel-group, double-blind, placebo- and active-comparator (IFN-β-1a), dose-finding study in RRMS. Results from the Phase II study showed that, at Week 24, ocrelizumab significantly reduced the number of Gd-enhancing lesions on T1-weighted brain MRI and annualized relapse rate compared with both placebo and the active comparator.

See the Ocrelizumab Investigator's Brochure for additional information.

1.2.1.1 Clinical Safety

Safety in Multiple Sclerosis

The safety data included are from three Phase III studies in RMS (Studies WA21092 and WA21093) and PPMS (Study WA25046) and one Phase II study in RRMS (Study WA21493).

Studies WA21092, WA21093, WA25046, and WA21493 have completed the controlled treatment period and are in open-label extension phase.

In the two RMS Phase III studies (pooled data of Studies WA21092 and WA21093) during the 96-week controlled treatment period, ocrelizumab was well tolerated with lower rates of treatment discontinuations for adverse events in patients treated with ocrelizumab 600 mg (3.5%) than in patients receiving IFN-β-1a (6.2%). The proportion of patients with adverse events (83.3% in both groups) as well as the total number of adverse events were similar in the ocrelizumab and the IFN-β-1a treatment groups over the 96-week treatment period. The proportion of patients reporting infections was higher in the ocrelizumab group compared with the IFN-β-1a group (58.4% vs. 52.4%, respectively). In addition, there were more events of infection in the ocrelizumab group (1224 events) compared with the IFN group (948 events) and these were primarily upper respiratory tract infections of Grade 1 or 2 intensity. The proportion of patients with serious adverse events was lower in the ocrelizumab treatment group than in the IFN-β-1a treatment group (6.9% in the ocrelizumab treatment group vs. 8.7% in the IFN-β-1a treatment group). Overall, the proportion of patients with serious infections was lower in the ocrelizumab group (1.3%) than in the IFN-β-1a group (2.9%). Two serious infusion-related reactions (IRRs) were reported; one in the IFN-β-1a group (Grade 3) and one in the ocrelizumab group (Grade 4). As expected, the proportion of patients experiencing IRRs were increased in the ocrelizumab group (34.3%) compared with the active control group (9.7%) who received dummy infusions. During the 96-week controlled treatment period, a total of 6 malignancies were reported, 2 events (1 mantle cell lymphoma and 1 squamous cell carcinoma) occurred in 2 patients (0.2%) in the IFN-β-1a treatment group and 4 events (2 invasive ductal breast carcinoma, 1 renal cancer, and 1 malignant melanoma) occurred in 4 patients (0.5%) in the ocrelizumab treatment group. Three deaths occurred in Studies WA21092 and WA21093; 2 patients

(suicide and mechanical ileus) in the IFN-β-1 treatment group and 1 patient (suicide) in the ocrelizumab treatment group.

In the PPMS Phase III, double-blind, placebo-controlled Study WA25046, ocrelizumab was well tolerated with a similar proportion of patients with adverse events leading to discontinuation from treatment (4.1%) compared with the placebo group (3.3%). The proportion of patients who experienced at least one adverse event was 90% in the placebo group compared with 95% in the ocrelizumab group. Taking into account that twice as many patients were randomized to ocrelizumab than placebo, the number of adverse events experienced by patients with an adverse event was similar (1762 events in the placebo group and 3690 events in the ocrelizumab group). The proportion of patients who experienced an infection was 69.8% in the ocrelizumab group compared with 67.8% in the placebo group. The proportion of patients with serious infections was similar in both groups: 5.9% in the placebo group compared with 6.2% in the ocrelizumab group. As expected, the proportion of patients who reported an IRR was higher in the ocrelizumab group (39.9%) compared with placebo (25.5%). Overall, 5 patients (1.0%) experienced a serious IRR in the ocrelizumab group. A total of 15 malignancies in 13 patients were reported: 2 events (basal cell carcinoma and adenocarcinoma of the cervix) occurred in 2 patients (0.8%) in the placebo group and 13 events (5 basal cell carcinoma, 2 invasive ductal breast carcinoma, 1 anaplastic large-cell lymphoma, 1 breast cancer, 1 endometrial cancer, 1 invasive breast carcinoma, 1 malignant fibrous histiocytoma, 1 pancreatic carcinoma metastatic) occurred in 11 patients (2.3%) in the ocrelizumab group. The proportion of patients with serious adverse events (22.2% in the placebo group compared with 20.4% in the ocrelizumab group) was similar in both groups. There were 5 deaths during the controlled treatment period, one in the placebo group (road traffic accident) and 4 in the ocrelizumab group (pulmonary embolism, pneumonia, pancreatic carcinoma, pneumonia aspiration).

In the RRMS Phase II study WA21493, treatment with 300 mg × 2 and 1000 mg × 2 ocrelizumab was generally well tolerated. The single most common adverse event by Preferred Term was IRR, reported by more ocrelizumab-treated patients compared with placebo. The proportion of patients reporting IRRs was higher in ocrelizumab-treated patients after the first infusion on Day 1 of the study (9.3% in placebo arm, 34.5% in the 300-mg × 2 arm, and 43.6% in the 1000-mg × 2 arm). Rates of infections and serious infections were similar in the ocrelizumab arms compared with placebo. The rate of infections remained consistent throughout the study, including the treatment period (up to Week 96) and the treatment-free period (up to Week 144). There was one malignancy (breast cancer) reported in Study WA21493 in the ocrelizumab group. The adverse event profile of ocrelizumab during the open-label treatment period up to Week 96 and during follow-up and monitoring/observation periods up to Week 144 was consistent with observations during the first 24 weeks.

A total of 3 deaths were reported in RRMS Study WA21493 up to the time of the Investigator's Brochure update in November 2015. Two fatalities occurred after

completion of the study treatment and during the Safety Follow-up Period when B cells had already repleted.

See the Ocrelizumab Investigator's Brochure for additional information regarding safety.

1.2.1.2 Clinical Activity

Study WA25046 met its primary endpoint of confirmed disability progression (CDP) sustained for at least 12 weeks, showing that treatment with ocrelizumab significantly reduced the progression of clinical disability for 12 weeks compared with placebo (risk reduction: 24%; hazard ratio: 0.76; 95% confidence interval [CI]: $0.59-0.98$; $p=0.0321$). The study also met its key secondary endpoints. Time to CDP sustained for 24 weeks was significantly ($p=0.0365$) reduced with ocrelizumab compared with placebo (risk reduction: 25%). Change in the 25-foot timed walk from baseline to Week 120 had a significantly ($p=0.0404$) reduction of 29% with ocrelizumab. Percent change in total volume of T2 lesions on MRI from baseline to Week 120 was significantly ($p<0.0001$) improved with ocrelizumab (decrease of 3.4%) compared with placebo (increase of 7.4%). Finally, percent change in whole brain volume from Week 24 to Week 120 was significantly ($p<0.0206$) improved with ocrelizumab (17.5% reduction) compared with placebo.

Study WA21493 results at Week 24 demonstrated that both doses of ocrelizumab achieved the primary endpoint by significantly reducing the number of Gd-enhancing lesions compared with placebo ($p<0.0001$). Both ocrelizumab dose groups showed statistically significant reductions in annualized relapse rate (ARR) compared with the placebo group (ARR = 0.125 for the ocrelizumab 300 mg × 2 group [$p=0.0005$] and ARR = 0.169 for the ocrelizumab 1000 mg × 2 group [$p=0.0014$]) compared with ARR = 0.637 for the placebo group, representing a relative reduction (RR) of 80% and 73% in ARR versus placebo group for the low- and high-dose ocrelizumab groups, respectively. In exploratory analyses, both ocrelizumab groups were superior to the IFN-β-1a group for the primary endpoint ($p<0.0001$) and the 300 mg × 2 group for ARR (ARR = 0.364 for the IFN-β-1a group, representing an RR of 66% in ARR [$p=0.03$] for the ocrelizumab 300 mg × 2 group versus the IFN-β-1a group and an RR of 53.6% in ARR [$p=0.086$] for the ocrelizumab 1000 mg × 2 group versus the IFN-β-1a group) (Kappos et al. 2011).

Patients from both the placebo and IFN-β-1a groups switched to ocrelizumab 300 mg × 2 after Week 24. By 48 weeks, the level of benefit of ocrelizumab in reduction of ARR was maintained, where the patients in the ocrelizumab 300 mg × 2 group continued to have a suppressed ARR of 0.086 from Week 24 to 48, and patients who switched to ocrelizumab from either placebo or IFN-β-1a derived a similar degree of efficacy to those randomized to ocrelizumab from onset (ARR for placebo to ocrelizumab = 0.161 and for IFN-β-1a to ocrelizumab = 0.137 after the switch, representing an RR of 74% and 62.4% compared with ARR before the switch, respectively). From baseline to Week 72,

patients originally randomized to ocrelizumab 300 mg × 2 maintained clinical efficacy, with an ARR of 0.186.

In studies WA21092 and WA21093, ocrelizumab was superior to IFN-β-1a in reducing the three major markers of disease activity over the two-year controlled treatment period. The studies met their primary endpoint of significantly reducing ARR, with a 50% reduction in the ocrelizumab group compared with the IFN-β-1a group over the two-year period. Additionally, the studies met their secondary endpoints of significantly delaying CDP (loss of physical abilities, measured by the EDSS) by approximately 40% sustained for both 12 and 24 weeks with ocrelizumab compared with IFN-β-1a in pre-specified, pooled analyses of the two studies ($p = 0.0006$ and $p = 0.0025$, respectively). Patients in the ocrelizumab group also had significantly reduced acute multiple sclerosis MS-related inflammation and brain injury (total number of T1 Gd-enhancing lesions measured by MRI) at 24, 48, and 96 weeks by more than 90% and the emergence of more chronic or growing areas of MS-related brain injury (T2 hyperintense lesions) at 24, 48, and 96 weeks by approximately 80% compared with patients in the IFN-β-1a group. See the Ocrelizumab Investigator's Brochure for additional information regarding efficacy.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This is an exploratory biomarker study designed to be hypothesis-generating in order to better understand the mechanism of action of ocrelizumab and B-cell biology in RMS *and PPMS*.

Data from the two pivotal Phase III ocrelizumab RMS studies (WA21092 and WA21093) confirmed the favorable benefit-risk of ocrelizumab seen in the Phase II study (WA21493)*, and a pivotal Phase III ocrelizumab PPMS study (WA25046) demonstrated favorable benefit-risk profile in PPMS* (see Section 1.2.1). Together, these data demonstrate that ocrelizumab 600 mg administered every 6 months is effective and well tolerated in patients with *PPMS or* relapsing forms of MS.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVES

The primary objectives for *the RMS cohort in* this study are:

- To understand the impact of ocrelizumab treatment on NfL as a biomarker of neuronal damage in CSF
- To assess the number of CD19+ B cells in CSF (cell number/microliter) before and after treatment with ocrelizumab
- To assess the number of CD3+ T cells in CSF (cell number/microliter) before and after treatment with ocrelizumab

2.2 EXPLORATORY OBJECTIVES

The exploratory objectives for *the PPMS cohort in* this study are:

- *To understand the impact of ocrelizumab treatment on NfL as a biomarker of neuronal damage in CSF*
- *To assess the number of CD19+B cells in CSF (cell number/microliter) before and after treatment with ocrelizumab*
- *To assess the number of CD3+T cells in CSF (cell number/microliter) before and after treatment with ocrelizumab*

The exploratory objectives for both cohorts in this study are:

- To understand the impact of ocrelizumab treatment on NfL and other biomarkers of neurodegeneration in CSF as a reflection of activity in the CNS and compared with peripheral blood
- To measure the impact of ocrelizumab treatment on B cells/B-cell subsets, T cells/T-cell subsets, and other cell types (e.g., natural killer [NK] cells, monocytes, etc.), functional parameters of B/T/other cell types (activation, cell products), and other biomarkers of inflammation in CSF as a reflection of activity in the CNS and compared with peripheral blood
- To assess potential correlation between change in blood or CSF biomarkers of neurodegeneration or inflammation and change in MRI or efficacy outcome measures, such as reduction in Gd-positive lesions or EDSS score

Exploratory objectives for the RMS delayed time to start control arm (Arm 4) will include comparisons between Arm 1 of the RMS cohort (second LP at 12 weeks) and Arm 4 (second LP at 12 weeks before the first dose of study drug), and may include but not be limited to changes in CSF, blood, and MRI biomarkers or efficacy, as outlined above.

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is:

- To assess pharmacokinetics of ocrelizumab in CSF compared with serum concentration

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is:

- To assess the incidence of anti-drug antibodies (ADAs) to ocrelizumab

2.5 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of ocrelizumab on the basis of the following endpoints:

- Nature, frequency, severity, and timing of adverse events

- Changes in vital signs, physical findings, and clinical laboratory results during and following ocrelizumab administration
- Adverse events related to biomarker sample collection

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, multicenter, biomarker study conducted at centers in multiple countries in which all eligible patients will be enrolled to a single treatment arm of ocrelizumab. *The study will include an RMS cohort and a PPMS cohort (see Table 1). The RMS cohort is the main cohort and will include the majority of study participants. The RMS cohort will be comprised of four arms, three of which will have patients randomized into one of three arms (Arms 1–3) depending on the time of their second lumbar puncture (LP). In Arm 4, treatment with ocrelizumab will be delayed for 12 weeks after the first LP. The PPMS cohort will comprise a smaller, hypothesis-generating portion of the trial, as less is known about PPMS biomarkers.*

Arm 4 will provide a control for Arm 1 of the RMS cohort. Due to the relapsing and remitting nature of RMS, some biomarkers may change due to disease course rather than based on influence of a drug treatment. Therefore, some biomarkers may "regress to the mean" across the disease course over time, and this change could then inaccurately be reported as a change due to drug treatment over time. Arm 4 will allow for an estimate of the natural variability of the disease when analyzing the other treated arms.

Male and female patients age 18–55 years with a diagnosis of RMS *or PPMS* in accordance with the 2010 revised McDonald criteria (Polman et al. 2011; Appendix 7) and an EDSS score of 0–5.5 points *for RMS patients, or an EDSS score of 3.0–6.5 for PPMS patients,* at screening will be eligible. Screening will occur over a 4-week period, after which eligible patients may begin treatment with ocrelizumab.

*For patients in the RMS cohort (Arms 1–3), o*crelizumab will be administered at Week 1, Week 3, Week 24, and Week 48. The first dose will be administered as two infusions of 300 mg given on Day 1 and Day 15. The subsequent doses will be given as single 600-mg infusions.

For patients in the RMS cohort (Arm 4), after receiving two LPs at Week –12 and Week 1, the first dose of ocrelizumab will be administered as two 300-mg infusions on Week 1 (Day 1) and Week 3 (Day 15), with subsequent doses given as single 600-mg infusions at Weeks 24 and 48. The timeline for Arm 4 will continue for an extra 12 weeks to accommodate the same one-year dosing regimen.

For patients in the PPMS cohort, ocrelizumab 600 mg will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks (see Appendix 3).

Treatment with ocrelizumab will continue for approximately 1 year after the first infusion; however, treatment may be stopped at any time due to lack of clinical benefit, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, or if the Sponsor decides to close the trial, whichever occurs first. Patients may be eligible to continue to receive treatment if ocrelizumab is not commercially available in the patient's country or is not reasonably accessible to the patient (see Section 4.3.6), and these patients will continue to be followed.

*P*atients who complete the 52-week study *(64 weeks for patients in Arm 4)* and choose not to continue *on ocrelizumab treatment*, or who discontinue from treatment early, should enter the Safety Follow-up Period and be assessed every 24 weeks for 48 weeks counting from the date of the last infusion of ocrelizumab. *After 48 weeks*, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is lower *(see Appendix 8*).

Biomarkers will be monitored in a longitudinal fashion before and after treatment with ocrelizumab in order to assess dynamic changes in biomarkers as they relate to drug exposure, length of time on drug, response to drug, and MS disease pathogenesis. Biomarkers will be assessed via blood draws throughout the study and via *LP in* CSF at baseline before the first dose of ocrelizumab and at one other timepoint.

Two LPs will be drawn from each patient during the study. The two LPs will allow for assessment of biomarkers in CSF that are indicative of response to drug, pharmacokinetic/pharmacodynamic relationships, and/or disease pathogenesis in the CNS.

*P*atients *in the RMS cohort (Arms 1–3)* will receive an LP before the start of dosing with ocrelizumab. Subsequently, *these* patients will be randomized into one of three *arms* for timing of the second LP, either Week 12, 24, or 52 following the first dose of ocrelizumab.

Patients in Arm 4 will receive two LPs, separated by a 12-week interval, before administration of the first dose of ocrelizumab. Patients in this arm will be asked if they are willing to give an optional CSF sample via LP 12 weeks after the ocrelizumab dose.

Patients in the PPMS cohort will receive an LP at the start of the study before dosing with ocrelizumab. Subsequently, they will receive a second LP at Week 52 following the first dose of ocrelizumab.

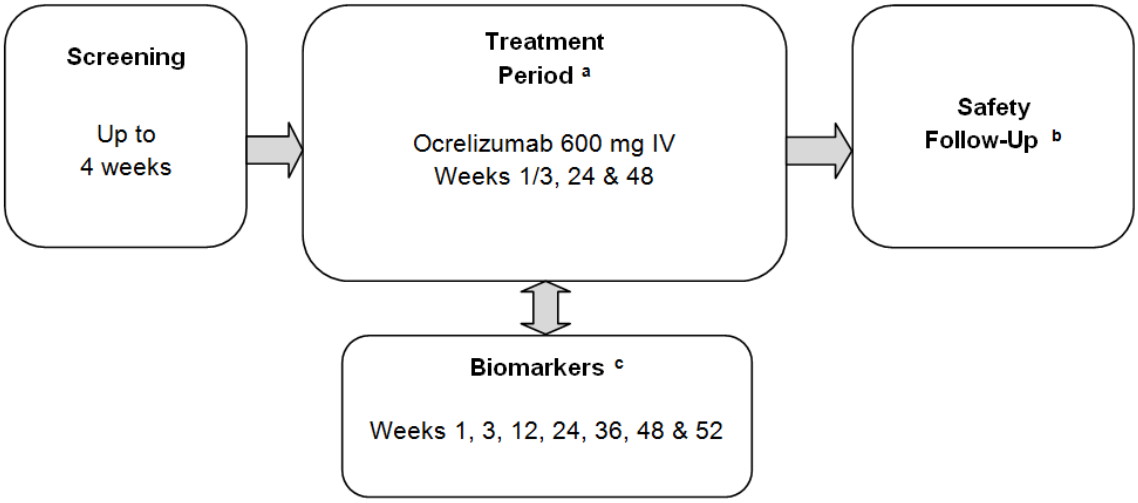
In the case of MS relapse *or worsening (for PPMS patients)* during the study, the patient should have an unscheduled visit and will be asked to receive an optional LP at the time of relapse *or worsening (for PPMS patients)*. The patient will have another LP at the originally scheduled time based on their randomization, or if a relapse occurs after they have already given the second LP, the relapse LP will remain optional.

*All p*atients will be evaluated for safety throughout the study.

In the case of early termination, the patient will be asked to have an early termination visit.

A *study schema for the RMS cohort Arms 1–3* is provided in Figure 1*, for the RMS cohort Arm 4 is provided in Figure 2, and for the PPMS cohort is provided in Figure 3. Organization of study cohorts and overall study design is provided in Table 1.*

Figure 1 Study Schema*: RMS Cohort Arms 1–3*



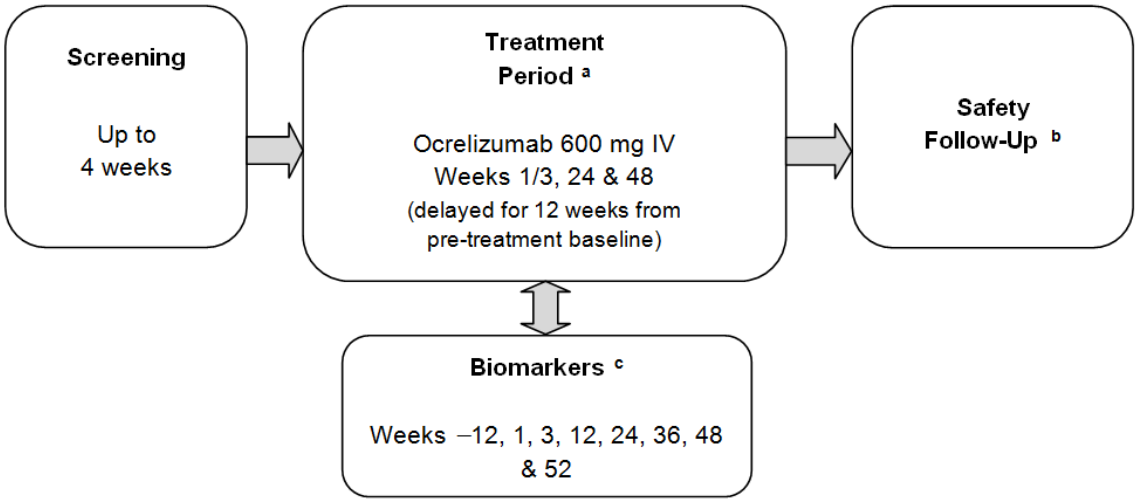
CSF = cerebrospinal fluid; LP = lumbar puncture; *RMS = relapsing multiple sclerosis.*

[a] *For the RMS cohort, o*crelizumab will be administered at Weeks 1, 3, 24, and 48. The first dose will be administered as two infusions of 300 mg given on Day 1 and Day 15. The subsequent doses will be given as single 600-mg infusions.

[b] *The Safety Follow-up Period will begin only if the patient discontinues from treatment early or completes the study and does not continue on ocrelizumab treatment (i.e., commercially available or from another source). Patients will be assessed in safety follow-up every 24 weeks for 48 weeks following the last infusion of ocrelizumab. After 48 weeks, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is lower.*

[c] Biomarkers will be assessed via blood draws at Week 1 (pre-dose Day 1), Week 3 (pre-dose Day 15), and at timepoints noted from Weeks 12 through 52. *B*iomarkers will also be assessed via *LP in* CSF before the first dose of ocrelizumab and *from* a second LP at either Week 12, 24, or 52 *following the first dose of ocrelizumab.*

Figure 2 Study Schema: RMS Cohort Arm 4



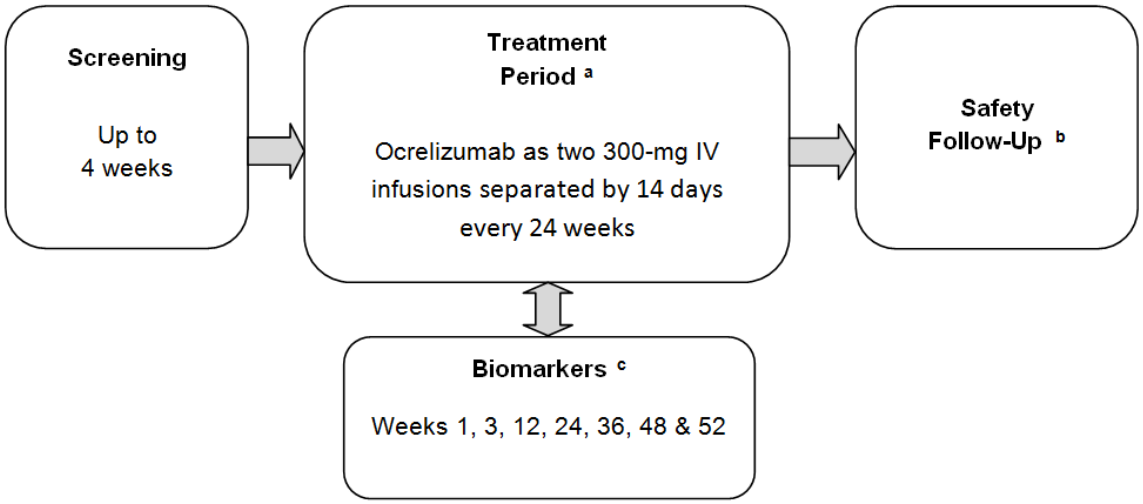
CSF =cerebrospinal fluid; LP =lumbar puncture; RMS =relapsing multiple sclerosis.

[a] *In the control arm (Arm 4), treatment with ocrelizumab will be delayed for 12 weeks to follow the first and second CSF collection, separated by 12 weeks. Ocrelizumab will then be administered at Weeks 1, 3, 24, and 48. The first dose will be administered as two infusions of 300 mg given on Day 1 and Day 15. The subsequent doses will be given as single 600-mg infusions.*

[b] *The Safety Follow-up Period will begin only if the patient discontinues from treatment early or completes the study and does not continue on ocrelizumab treatment (i.e., commercially available or from another source). Patients will be assessed in safety follow-up every 24 weeks for 48 weeks following the last infusion of ocrelizumab. After 48 weeks, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is lower.*

[c] *Biomarkers will be assessed via blood draws at Weeks –12, 1 (pre-dose Day 1), 3 (pre-dose Day 15), and at timepoints noted from Weeks 12 through 52. Biomarkers will also be assessed via LP in CSF, in two LPs separated by a 12-week interval, before administration of the first dose of ocrelizumab. Patients in this arm will be asked if they are willing to give an optional CSF sample via LP 12 weeks after the ocrelizumab dose.*

Figure **3** *Study Schema: PPMS Cohort*



CSF =cerebrospinal fluid; LP =lumbar puncture; PPMS =primary progressive multiple sclerosis.

[a] *For the PPMS cohort, ocrelizumab 600 mg will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks.*

[b] *The Safety Follow-up Period will begin only if the patient discontinues from treatment early or completes the study and does not continue on ocrelizumab treatment (i.e., commercially available or from another source). Patients will be assessed in safety follow-up every 24 weeks for 48 weeks following the last infusion of ocrelizumab. After 48 weeks, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is lower.*

[c] *Biomarkers will be assessed via blood draws at Week 1 (pre-dose Day 1), Week 3 (pre-dose Day 15), and at timepoints noted from Weeks 12 through 52. Biomarkers will be assessed via LP in CSF before the first dose of ocrelizumab and from a second LP at Week 52 following the first dose of ocrelizumab.*

Table 1 Study Cohorts and Overall Design

RMS Cohort		
	First LP	***Second LP***
Arm 1	*Treatment baseline/Week 1*	*Week 12*
Arm 2	*Treatment baseline/Week 1*	*Week 24*
Arm 3	*Treatment baseline/Week 1*	*Week 52*
Arm 4 (control arm)	*Pre-treatment baseline/ Week –12*	*Treatment baseline/ Week 1*
PPMS Cohort		
	First LP	***Second LP***
All PPMS patients	*Treatment baseline/Week 1*	*Week 52*

LP =lumbar puncture; PPMS =primary progressive multiple sclerosis; RMS =relapsing multiple sclerosis.

Note: Study Day 1 is the day of the first dose of study drug, and all relative day calculations are based on number of days from Study Day 1.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

The total length of the study is expected to be approximately *3.5* years from the first patient enrolled to LPLV.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Ocrelizumab Dose and Schedule

The dose level of ocrelizumab administered in this study is 600 mg. The first dose will be administered as two 300-mg IV infusions separated by 14 days in order to lower amount of ocrelizumab administered upon first exposure. *For the RMS cohort, t*he remaining doses will be administered as single 600-mg doses every 24 weeks. *For the PPMS cohort, ocrelizumab will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks during the treatment period.*

This dosing regimen is anticipated to be well tolerated and is consistent with the dosing regimen used in Study WA21092 and WA21093 in patients with RMS *and in Study WA25046 in patients with PPMS* (see Section 1.2.1).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 104 patients will be enrolled in this study; 88 patients with RMS and 16 patients with PPMS.

4.1.1 Inclusion Criteria

General Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with the protocol, in the investigator's judgment
- Age 18 – 55 years, inclusive
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 24 weeks after the last dose of study treatment or until their B cells have repleted, whichever is longer
  - 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).
  - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Inclusion Criteria Specific to RMS Patients

- Diagnosis of RMS in accordance with the 2010 revised McDonald criteria (Polman et al. 2011; Appendix 7)
- EDSS score of 0 – 5.5 points, inclusive, at screening
- Disease duration from the onset of MS symptoms:
  - Less than 15 years in patients with an EDSS > 5.0 at screening
- Either treatment-naïve or receiving treatment with disease-modifying therapies, including prior use of IFN-β-1a (Avonex®, Rebif®), IFN-β-1b (Betaseron®/Betaferon), or glatiramer acetate (Copaxone®)
- At least one clinically documented relapse in the past year and/or at least one T1-weighted Gd-enhancing lesion in the past year and/or at least one new T2 lesion in the past year at the time of enrollment

Inclusion Criteria Specific to RMS Cohort Arm 4

- *Must meet inclusion criteria for the RMS cohort*
- *Separate signed Informed Consent Form for the RMS Delayed Time to Start Control Arm (Arm 4)*
- *Must be willing to remain on the same dose and regimen of current standard of care, or no treatment if treatment-naïve, for 12 weeks after study enrollment*
  - *The treating and/or study physician must agree that the patient is eligible to remain on the same dose and regimen of their current standard of care at screening, or to receive no treatment if the patient is treatment-naïve, for 12 weeks after study enrollment.*

Inclusion Criteria Specific to PPMS Patients

- *Diagnosis of PPMS in accordance with the 2010 revised McDonald criteria (Polman et al. 2011; Appendix 7)*
- *EDSS score of 3.0 –6.5 points, inclusive, at screening*
- *Disease duration from the onset of MS symptoms:*
  - *Less than 10 years in patients with an EDSS at screening ≤5.0*
- *Documented history of at least one of the following laboratory findings in CSF:*
  - *Elevated IgG Index*
  - *One or more IgG OCBs detected by isoelectric focusing*

4.1.2 Exclusion Criteria

General Exclusion Criteria

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

- Diagnosis of secondary progressive MS without relapses for at least 1 year
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, tuberculosis)
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- History of cancer, including solid tumors and hematological malignancies (except basal cell, in situ squamous cell carcinomas of the skin, and in situ carcinoma of the cervix or the uterus that have been excised and resolved with documented clean margins on pathology)
- History of or currently active primary or secondary immunodeficiency
- History of coagulation disorders
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of alcohol or other drug abuse within 24 weeks prior to enrollment

- Known presence or history of other neurologic disorders, including but not limited to, the following:
  - History or known presence of progressive multifocal leukoencephalopathy (PML)
  - 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, HTLV-1, herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS])
  - History or known presence of systemic autoimmune disorders, potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis
  - Neuromyelitis optica
  - Ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - Severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including chronic obstructive pulmonary disease), renal, hepatic, endocrine, gastrointestinal, or any other significant disease
- Congestive heart failure (according to New York Heart Association III or IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis or atypical mycobacterial disease, but excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- Contraindications for, or intolerance to, oral or IV corticosteroids, including IV methylprednisolone, according to the country label, including:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the treatment drug constituents
- Contraindication for LP

- Previous treatment with B cell-targeted therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Previous treatment with natalizumab (Tysabri®), alemtuzumab, anti-CD4 agents, cladribine, teriflunomide, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation
- Treatment with fingolimod (Gilenya®), dimethyl fumarate (Tecfidera®), or similar treatment within 6 months prior to enrollment
- Receipt of a live vaccine within 6 weeks prior to enrollment
  - Vaccinations before baseline: In rare cases where a live vaccine must be administered by the patient's physician, the screening period may need to be prolonged but cannot exceed 12 weeks.
- Systemic corticosteroid therapy within 4 weeks prior to baseline
  - The screening period may be extended (but cannot exceed 8 weeks) for patients who have used systemic corticosteroids for their MS before screening.
- Previous or concurrent treatment with any investigational agent or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Certain laboratory abnormalities or findings at screening, including the following:
  - Positive serum β-hCG
  - Positive for hepatitis B (hepatitis B surface antigen [HBsAg] positive or hepatitis B core antibody [total HBcAb] confirmed by positive viral DNA polymerase chain reaction [PCR]) or hepatitis C (HepCAb)
  - AST or ALT ≥ 2.0 upper limit of normal (ULN)
  - Platelet count $< 100{,}000/\mu L$ ($< 100 \times 10^9/L$)
  - ANC $< 1.5 \times 10^3/\mu L$
  - Abnormal lymphocyte count *(below LLN)*

    Re-testing before baseline: in rare cases in which the screening laboratory samples are rejected by the laboratory (e.g., hemolyzed sample) or the results are not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated. 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 randomization must meet study criteria. In such circumstances, the screening period may need to be prolonged but should not exceed 8 weeks.
- Inability to complete an MRI (contraindications for MRI include but are not restricted to weight ≥ 140 kg, pacemaker, cochlear implants, 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, contraindication to gadolinium, etc.)
- Lack of peripheral venous access

- Pregnant or lactating, or intending to become pregnant during the study
  - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

Exclusion Criteria Specific to RMS Patients

- *Diagnosis of PPMS or SPMS without relapses*

4.2 *METHOD OF DETERMINATION OF THE TIME OF LUMBAR PUNCTURE*

Patients *in Arms 1–3 of the RMS cohort* will be randomized into *each of the* three *arms* at 1:1:1 ratio according to the timing of the second LP at Week 12, 24, or 52 following the first dose of ocrelizumab *(see Table 1)*. An independent interactive voice/web response system (IxRS) provider will conduct randomization and maintain the treatment assignment code. Enrolled patients will be stratified by the previous disease-modifying therapy (DMT) treatment status (DMT-naïve vs. DMT-experienced). Therefore, the proportion of DMT-naïve patients will be approximately equal in each of three *arms*.

A fourth RMS arm with delayed treatment start (Arm 4) will not be a part of the randomization and will be recruited separately.

All patients in the PPMS cohort will receive the second LP at 52 weeks and therefore will not be randomized.

Enrollment of the PPMS cohort and/or the RMS control arm (Arm 4) is open to all sites choosing to participate.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Ocrelizumab

Ocrelizumab will be supplied by the Sponsor as a liquid formulation containing 30-mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 4% trehalose and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15-cc, type I USP, glass vial fitted with a 20-mm, fluoro-resin, laminated stopper and an aluminum seal with a flip-off plastic cap and contains a nominal 300 mg ocrelizumab. No preservative is used as each vial is designed for single use.

The ocrelizumab drug product must be diluted before administration. Solutions of ocrelizumab for IV administration are prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride to a final drug concentration of 1 to 2 mg/mL.

Ocrelizumab may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter.

The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of up to 0.2 micrometer).

The prepared infusion solution of ocrelizumab is physically and chemically stable for 24 hours at 2–8°C and subsequently 8 hours at room temperature. The prepared infusion solution should be used immediately. If not used immediately, it can be stored up to 24 hours at 2–8°C. Infusion solution must be completely administered to the patient within 32 hours of preparation (not exceeding 24 hours at 2–8°C and 8 hours at room temperature). In the event an IV infusion cannot be completed the same day, the remaining solution should be discarded.

For information on the formulation and handling of ocrelizumab, see the Ocrelizumab Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Ocrelizumab

*For the RMS cohort, d*ose 1 of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) separated by 14 days (i.e., Day 1 [Week 1] and Day 15 [Week 3]). Subsequent doses will be administered as one 600-mg IV infusion every 24 weeks for a maximum of 3 doses *(see Table 2)*.

For the PPMS cohort, ocrelizumab 600 mg will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks (see Table 3).

Although ocrelizumab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Ocrelizumab infusions should always be administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member. *It is anticipated that the patient will need to stay at the hospital or clinic for a full day for the infusion visits.*

Each ocrelizumab infusion should be given as a slow IV infusion over approximately 150 minutes (2.5 hours) for the 300-mg dose and approximately 240 minutes (4 hours) for the 600-mg dose. To reduce potential IRRs, all patients will receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent IV steroid), administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion.

It is also strongly recommended that the infusion is accompanied by prophylactic treatment with an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) and an IV or oral antihistamine (such as IV diphenhydramine 50 mg or equivalent dose of alternative) 30 – 60 minutes prior to the start of an infusion to reduce potential IRRs. Patients administered a sedating antihistamine for the treatment or prevention of IRRs

should be given appropriate warnings concerning drowsiness and potential impairment of ability to drive or operate machinery.

Since transient hypotension may occur during ocrelizumab infusion, the investigator may wish to withhold anti-hypertensive medications 12 hours prior to ocrelizumab infusion.

Ocrelizumab must not be administered as an IV push or bolus. Well-adjusted infusion pumps should be used to control the infusion rate, and ocrelizumab should be infused through a dedicated line. It is important not to use evacuated glass containers, which require vented administration sets, to prepare the infusion because this causes foaming as air bubbles pass through the solution.

After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs intravenously, if necessary, in the event of a delayed reaction. If no adverse events occur during this period of time, the IV cannula may be removed and the patient may be discharged.

See the Ocrelizumab Investigator's Brochure for detailed instructions on drug preparation, storage, and administration.

An overview of the ocrelizumab dosing is presented in Table 2 *and Table 3*.

Table 2 Overview of Ocrelizumab Dosing*: RMS Cohort*

	1st Dose [a,c]		*Subsequent* Dose*(s)* [b,c]
	Day 1 Infusion	Day 15 Infusion	
Ocrelizumab	300 mg IV	300 mg IV	600 mg IV

IV = intravenous*; RMS = relapsing multiple sclerosis*.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV will be administered to reduce the potential for infusion-related reactions. Each treatment *period* has a duration of 24 weeks.

[a] The first dosing will consist of two IV infusions separated by 14 days (i.e., Days 1 and 15).

[b] Beginning with the second dose, a single infusion of ocrelizumab will be administered.

[c] Prior to the next infusion, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

Table 3 Overview of Ocrelizumab Dosing: PPMS Cohort

Group	1st Dose [a]		Subsequent Dose(s) [a]	
	Day 1 Infusion	Day 15 Infusion	First Infusion	Next Infusion (14 days later)
Ocrelizumab	300 mg IV	300 mg IV	300 mg IV	300 mg IV

IV =intravenous; PPMS =primary progressive multiple sclerosis.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV (or equivalent IV steroid) will be administered to reduce the potential for infusion-related reactions. Each treatment period has a duration of 24 weeks.

[a] *Prior to the next infusion, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.*

Because of possible need to vary infusion rates depending on tolerance of the infusion, the total infusion time may exceed the time stated. **Unless an IRR occurs necessitating discontinuation, the entire contents of the infusion bag must be administered to the patient.**

Guidelines for treatment discontinuation are provided in Section 4.6.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Methylprednisolone

Premedicate with 100 mg of methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion to reduce the frequency and severity of IRRs.

Any overdose or incorrect administration of methylprednisolone should be noted on the Methylprednisolone Administration eCRF. Adverse events associated with an overdose or incorrect administration of methylprednisolone should be recorded on the Adverse Event eCRF.

4.3.4 Other Prophylactic Treatment

Additional premedication with an antihistaminic drug (e.g., diphenhydramine) is recommended approximately 30 – 60 minutes before each infusion of ocrelizumab to further reduce the frequency and severity of IRRs. The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered.

4.3.5 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (ocrelizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will

acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.6 Post-Trial Access to Ocrelizumab

The Sponsor (Genentech, a member of the Roche Group) will offer post-trial access to the study drug (ocrelizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- *The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being*
- *There are no appropriate alternative treatments available to the patient*
- *The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- *The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- *The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for MS*
- *The Sponsor has reasonable safety concerns regarding the study drug as treatment for MS*
- *Provision of study drug is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from *4 weeks* prior to *screening* to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Medications used after treatment discontinuation should be recorded during the Safety Follow-up Period.

4.4.1 Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

- Anti-hypertensive medications
  - Since transient hypotension may occur during ocrelizumab infusion, the investigator may wish to withhold anti-hypertensive medications 12 hours prior to ocrelizumab infusion.
- *IV or oral corticosteroids*
  - *Patients who experience a relapse may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. Such patients should not discontinue treatment solely based on the occurrence of a relapse, unless the patient or investigator feels he or she has met the criteria for withdrawal (Section 4.6.3).*

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the program and for at least 7 days prior to initiation of ocrelizumab, unless otherwise specified below:

- Therapies for MS other than systemic corticosteroids
- Immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers while patient is B-cell depleted

See the Ocrelizumab Investigator's Brochure for a more detailed safety profile.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities *for the RMS cohort Arms 1–3, Appendix 2 for the schedule of activities for the RMS cohort Arm 4, and Appendix 3 for the schedule of activities for the PPMS cohort.*

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the screening visit. *In addition, use of any previous MS medication should be recorded.*

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A full physical examination will be conducted at the screening and early termination visits. At all other visits, a limited physical examination will be conducted per the schedule of activities. Any abnormality identified at baseline should be recorded on the eCRF.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.

Height and weight will be measured at screening. After the screening visit, only weight will be measured per the schedule of activities.

4.5.4 Vital Signs

Vital signs should be performed at all visits. Vital signs will include the measurements of heart rate, systolic and diastolic blood pressure, and temperature.

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 for the first hour, followed by every 30 minutes until 1 hour after the end of the infusion.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

4.5.5 Assessment of Disability

Disability in MS will be measured by the EDSS, which will be assessed *at timepoints according to the appropriate schedule of activities*.

The EDSS is based on a standard neurological examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual,

and cerebral [or mental], plus "other") rated and scored as Functional Systems (FS) scores. Each FS score is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death) (see Appendix 4).

4.5.6 Neurological Examinations

Neurological examinations will be performed *at timepoints according to the appropriate schedule of activities* and in the case of relapse or early termination so that the investigator can assess whether the patient is experiencing a relapse of MS or another neurological (non-MS) disorder.

Investigators will also screen patients for signs and symptoms of worsening neurologic function localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/sings (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 (see Appendix 6). A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor.

Potential relapses should be recorded throughout the treatment period. Protocol-defined relapse is the 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 preceded by a stable or improving neurological state for least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS scale, or 2 points on one of the appropriate FS scales, or 1 point on two or more of the appropriate FS scales. The change must affect the selected FS (i.e., 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. Sexual dysfunction and fatigue will not be scored. (Note: Adjudication of protocol-defined relapses will be performed by the Sponsor based on pre-specified criteria, applied to data collected by investigator, in a blinded fashion.)

For patients in the PPMS cohort, disease worsening or improvement over the treatment period will also be assessed and is defined as a 20% change in timed 25-foot walk test or a 20% change in 9-hole peg test time (see Appendix 3).

4.5.7 Brain Magnetic Resonance Imaging

MRI will be used to monitor CNS lesions and potentially other pathophysiology, such as inflammation and neurodegeneration. Brain MRI scans will be obtained at study visits as shown in the schedule of activities and at the study completion/early termination visit.

MRI scans will be read by a centralized reading center for both efficacy and safety endpoints. Further details on scanning acquisition sequences, methods, handling, transmission of the scans, and certification of site MRI *scanner* are described in a separate MRI technical manual.

Assessments will include T1-weighted scans before and after injection of multicyclic gadolinium contrast agent and may also include, but may not be limited to: fluid-attenuated inversion-recovery (FLAIR), proton density-weighted, and T2-weighted scans.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis according to the schedule of activities.

Pre-infusion laboratory samples *may* be drawn up to 14 days before the start of infusion so that routine laboratory test results are available for review before the infusion, unless otherwise specified.

- Hematology (hemoglobin, hematocrit, RBCs, WBC absolute and differential, ANC, and quantitative platelet count)
- Serum chemistry (AST, ALT, GGT, total bilirubin, urea, uric acid, creatinine, potassium, sodium, calcium, phosphorus)
- *Urine dipstick* (standard to assess kidney function)
- Pregnancy test
  - All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Viral serology
  - Hepatitis screening
  - Must be negative for HBsAg and HepCAb prior to enrollment; if HBcAb is positive at screening, HBV DNA by PCR must be negative. For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 24 weeks during the treatment period.

Biomarkers

- Biomarker samples for the following tests should be drawn according to the schedule of activities timepoint and will be sent to the study site's local laboratory for same-day analysis and processing:
  - Blood: analysis of B and T cells, which may include but will not be limited to number, activation status or markers, functional attributes, activity, and/or molecular status of cells
  - CSF: analysis of B and T cells, which may include but will not be limited to number, activation status or markers, functional attributes, activity, and/or molecular status of cells (supernatant, i.e., non-cellular portion of sample to be aliquoted, frozen, and sent to central laboratory and/or Sponsor or designee)
- Biomarker samples for the following tests should be drawn according to the SOA timepoint and will be sent to the central laboratory and/or to the Sponsor or designated processing site, and may be processed by the Sponsor's laboratory or the Sponsor's qualified designated laboratory (CRO and/or academic research laboratory affiliated with the study):
  - Quantitative immunoglobulin: Ig levels (including total Ig, IgG, IgM, and IgA isotypes)
  - Blood TBNK/B-cell subset panel sample for CD19 and other circulating B-cell subsets, T cells, NK cells, and other leukocytes
  - Serum sample for PK analysis
  - Serum sample for measurement of ADAs to ocrelizumab
  - CSF supernatant: analysis may include but will not be limited to NfL, levels of soluble neurodegeneration markers, and/or inflammatory markers; and the relationship between ocrelizumab exposure and selected pharmacodynamics
  - Serum and plasma: analysis may include but will not be limited to levels of soluble neurodegeneration markers (i.e., NfL) and/or inflammatory markers (i.e., CXCL13); and the relationship between ocrelizumab exposure and selected pharmacodynamics
  - Blood samples for RNA extraction for exploratory research on non-inherited biomarkers, which may include but not be limited to immune gene expression markers
  - Peripheral blood mononuclear cells (PBMCs): B- and T-cell numbers, other cell types, activation markers, functional attributes, activity, and/or molecular status of cells; and levels of soluble inflammatory markers

Exploratory biomarker research may include, but will not be limited to, the assessments listed above. Given the complexity and exploratory nature of biomarker analyses, results from the analyses will not be shared with investigators or study participants, unless required by law.

In the case of suspected PML, serum or plasma biomarker, PK, or ADA samples may be used to assess status of JC virus (JCV) antibodies.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. *Fluoroscopy can be used, if required, for the LP to draw the CSF.*

Biological samples will be destroyed when the final clinical study report has been completed, with the following exceptions:

- Biomarker samples, including CSF, plasma, serum, blood collected for RNA extraction, and PBMC samples, will be destroyed no later than 15 years after the date of final closure of the clinical database.

4.5.9 Optional Samples for Roche Clinical Repository

Genentech is a member of the Roche group and participates in the collection and/or submission of biological samples to the Roche Clinical Repository (RCR). Collection and submission of biological samples to the RCR is contingent upon the review and approval of the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site is not granted the necessary approval for RCR sampling, this section of the protocol will not be applicable at that site.

4.5.9.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.9.2 Sample Collection

The following samples will be collected for research purposes, including, but not limited to, research on inherited or non-inherited biomarkers related to ocrelizumab, RMS, or MS:

- Blood for plasma non-heritable protein analysis
- Blood for non-heritable RNA expression profiling
- Blood for DNA collection and genetic analysis

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. For DNA collection, only a single sample is needed and will be obtained at baseline. However, if the sample collection is missed for any reason, the sample may be obtained at any subsequent visit.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.9.3 Confidentiality

Confidentiality for All RCR Specimens

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

Additional Confidentiality for Specimens Used for Genetic Research

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens collected for genetic research. Upon receipt by the RCR, specimens for genetic research are "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

4.5.9.4 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the DNA Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.9.5 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the DNA Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study ML29966 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study ML29966.

4.5.9.6 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information

management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 *Criteria for Re-Treatment with Ocrelizumab*

Prior to re-treatment with ocrelizumab, patients will be evaluated for the following conditions and laboratory abnormalities. If any of these are present prior to re-dosing, further administration of ocrelizumab should be suspended until these are resolved or held indefinitely:

- *Life-threatening (Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion*
- *Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality*
- *Active infection*
- *Ongoing pregnancy*

In addition to the criteria above, patients with PPMS will also be evaluated for:

- *ANC $<1.5 \times 10^3/\mu L$*

4.6.2 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as failure to follow dosing instructions or to complete program visits

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

4.6.3 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Ongoing pregnancy: Please note that the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications.
- Life-threating IRR or serious hypersensitivity reaction
- Active hepatitis B infection or reactivation
- PML
- Active tuberculosis, either new onset or reactivation

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.4 Study and Site Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab is currently in clinical development for the treatment of MS. Identified and potential risks associated with ocrelizumab treatment will continue to be closely monitored throughout the clinical program. Patient safety during the ocrelizumab program is ensured by targeting the most appropriate patient population, stringent safety

monitoring by the Sponsor, and protocol-specified ocrelizumab treatment interruption criteria. Patients will be evaluated clinically and with standard laboratory tests before the study and at regular intervals during the study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and standard laboratory measurements. Adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

Administration of ocrelizumab will be performed in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member with immediate availability of full resuscitation facilities. All adverse events and serious adverse events will be recorded during the study and for up to 48 weeks after the last dose of ocrelizumab as provided through this study. Related serious adverse events must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. If the patient is unable to return for the safety follow-up visit, the discontinuation visit information may be collected via phone call.

Safety assessments will include the incidence, nature, and severity of (serious) adverse events graded per the NCI CTCAE v4.0. Safety assessments will be conducted *for the RMS cohort Arms 1–3* per the schedule of activities in Appendix 1, *for the RMS cohort Arm 4 per the schedule of activities in Appendix 2, and for the PPMS cohort per the schedule of activities in Appendix 3*.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize these issues, are outlined in the following sections.

5.1.1 Risks Associated with Ocrelizumab

5.1.1.1 *Identified Risks and Adverse Drug Reactions*

5.1.1.1.1 *Infusion-Related Reactions*

All CD20-depleting agents administered via the intravenous route, including ocrelizumab, have been associated with acute IRRs. Symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia.

Patients should be observed for at least one hour after the completion of the infusion for any symptom of IRR. They will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Hypotension, as a symptom of IRR, may occur during ocrelizumab infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

5.1.1.1.2 *Infections*

Infection is an identified risk associated with ocrelizumab treatment, predominantly involving mild to moderate respiratory tract infections. Non-disseminated herpes virus-associated infections, mostly mild to moderate, were also reported more frequently with ocrelizumab (approximately 5% to 6%, simplex and zoster) than with comparators (approximately 3%).

During the controlled period of the pivotal trials, the proportion of patients with serious infections was lower in RMS in the ocrelizumab group (1.3%) than in the interferon beta-1a group (2.9%); in PPMS, the proportion of patients with serious infections was similar in both groups: 6.7% in the placebo group compared with 6.2% in the ocrelizumab group.

Serious, opportunistic, and fatal infections have occurred in patients with lupus and rheumatoid arthritis (RA) treated with ocrelizumab in Phase III clinical trials. Data from completed studies regarding infection risks with ocrelizumab treatment in these patient populations are provided in the Ocrelizumab Investigator's Brochure.

No opportunistic infections were reported by any MS patient treated with ocrelizumab.

There were no reports of hepatitis B reactivation in MS patients treated with ocrelizumab, but it had been reported in one RA patient treated with ocrelizumab. HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active hepatitis B virus should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before the start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

There were no reports of PML in patients treated with ocrelizumab. JCV infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies and associated with risk factors (e.g., patient population, polytherapy with immunosuppressants). However, a risk of PML cannot be ruled out. Healthcare professionals should be alerted to the early signs and symptoms of PML, which can include any new onset or worsening of neurological signs or symptoms as these can be similar to an MS relapse. Please refer to Appendix 6 for guidance for diagnosis of PML.

Delay ocrelizumab administration in patients with an active infection until the infection is resolved.

5.1.1.1.3 *Decrease in Immunoglobulins*

Treatment with ocrelizumab resulted in a decrease in total immunoglobulins (Igs) over 2 years, mainly driven by reduction in IgM, with no observed association with serious infections. The proportion of patients with decrease in Igs below the LLN increased over time and with successive dosing.

5.1.1.1.4 *Delayed Return of Peripheral B Cells*

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post-treatment (first timepoint of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B cells was 72 weeks (range: 27–175 weeks). Patients with prolonged B-cell depletion should be monitored until their B cells have repleted.

5.1.1.2 *Potential Risks*

5.1.1.2.1 *Hypersensitivity Reactions*

No hypersensitivity reactions to ocrelizumab were reported in the controlled clinical trials.

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

5.1.1.2.2 *Impaired Response to Vaccination*

The degree of impairment of B cell-dependent humoral response to neoantigens and polysaccharide antigens and its clinical relevance are currently unknown in patients with MS.

After treatment with ocrelizumab over 2 years, the proportion of patients with positive antibody titers against Streptococcus pneumoniae, mumps, rubella, and varicella were generally similar to the proportions at baseline.

No data are available on the effects of vaccination in patients receiving ocrelizumab. Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab.

The safety of immunization with live or live-attenuated viral vaccines following ocrelizumab therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended while B cells are depleted.

5.1.1.2.3 *Malignancies including Breast Cancer*

Malignancies are considered a potential risk with ocrelizumab due to the potential decreased immune surveillance associated with B-cell depletion in the context of treatments that are used long-term to treat chronic diseases. During the controlled treatment period, the incidence rate of malignancies in the ocrelizumab treatment groups across the MS program was higher than IFN or placebo groups with overlapping confidence intervals. The incidence rates were within the expected ranges for the MS population from epidemiology sources. The only cluster identified was for breast cancer. No firm conclusion can be made to date concerning the risk due to the low number and the limited follow-up; hence, the risk remains potential to date.

5.1.1.2.4 *Neutropenia*

In the controlled treatment period, decreased neutrophils were observed in 12% and 15% of MS patients treated with ocrelizumab in PPMS and RMS, respectively. Most were mild to moderate in severity, and approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified.

Detailed information for all risks can be found in the current Ocrelizumab Investigator's Brochure.

5.1.2 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 4. Additional guidelines are provided in the subsections below.

Table 4 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Mild to moderate IRR	• If the event that a patient experiences is a mild to moderate IRR (e.g. headache), the infusion rate should be reduced to half the rate at the time of the event. • This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion schedule.
Severe IRR (or complex of flushing, fever, and throat pain)	• If a patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive symptomatic treatment. • The infusion should be restarted only after all symptoms have resolved. • The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction.

Table 4 Guidelines for Management of Specific Adverse Events (cont.)

Life-threatening or disabling IRR (e.g., anaphylaxis)	• Immediately stop ocrelizumab if there are signs of a life-threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. • The patient should receive appropriate treatment. • Permanently discontinue ocrelizumab in these patients.

IRR = infusion-related reaction.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as lumbar puncture)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Standard adverse events of special interest include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is

considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 – Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported for up to 48 weeks after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

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

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

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

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration *and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.*

Further details on prevention and management of IRRs are described in Section 5.1.1.1.1, Section 5.1.2 (Table 4), and in the Ocrelizumab Investigator's Brochure.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a

constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

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

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of MS.

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

If the death is attributed to progression of MS, "MS progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

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

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Relapsing Multiple Sclerosis

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on EDSS score. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported for up to 48 weeks after the last dose of study drug, regardless of causal relation with the investigational product. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be

recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 *Pregnancies in Female Partners of Male Patients*

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 48 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Ocrelizumab Investigator's Brochure
- Ocrelizumab Core Data Sheet

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This study is designed to assess levels of NfL, levels of lymphocyte populations in CSF, and to generate hypotheses about biomarkers of ocrelizumab treatment in patients with

RMS and PPMS. Levels of NfL in CSF and levels of lymphocyte populations in CSF will be compared to baseline levels. In addition, Arm 1 of the RMS cohort (second LP at 12 weeks) will be compared to Arm 4 (second LP at 12 weeks before the first dose of study drug).

In this exploratory biomarker study, the analyses will be mostly descriptive and hypothesis-generating. Unless otherwise specified, statistical tests will be two sided and the statistical significance level will be 5%. Corresponding 95% confidence intervals will be presented as appropriate. No corrections for multiple testing will be applied to the primary endpoint analyses, exploratory endpoint analyses, or interim analysis.

The statistical summaries will be descriptive if not otherwise specified. For continuous variables, the mean, median, standard deviation, 25th and 75th percentiles, minimum and maximum will be calculated. For categorical variables, number and percentage in each category will be displayed.

When establishing statistical significance, the non-parametric method will be applied as appropriate, i.e., the Mann-Whitney test will be used between two groups and the Kruskal-Wallis test will be used for three or more groups. For the analysis of continuous data, the paired/unpaired t-test and non-parametric test (i.e., the Wilcoxon matched pairs test) will be performed as appropriate. Some variables may be appropriately transformed as needed before performing statistical analysis. The Spearman's rank-correlation coefficient will be used to evaluate the relationship among the levels of biomarkers or between levels of biomarkers and clinical parameters.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size calculations for this study are based on the assumed reduction from baseline in NfL (Gunnarsson et al. 2011) at Weeks 24 and 52 combined (Arms 2 and 3) in the RMS cohort. Other biomarker measures are not considered for power determination.

Assuming (a) a 30% reduction from pre-treatment NfL (mean [SD]=860 pg/mL [780 pg/mL]) to post-treatment NfL (mean [SD]=602 pg/mL [310 pg/mL]) and a correlation coefficient of 0.6, resulting in an SD of 643 pg/mL for the change from pre- to post-treatment, and (b) a desired power of 80% with a Type 1 error of 5%, a sample size of 51 patients is required, with approximately 25 patients in Arm 2 and 26 patients in Arm 3.

This is the first study to explore the impact of ocrelizumab on CSF B-cell count. In a study by Piccio et al. (2010), the rate of undetectable B cells in CSF was 74% (21/26) after 24–30 weeks of rituximab as an add-on to immunomodulatory therapy. Based on this information and a sample size of 51 patients (Arm 2 and 3 combined), the expected 95% CI for the CSF B-cell undetectable rate will be: (0.61, 0.85).

In the RMS cohort, 15 patients will be included in Arm 1 to explore the possible reduction in NfL at Week 12 post-treatment and 15 patients will be assigned to the delayed start RMS control arm (Arm 4). Fifteen patients will be recruited to the PPMS cohort. The above sample sizes are not based on statistical considerations and are meant to help explore the changes in biomarkers and generate hypotheses for future studies.

Based on the above, the total sample size for this study will be 96 patients. The sample size will be increased by approximately 10% in order to account for *potential missing* post-treatment CSF *information*; *therefore*, the number of patients *to be* enrolled *in the RMS cohort* will be N*=88 (Arm 1: 16 patients, Arm 2: 28 patients, Arm 3: 28 patients, and Arm 4: 16 patients), and N =16 in the PPMS cohort. Therefore, the total number of patients to be enrolled is 104.*

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, ocrelizumab administration, and discontinuations from the study will be summarized. Patient disposition and the incidence of treatment discontinuation for reasons other than disease progression will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographics, medical history, and neurological examination will be summarized. MS disease history (duration since MS first symptom, duration since MS diagnosis), MS disease status (MS treatment naïve or experienced), and MS prior treatment (for those being treated) will be summarized. Also, the baseline measures of key CSF biomarkers, MRI, EDSS, or other important endpoints will be summarized. *It should be noted that two baseline measures for the RMS control arm (Arm 4) will be obtained: the first at the Week –12 visit, which is 12 weeks before the first infusion of ocrelizumab, and the second at the first treatment visit pre-infusion.*

6.4 ANALYSES

Statistical analyses will be performed on the analysis population, defined as all enrolled patients who *(a)* received at least one infusion of ocrelizumab, even if the infusion was incomplete *or (b) received at least one LP*.

6.4.1 Primary Endpoints

Primary endpoints *for the RMS cohort (Arms 1–3)* include:

- Change in levels of NfL in CSF from *treatment* baseline to post-treatment with ocrelizumab
- Change in number of CD19+ B cells in CSF from *treatment* baseline to post-treatment with ocrelizumab

- Change in number of CD3+ T cells in CSF from *treatment* baseline to post-treatment with ocrelizumab

6.4.2 Exploratory Endpoints

Exploratory endpoints for the PPMS cohort include:

- *Change in levels of NfL in CSF from treatment baseline to post-treatment with ocrelizumab*
- *Change in number of CD19+ B cells in CSF from treatment baseline to post-treatment with ocrelizumab*
- *Change in number of CD3+ T cells in CSF from treatment baseline to post-treatment with ocrelizumab*

CSF biomarker endpoints *for both cohorts* may include, but may not be limited to:

- Activation markers, functional attributes, activity, and/or molecular status of cells (e.g., proteins, non-heritable RNA levels, etc.) at *all collected timepoints* before and after treatment with ocrelizumab*, including optional samples*
- Levels of soluble neurodegeneration markers and/or inflammatory markers at *all collected timepoints* before and after treatment with ocrelizumab*, including optional samples*

Blood biomarker endpoints *for both cohorts* may include, but may not be limited to:

- Change in number of CD19+ B and CD3+ T cells in blood *at all collected timepoints before and after treatment with* ocrelizumab*, including at unscheduled visits*
- Activation markers, functional attributes, activity, and/or molecular status of PBMCs or cell products (e.g., proteins, non-heritable RNA levels) at *all collected timepoints* before and after treatment with ocrelizumab*, including at unscheduled visits*
- Levels of NfL, levels of soluble neurodegeneration markers, and/or inflammatory markers in the peripheral blood serum or plasma at *all collected timepoints* before and after treatment with ocrelizumab*, including at unscheduled visits*

MRI biomarker endpoints *for both cohorts* may include, but may not be limited to:

- Total number of T1 Gd-enhanced lesions at *all collected timepoints before and after treatment with ocrelizumab, including at unscheduled visits*
- Change in total T2 lesion volume *at all collected timepoints before and after treatment with ocrelizumab, including at unscheduled visits*
- Total number of new and/or enlarging T2 lesions at *all collected timepoints before and after treatment with ocrelizumab, including at unscheduled visits*
- Changes in regional or total brain volume *at all collected timepoints before and after treatment with ocrelizumab, including at unscheduled visits*
- *Total number of leptomeningeal-enhancing regions at all collected timepoints before and after treatment with ocrelizumab, including at unscheduled visits*

Efficacy endpoints *for both cohorts* may include, but may not be limited to:

- Change in EDSS score from baseline

Other analyses may include evaluation of the possible associations between the changes in biomarkers of neurodegeneration or inflammation and change in MRI or efficacy outcome measures, such as reduction in Gd-positive lesions or *time to worsening as measured by the* EDSS score *(RMS and PPMS cohort), or the 25-foot timed walk or the 9-hole peg test (PPMS cohort only).*

Endpoints for the RMS control arm (Arm 4) will include comparisons between Arm 1 of the RMS cohort (treatment baseline to second LP at 12 weeks) and Arm 4 (pre-treatment baseline to treatment baseline, second LP at 12 weeks before the first dose of study drug), and may include, but may not be limited to, changes in CSF at all collected timepoints including optional samples, blood, and MRI biomarkers or efficacy, as outlined above.

6.4.3 Pharmacokinetic and Immunogenicity Endpoints

Pharmacokinetics and immunogenicity may be explored in relation to the pharmacodynamics of blood and/or CSF biomarkers *in both cohorts*. Serum concentration of ocrelizumab may be measured at Weeks 12, 24, 48, and 52; in the case of early termination; and at safety follow-up. The level of ocrelizumab may be measured in the CSF at Weeks 12, 24, and*/or* 52 *for the RMS cohort; and at Week 52 for the PPMS cohort*; and/or in a CSF sample taken at an unscheduled visit *or from an optional sample*.

Assessment may include, but may not be limited to, the relationship of pharmacokinetics in CSF to levels of cells in CSF, or to NfL levels in CSF, and/or compared with serum concentration.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the analysis population.

Safety will be assessed through summaries of adverse events (including incidence rates and corresponding 95% CIs) and clinical laboratory abnormalities. All adverse events occurring on or after treatment on Day 1 will be coded, summarized by NCI CTCAE v4.0 grade, and tabulated by body system and Preferred Term for individual events within each body system. Grade 3 to 5 adverse events, serious adverse events, adverse events leading to treatment discontinuation, time to withdrawal of the study due to an adverse event, adverse events leading to infusion adjustment, and treatment-related events will be summarized. In addition, all serious adverse events and deaths will be listed.

Associated laboratory parameters, such as hepatic function, renal function, and hematology values, will be grouped and presented together. Marked abnormalities will also be flagged.

Ocrelizumab exposure will be summarized, including duration and dosage.

6.6 INTERIM ANALYSIS

An interim analysis may be performed when *approximately* 50% of patients have had their second LP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results *(including flow cytometry data)*, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports

or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and

data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech, a member of the Roche group, and will be managed by Genentech and CROs. CROs will provide clinical operations management, data management, biostatistics, and medical monitoring.

An IxRS will be used to assign patient numbers, monitor enrollment and patient status, and to manage study treatment requests and study drug shipments.

Patient data will be recorded via an EDC system using eCRFs.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Activities *the RMS Cohort Arms 1–3*

Week	Screening [a]	Treatment Period								Early Termination Visit	Safety Follow-Up [c]
	–4	1 *(Treat-ment* Baseline)	3	12	24	36	48	52	Unsched-uled Visit *(due to relapse)* [b]		
Day		**1**	**15 (±2)**	**84 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**	**364 (±7)**			
Informed consent [d]	x										
Medical history & demographic data [e]	x										
Review inclusion & exclusion criteria	x	x [f]									
Physical examination [g]	x	x [f]	*x* [f]		x [f]		*x* [f]	x	x	x	x
Weight & height	x			x [h]		*x* [h]		x [h]		x [h]	x [h]
Vital signs [i]	x	x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	x
Laboratory, Biomarker, and Other Biological Samples											
Hematology, chemistry, and urinalysis [j, k, l]	x	x [f]			x [f]		x [f]	x	x	x	x

Appendix 1
Schedule of Activities *for the RMS Cohort Arms 1–3* (cont.)

	Screening [a]	Treatment Period								Early Termination Visit	Safety Follow-Up [c]
Week	**–4**	**1** *(Treatment* **Baseline)**	**3**	**12**	**24**	**36**	**48**	**52**	**Unscheduled Visit** *(due to relapse)* [b]		
Day		**1**	**15 (±2)**	**84 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**	**364 (±7)**			
Pregnancy test [m]	x	x [f]			x [f]	x	x [f]	x		x	x
Hepatitis screening [n]	x										
Hepatitis B virus DNA test [n]	x	(x)			(x)		(x)			(x)	(x)
Quantitative Ig (total Ig, IgG, IgM, and IgA)	x				x [f]		x [f]			x	x
Local/on-site CSF specimen (LP) [o, p]		x [f]		x	x [f]			x	x [q]		
Local/on-site blood flow cytometry sample [r]		x [f]		x	x [f]			x	x		
Blood TBNK/B-cell subset panel [r]		x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	x

Appendix 1
Schedule of Activities *for the RMS Cohort Arms 1–3* (cont.)

	Screening [a]	Treatment Period								Early Termination Visit	Safety Follow-Up [c]
Week	**–4**	**1** *(Treatment* **Baseline)**	**3**	**12**	**24**	**36**	**48**	**52**	**Unscheduled Visit** *(due to relapse)* [b]		
Day		**1**	**15 (±2)**	**84 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**	**364 (±7)**			
Plasma		x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	
Serum		x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	
PBMC		x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	
RNA		x [f]	x [f]	x	x [f]			x	x	x	
Serum sample for PK		x [f]		x	x [f]		x [f]	x		x	x
Serum sample for ADAs		x [f]			x [f]		x [f]			x	x
Neurological Assessments											
EDSS	x	x [f, j]		x	x [f]	*x*	x *[f]*	x	x	x	x
Neurological exam [s]	x	x [f]		x	x [f]		x *[f]*	x	x	x	x
Recording of relapse	x	x [f]	x	x	x [f]	x	x *[f]*	x	x	x	x
Brain MRI [o, p]		x [f, t]		x	x [f]			x	x [q]	x	
Safety Assessments											
Adverse events [u]	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Activities *for the RMS Cohort Arms 1–3* (cont.)

	Screening [a]	Treatment Period									
Week	**–4**	**1** *(Treatment* **Baseline)**	**3**	**12**	**24**	**36**	**48**	**52**	**Unscheduled Visit** *(due to relapse)* [b]	**Early Termination Visit**	**Safety Follow-Up** [c]
Day		**1**	**15 (±2)**	**84 (±7)**	**168 (±7)**	**252 (±7)**	**336 (±7)**	**364 (±7)**			
Concomitant treatment review	x	x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	x [v]
Premedication and Study Drug Administration											
Methylprednisolone premedication [w]		x [f]	x [f]		x [f]		x [f]				
Ocrelizumab administration [x]		x	x		x		x				
Optional RCR Sample Collection [y]											
Plasma [y]		x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	
RNA [y]		x [f]	x [f]	x	x [f]			x	x	x	
DNA [y, z]		x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	

Appendix 1
Schedule of Activities *for the RMS Cohort Arms 1–3* (cont.)

ADAs = anti-drug antibodies; CSF = cerebrospinal fluid; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepCAb = hepatitis C; Ig = immunoglobulin; LP = lumbar puncture; MRI = magnetic resonance imaging; MS = multiple sclerosis; NfL = neurofilament light; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; RCR = Roche Clinical Repository; *RMS = relapsing multiple sclerosis;* TBNK = T cells, B cells, and natural killer cells.

Note: (x) indicates that an assessment will only be done if needed.

[a] The screening window is *up to* 4 weeks *prior to baseline*. However, the screening window can be extended up to 8 weeks *prior to baseline* per the exclusion criteria for systemic corticosteroid therapy and/or laboratory abnormalities.

[b] In the case of MS relapse during the study, the patient should have an unscheduled visit and will be asked to receive an optional LP at the time of relapse. The patient will have another LP at the originally scheduled time based on their randomization, or if a relapse occurs after they have already given the second LP, the relapse LP will remain optional. *If the patient comes into the clinic for an unscheduled visit for reasons other than relapse, procedures should be performed per standard of care.*

[c] The Safety Follow-up Period will begin *only if* the patient *discontinues from treatment early or* completes the study and *does not* continue *on* ocrelizumab *treatment (i.e., commercially available or from another source)*. Patients *will be assessed* in safety follow-up *every 24 weeks for 48 weeks following* the last infusion of ocrelizumab. *After 48 weeks*, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is lower *(see Appendix 8)*.

[d] Written informed consent will be obtained from all patients during screening in order to be eligible.

[e] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the screening visit. *In addition, use of any previous MS medication should be recorded.* Demographic data will include age, sex, and self-reported race/ethnicity.

[f] To be obtained/performed before administration of ocrelizumab (i.e., pre-dose).

[g] A full physical examination will be conducted at the screening and early termination visits. At all other visits, a limited physical examination will be conducted. Any abnormality identified at baseline should be recorded on the eCRF. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.

[h] After the screening visit, only weight will be measured.

[i] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressure, and temperature. 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 for the first hour, followed by every 30 minutes until 1 hour after the end of the infusion.

Appendix 1
Schedule of Activities *for the RMS Cohort Arms 1–3* (cont.)

[j] If the screening assessment has been conducted within 14 days prior to baseline dosing, it does not need to be conducted again prior to baseline dosing.

[k] Results should be available prior to dosing (*may* be taken up to 14 days prior to dosing) *to ensure patient eligibility per the investigator's discretion (see Section 4.6.1).*

[l] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute and differential, ANC, and quantitative platelet count. Chemistry will include AST, ALT, GGT, total bilirubin, urea, uric acid, creatinine, potassium, sodium, calcium, and phosphorus. Standard urinalysis will be used to assess kidney function.

[m] Serum β-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 and pregnancy status confirmed with serum β-hCG test.

[n] All patients must have negative HBsAg result and negative HepCAb screening tests prior to study enrollment. If HBcAb is positive at screening, HBV DNA measured by PCR must be negative. For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 24 weeks during the treatment period.

[o] CSF specimen will be obtained at Week 1 (baseline, pre-dose) and at either Week 12, 24 (pre-dose), or 52 according to randomization; AND at an unscheduled visit in case of relapse (two CSF samples per patient, unless consent for optional relapse sample is given). The collection of the CSF specimen should precede the brain MRI.

[p] *The brain MRI requires 2 business days to be quality checked before dosing of ocrelizumab. In order to facilitate scheduling before an ocrelizumab dose, the CSF specimen collection, followed by the brain MRI, may precede the administration of ocrelizumab by up to 7 business days.*

[q] To be obtained/performed optionally in case of relapse or suspected relapse.

[r] Local blood flow cytometry and blood TBNK/B-cell subset panel samples (where indicated at the same timepoints as CSF, including optional relapse CSF) should be collected on the same day and as close as possible in time to the CSF sample, prior to ocrelizumab administration by up to *7* days.

[s] 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 worsening neurologic function localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/sings (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 (see Appendix 6). A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor.

Appendix 1
Schedule of Activities *for the RMS Cohort Arms 1–3* (cont.)

[t] If an MRI was obtained during the 4-week screening period then that MRI can be used as the baseline brain MRI and the brain MRI does not need to be repeated at baseline (Day 1).

[u] Adverse events will be reported throughout the study and for up to 48 weeks after the last dose of ocrelizumab as provided through this study. If the patient is unable to return for the safety follow-up visit, the discontinuation visit information may be captured via phone call.

[v] *Medications used after treatment discontinuation should be recorded during the Safety Follow-up Period.*

[w] All patients must receive prophylactic treatment with 100 mg of methylprednisolone *(or equivalent)*, administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion.

[x] Ocrelizumab will be administered at Weeks 1, 3, 24, and 48. The first dose will be administered as two infusions of 300 mg given on Day 1 and Day 15. The subsequent doses will be given as single 600-mg infusions.[y] For patients consenting to optional RCR sampling only. Not applicable in countries not participating in RCR sampling.

[z] For DNA collection, only a single sample is needed and will be obtained at baseline. However, if the sample collection is missed for any reason, the sample may be obtained at any subsequent visit.

Appendix 2
Schedule of Activities for the RMS Cohort Arm 4

	Screening [a]	Treatment Period									Early Termination Visit	Safety Follow-Up [c]
Week	–16	–12 (Pre-treatment Baseline)	1 (Treatment Baseline)	3	12	24	36	48	52	Unscheduled Visit (due to relapse) [b]		
Day	–112	–84 (±7)	1	15 (±2)	84 (±7)	168 (±7)	252 (±7)	336 (±7)	364 (±7)			
Informed consent [d]	x											
Medical history & demographic data [e]	x											
Review inclusion & exclusion criteria	x	x	x [f]									
Physical examination [g]	x	x	x [f]	x [f]		x [f]		x [f]	x	x	x	x
Weight & height	x	x [h]	x [h]		x [h]		x [h]		x [h]		x [h]	x [h]
Vital signs [i]	x	x	x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	x

Appendix 2
Schedule of Activities for the RMS Cohort Arm 4 (cont.)

	Screening [a]	Treatment Period									Early Termination Visit	Safety Follow-Up [c]
Week	–16	–12 (Pre-treatment Baseline)	1 (Treatment Baseline)	3	12	24	36	48	52	Unscheduled Visit (due to relapse) [b]		
Day	–112	–84 (±7)	1	15 (±2)	84 (±7)	168 (±7)	252 (±7)	336 (±7)	364 (±7)			
Laboratory, Biomarker, and Other Biological Samples												
Hematology, chemistry, and urinalysis [j, k, l]	x	x	x [f]			x [f]		x [f]	x	x	x	x
Pregnancy test [m]	x	x	x [f]			x [f]	x	x [f]	x		x	x
Hepatitis screening [n]	x											
Hepatitis B virus DNA test [n]	x	(x)	(x)			(x)		(x)			(x)	(x)
Quantitative Ig (total Ig, IgG, IgM, and IgA)	x					x [f]		x [f]			x	x
Local/on-site CSF specimen (LP) [o]		x	x [f, p]		x [q]					x [q]		

Appendix 2
Schedule of Activities for the RMS Cohort Arm 4 (cont.)

	Screening [a]	Treatment Period									Early Termination Visit	Safety Follow-Up [c]
Week	–16	–12 (Pre-treatment Baseline)	1 (Treatment Baseline)	3	12	24	36	48	52	Unscheduled Visit (due to relapse) [b]		
Day	–112	–84 (±7)	1	15 (±2)	84 (±7)	168 (±7)	252 (±7)	336 (±7)	364 (±7)			
Local/on-site blood flow cytometry sample [r]		x	x [f]		x	x [f]			x	x		
Blood TBNK/B-cell subset panel [r]		x	x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	x
Plasma		x	x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	
Serum		x	x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	
PBMC		x	x [f]	x [f]	x	x [f]	x	x [f]	x	x	x	
RNA		x	x [f]	x [f]	x	x [f]			x	x	x	
Serum sample for PK			x [f]		x	x [f]		x [f]	x		x	x
Serum sample for ADAs			x [f]			x [f]		x [f]			x	x
Neurological Assessments												
EDSS	x	x [j]	x [f]		x	x [f]	x	x [f]	x	x	x	x

Appendix 2
Schedule of Activities for the RMS Cohort Arm 4 (cont.)

	Screening [a]	Treatment Period									Early Termination Visit	Safety Follow-Up [c]
Week	–16	–12 (Pre-treatment Baseline)	1 (Treatment Baseline)	3	12	24	36	48	52	Unscheduled Visit (due to relapse) [b]		
Day	–112	–84 (±7)	1	15 (±2)	84 (±7)	168 (±7)	252 (±7)	336 (±7)	364 (±7)			
Neurological exam [s]	x	x	x[f]		x	x[f]		x[f]	x	x	x	x
Recording of relapse	x	x	x[f]	x	x	x[f]	x	x[f]	x	x	x	x
Brain MRI [o, p]		x [s, t]	x[f]		x	x[f]			x	x [q]	x [p]	
Safety Assessments												
Adverse events [u]	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant treatment review	x	x	x[f]	x[f]	x	x[f]	x	x[f]	x	x	x	x [v]
Premedication and Study Drug Administration												
Methylprednisolone premedication [w]			x[f]	x[f]		x[f]		x[f]				
Ocrelizumab administration [x]			x	x		x		x				

Appendix 2
Schedule of Activities for the RMS Cohort Arm 4 (cont.)

	Screening [a]	Treatment Period									Early Termination Visit	Safety Follow-Up [c]
Week	–16	–12 (Pre-treatment Baseline)	1 (Treatment Baseline)	3	12	24	36	48	52	Unscheduled Visit (due to relapse) [b]		
Day	–112	–84 (±7)	1	15 (±2)	84 (±7)	168 (±7)	252 (±7)	336 (±7)	364 (±7)			
Optional RCR Sample Collection [y]												
Plasma [y]		x	x[f]	x[f]	x	x[f]	x	x[f]	x	x	x	
RNA [y]		x	x[f]	x[f]	x	x[f]			x	x	x	
DNA [y, z]		x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	

ADAs =anti-drug antibodies; CSF =cerebrospinal fluid; eCRF =electronic Case Report Form; EDSS =Expanded Disability Status Scale; HBcAb =hepatitis B core antibody; HBsAg =hepatitis B surface antigen; HBV =hepatitis B virus; HepCAb =hepatitis C; Ig =immunoglobulin; LP =lumbar puncture; MRI =magnetic resonance imaging; MS =multiple sclerosis; PBMC =peripheral blood mononuclear cell; PCR =polymerase chain reaction; PK =pharmacokinetic; PML =progressive multifocal leukoencephalopathy; RCR =Roche Clinical Repository; RMS =relapsing multiple sclerosis; TBNK =T cells, B cells, and natural killer cells.

Note: (x) indicates that an assessment will only be done if needed.

[a] *The screening window is up to 4 weeks prior to Week –12. However, the screening window can be extended up to 8 weeks prior to Week –12 per the exclusion criteria for systemic corticosteroid therapy and/or laboratory abnormalities.*

[b] *In the case of MS relapse during the study and after a patient has already given 2 LPs at the start, the patient should have an unscheduled visit and will be asked to receive an optional LP at the time of relapse. If the patient comes into the clinic for an unscheduled visit for reasons other than relapse, procedures should be performed per standard of care.*

Appendix 2
Schedule of Activities for the RMS Cohort Arm 4 (cont.)

[c] *The Safety Follow-up Period will begin only if the patient discontinues from treatment early or completes the study and does not continue on ocrelizumab treatment (i.e., commercially available or from another source). Patients will be assessed in safety follow-up every 24 weeks for 48 weeks following the last infusion of ocrelizumab. After 48 weeks, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is lower (see Appendix 8).*

[d] *Written informed consent will be obtained from all patients during screening in order to be eligible.*

[e] *Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the screening visit. In addition, use of any previous MS medication should be recorded. Demographic data will include age, sex, and self-reported race/ethnicity.*

[f] *To be obtained/performed before administration of ocrelizumab (i.e., pre-dose).*

[g] *A full physical examination will be conducted at the screening and early termination visits. At all other visits, a limited physical examination will be conducted. Any abnormality identified at baseline should be recorded on the eCRF. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.*

[h] *After the screening visit, only weight will be measured.*

[i] *Vital signs will include the measurements of heart rate, systolic and diastolic blood pressure, and temperature. 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 for the first hour, followed by every 30 minutes until 1 hour after the end of the infusion.*

[j] *If the screening assessment has been conducted within 14 days prior to baseline dosing, it does not need to be conducted again prior to baseline dosing.*

[k] *Results should be available prior to dosing (may be taken up to 14 days prior to dosing) to ensure patient eligibility per the investigator's discretion (see Section 4.6.1).*

[l] *Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute and differential, ANC, and quantitative platelet count. Chemistry will include AST, ALT, GGT, total bilirubin, urea, uric acid, creatinine, potassium, sodium, calcium, and phosphorus. Standard urinalysis will be used to assess kidney function.*

[m] *Serum β-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 and pregnancy status confirmed with serum β-hCG test.*

Appendix 2
Schedule of Activities for the RMS Cohort Arm 4 (cont.)

[n] *All patients must have negative HBsAg result and negative HepCAb screening tests prior to study enrollment. If HBcAb is positive at screening, HBV DNA measured by PCR must be negative. For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 24 weeks during the treatment period.*

[o] *CSF specimen will be obtained at Week –12 (pre-treatment baseline) and Week 1(treatment baseline, pre-dose); optionally at 12 weeks post-ocrelizumab dose; AND at an unscheduled visit in case of relapse (two CSF samples per patient, unless consent for optional 12-week post-dose or relapse sample is given). The collection of the CSF specimen should precede the brain MRI.*

[p] *The brain MRI requires 2 business days to be quality checked before dosing of ocrelizumab. In order to facilitate scheduling before an ocrelizumab dose, the CSF specimen collection, followed by the brain MRI, may precede the administration of ocrelizumab by up to 7 business days.*

[q] *To be obtained/performed optionally at 12 weeks post-ocrelizumab dose and/or in case of relapse or suspected relapse.*

[r] *Local blood flow cytometry and blood TBNK/B-cell subset panel samples (where indicated at the same timepoints as CSF, including optional 12-week post-dose or relapse CSF) should be collected on the same day and as close as possible in time to the CSF sample, even if CSF is collected prior to ocrelizumab administration by up to 7 days.*

[s] *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 worsening neurologic function localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/sings (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 (see Appendix 6). A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor.*

[t] *If an MRI was obtained during the 4-week screening period then that MRI can be used as the baseline brain MRI and the brain MRI does not need to be repeated at pre-treatment baseline (Day 1).*

[u] *Adverse events will be reported throughout the study and for up to 48 weeks after the last dose of ocrelizumab as provided through this study. If the patient is unable to return for the safety follow-up visit, the discontinuation visit information may be captured via phone call.*

[v] *Medications used after treatment discontinuation should be recorded during the Safety Follow-up Period.*

[w] *All patients must receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent), administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion.*

[x] *Ocrelizumab will be administered at Weeks 1, 3, 24, and 48. The first dose will be administered as two infusions of 300 mg given on Day 1 and Day 15. The subsequent doses will be given as single 600-mg infusions.*

[y] *For patients consenting to optional RCR sampling only. Not applicable in countries not participating in RCR sampling.*

[z] *For DNA collection, only a single sample is needed and will be obtained at baseline. However, if the sample collection is missed for any reason, the sample may be obtained at any subsequent visit.*

Appendix 3
Schedule of Activities for the PPMS Cohort

	Screening [a]	*Treatment Period*									*Unscheduled Visit (due to relapse)* [b]	*Early Termination Visit*	*Safety Follow-Up* [c]
Week	***–4***	***1 (Treatment Baseline)***	***3***	***12***	***24***	***26***	***36***	***48***	***50***	***52***			
Day		***1***	***15 (±2)***	***84 (±7)***	***168 (±7)***	***182 (±7)***	***252 (±7)***	***336 (±7)***	***350 (±7)***	***364 (±7)***			
Informed consent [d]	*x*												
Medical history & demographic data [e]	*x*												
Review inclusion & exclusion criteria	*x*	*x* [f]											
Physical examination [g]	*x*	*x* [f]	*x* [f]		*x* [f]	*x* [f]		*x* [f]	*x* [f]	*x*	*x*	*x*	*x*
Weight & height	*x*			*x* [h]			*x* [h]			*x* [h]		*x* [h]	*x* [h]
Vital signs [i]	*x*	*x* [f]	*x* [f]	*x*	*x* [f]	*x* [f]	*x*	*x* [f]	*x* [f]	*x*	*x*	*x*	
Laboratory Assessments													
Hematology, chemistry, and urinalysis [j, k, l]	*x*	*x* [f]			*x* [f]			*x* [f]		*x*	*x*	*x*	*x*
Pregnancy test [m]	*x*	*x* [f]			*x* [f]		*x*	*x* [f]		*x*		*x*	*x*
Hepatitis screening [n]	*x*												
Hepatitis B virus DNA test [n]	*x*	*(x)*			*(x)*			*(x)*				*(x)*	*(x)*
Quantitative Ig (total Ig, IgG, IgM, and IgA)	*x*				*x* [f]			*x* [f]				*x*	*x*

Appendix 3
Schedule of Activities for the PPMS Cohort (cont.)

	Screening [a]	Treatment Period									Unscheduled Visit (due to relapse) [b]	Early Termination Visit	Safety Follow-Up [c]
Week	**–4**	**1 (Treatment Baseline)**	**3**	**12**	**24**	**26**	**36**	**48**	**50**	**52**			
Day		**1**	**15 (±2)**	**84 (±7)**	**168 (±7)**	**182 (±7)**	**252 (±7)**	**336 (±7)**	**350 (±7)**	**364 (±7)**			
Local/on-site CSF specimen (LP) [o, p]		x [f]								x	x		
Local/on-site blood flow cytometry sample		x [f, q]		x	x [f]					x [q]	x [q]		
Blood TBNK/B-cell subset panel [q]		x [f]	x [f]	x	x [f]		x	x [f]		x	x	x	x
Plasma		x [f]	x [f]	x	x [f]		x	x [f]		x	x	x	
Serum		x [f]	x [f]	x	x [f]		x	x [f]		x	x	x	
PBMC		x [f]	x [f]	x	x [f]		x	x [f]		x	x	x	
RNA		x [f]	x [f]	x	x [f]					x	x	x	
Serum sample for PK		x [f]		x	x [f]			x [f]		x		x	x
Serum sample for ADAs		x [f]			x [f]			x [f]				x	x
Neurological Assessments													
EDSS score	x	x [f, j]		x	x [f]		x	x [f]		x	x	x	x
25-foot timed walk test	x	x [f]		x	x [f]		x	x [f]		x	x	x	

Appendix 3
Schedule of Activities for the PPMS Cohort (cont.)

	Screening [a]	*Treatment Period*									*Unscheduled Visit (due to relapse)* [b]	*Early Termination Visit*	*Safety Follow-Up* [c]
Week	***–4***	***1 (Treatment Baseline)***	***3***	***12***	***24***	***26***	***36***	***48***	***50***	***52***			
Day		***1***	***15 (±2)***	***84 (±7)***	***168 (±7)***	***182 (±7)***	***252 (±7)***	***336 (±7)***	***350 (±7)***	***364 (±7)***			
9-hole peg test	*x*	*x* [f]		*x*	*x* [f]		*x*	*x* [f]		*x*	*x*	*x*	
Neurological examination [r]	*x*	*x* [f]		*x*	*x* [f]			*x* [f]		*x*	*x*	*x*	*x*
Recording of potential relapses	*x*	*x* [f]	*x*	*x*	*x* [f]	*x*	*x*	*x* [f]	*x*	*x*	*x*	*x*	*x*
Brain MRI [o, p]		*x* [f, s]		*x*	*x* [f]					*x*	*x*	*x*	
Safety Assessments													
Adverse event assessment [t]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Concomitant treatment review	*x*	*x* [f]	*x* [f]	*x*	*x* [f]	*x*	*x*	*x* [f]	*x*	*x*	*x*	*x*	*x* [u]
Premedication and Study Drug Administration													
Methylprednisolone premedication [v]		*x*	*x*		*x*	*x*		*x*	*x*				
Ocrelizumab administration [w]		*x*	*x*		*x*	*x*		*x*	*x*				
Optional RCR Sample Collection [x]													
Plasma [x]		*x* [f]	*x* [f]	*x*	*x* [f]		*x*	*x* [f]		*x*	*x*	*x*	

Appendix 3
Schedule of Activities for the PPMS Cohort (cont.)

	Screening [a]	Treatment Period									Unscheduled Visit (due to relapse) [b]	Early Termination Visit	Safety Follow-Up [c]
Week	**–4**	**1 (Treatment Baseline)**	**3**	**12**	**24**	**26**	**36**	**48**	**50**	**52**			
Day		**1**	**15 (±2)**	**84 (±7)**	**168 (±7)**	**182 (±7)**	**252 (±7)**	**336 (±7)**	**350 (±7)**	**364 (±7)**			
RNA [x]		*x* [f]	*x* [f]	*x*	*x* [f]					*x*	*x*	*x*	
DNA [x, y]		*x*	*(x)*	*(x)*	*(x)*		*(x)*	*(x)*		*(x)*	*(x)*	*(x)*	

CSF =cerebrospinal fluid; eCRF =electronic Case Report Form; EDSS =Expanded Disability Status Scale; HBcAb =hepatitis B core antibody; HBsAg =hepatitis B surface antigen; HBV =hepatitis B virus; HepCAb =hepatitis C antibody; Ig =immunoglobulin; IV =intravenous; LP =lumbar puncture; MRI =magnetic resonance imaging; MS =multiple sclerosis; PCR =polymerase chain reaction; PML =progressive multifocal leukoencephalopathy; PPMS =primary progressive multiple sclerosis; TBNK =T cells, B cells, and natural killer cells.

Note: (x) indicates that an assessment will be performed only if indicated.

[a] *The screening window is up to 4 weeks prior to baseline. However, the screening window can be extended up to 8 weeks prior to baseline per the exclusion criteria for systemic corticosteroid therapy and/or laboratory abnormalities.*

[b] *In the case of MS relapse during the study, the patient should have an unscheduled visit and will be asked to receive an optional LP at the time of relapse. The patient will have another LP at the originally scheduled time based on their randomization, or if a relapse occurs after they have already given the second LP, the relapse LP will remain optional. If the patient comes into the clinic for an unscheduled visit for reasons other than relapse, procedures should be performed per standard of care.*

[c] *The Safety Follow-up Period will begin only if the patient discontinues from treatment early or completes the study and does not continue on ocrelizumab treatment (i.e., commercially available or from another source). Patients will be assessed in safety follow-up every 24 weeks for 48 weeks following the last infusion of ocrelizumab. After 48 weeks, if the peripheral blood B-cell count remains depleted, monitoring of the patient should continue at 24-week intervals until the B-cell count has returned to the baseline value or to the lower limit of the normal range, whichever is lower (see Appendix 8).*

[d] *Written informed consent will be obtained from all patients during screening in order to be eligible.*

Appendix 3
Schedule of Activities for the PPMS Cohort (cont.)

[e] *Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the screening visit. In addition, use of any previous MS medication should be recorded. Demographic data will include age, sex, and self-reported race/ethnicity.*

[f] *To be obtained/performed before administration of ocrelizumab (i.e., pre-dose).*

[g] *A full physical examination will be conducted at the screening and early termination visits. At all other visits, a limited physical examination will be conducted. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.*

[h] *After the screening visit, only weight will be measured.*

[i] *Vital signs will include the measurements of heart rate, systolic and diastolic blood pressure, and temperature. 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 for the first hour, followed by every 30 minutes until 1 hour after the end of the infusion.*

[j] *If the screening assessment has been conducted within 14 days prior to baseline dosing, it does not need to be conducted again prior to baseline dosing.*

[k] *Results must be available and reviewed prior to dosing (may be taken up to 14 days prior to dosing) to ensure patient eligibility per the investigator's discretion (see Section 4.6.1).*

[l] *Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute and differential, ANC, and quantitative platelet count. Chemistry will include AST, ALT, GGT, alkaline phosphatase, amylase, lipase, total protein, albumin, cholesterol, total bilirubin, urea, uric acid, creatinine, random glucose, potassium, sodium, calcium, phosphorus, LDH, creatine phosphokinase, and triglycerides. Urinalysis will include specific gravity, pH, glucose, protein, ketones, and blood.*

[m] *Serum β-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 and pregnancy status confirmed by a serum β-hCG test.*

[n] *All patients must have negative HBsAg result and negative HepCAb screening tests prior to study 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 during the treatment period.*

[o] *CSF specimen will be obtained at Week 1 (baseline, pre-dose) and Week 52 according to randomization; AND at an unscheduled visit in case of disease worsening (two CSF samples per patient, unless consent for optional worsening sample is given). The collection of the CSF specimen should precede the brain MRI.*

[p] *The brain MRI requires 2 business days to be quality checked before dosing of ocrelizumab. In order to facilitate scheduling before an ocrelizumab dose, the CSF specimen collection, followed by the brain MRI, may precede the administration of ocrelizumab by up to 7 business days.*

Appendix 3
Schedule of Activities for the PPMS Cohort (cont.)

[q] *Local blood flow cytometry and blood TBNK/B-cell subset panel samples (where indicated at the same timepoints as CSF, including optional relapse CSF) should be collected on the same day and as close as possible in time to the CSF sample, even if CSF is collected prior to ocrelizumab administration by up to 7 days.*

[r] *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/sings (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 (see Appendix 6). A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor.*

[s] *If an MRI was obtained during the 4-week screening period then that MRI can be used as the baseline brain MRI and the brain MRI does not need to be repeated at baseline (Day 1).*

[t] *Adverse events will be reported throughout the study and for up to 48 weeks after the last dose of ocrelizumab as provided through this study. If the patient is unable to return for the safety follow-up visit, the discontinuation visit information may be captured via phone call.*

[u] *Medications used after treatment discontinuation should be recorded during the Safety Follow-up Period.*

[v] *All patients must receive prophylactic treatment with 100 mg methylprednisolone (or equivalent), administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion.*

[w] *Ocrelizumab 600 mg will be administered as two 300-mg IV infusions separated by 14 days at a scheduled interval of every 24 weeks.*

[x] *For patients consenting to optional RCR sampling only. Not applicable in countries not participating in RCR sampling.*

[y] *For DNA collection, only a single sample is needed and will be obtained at baseline. However, if the sample collection is missed for any reason, the sample may be obtained at any subsequent visit.*

Appendix 4
Expanded Disability Status Scale

Kurtzke Expanded Disability Status Scale (EDSS)

- ❑ 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- ❑ 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
- ❑ 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
- ❑ 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- ❑ 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- ❑ 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- ❑ 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- ❑ 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- ❑ 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- ❑ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- ❑ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- ❑ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

Appendix 4
Expanded Disability Status Scale (cont.)

- ❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
- ❑ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).
- ❑ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).
- ❑ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).
- ❑ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).
- ❑ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).
- ❑ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).
- ❑ 10.0 - Death due to MS.

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*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

Source: http://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-(FSS)-and-Expanded-Disab

Appendix 5
New York Heart Association Classification of Functional Cardiac Capacity

Class	Description
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix 6
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

ACTION STEPS IF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IS SUSPECTED:

- If the clinical presentation is suggestive of PML, further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Figure 1), a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) for the detection of JC virus (JCV) DNA should be undertaken. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007).

MRI ASSESSMENT

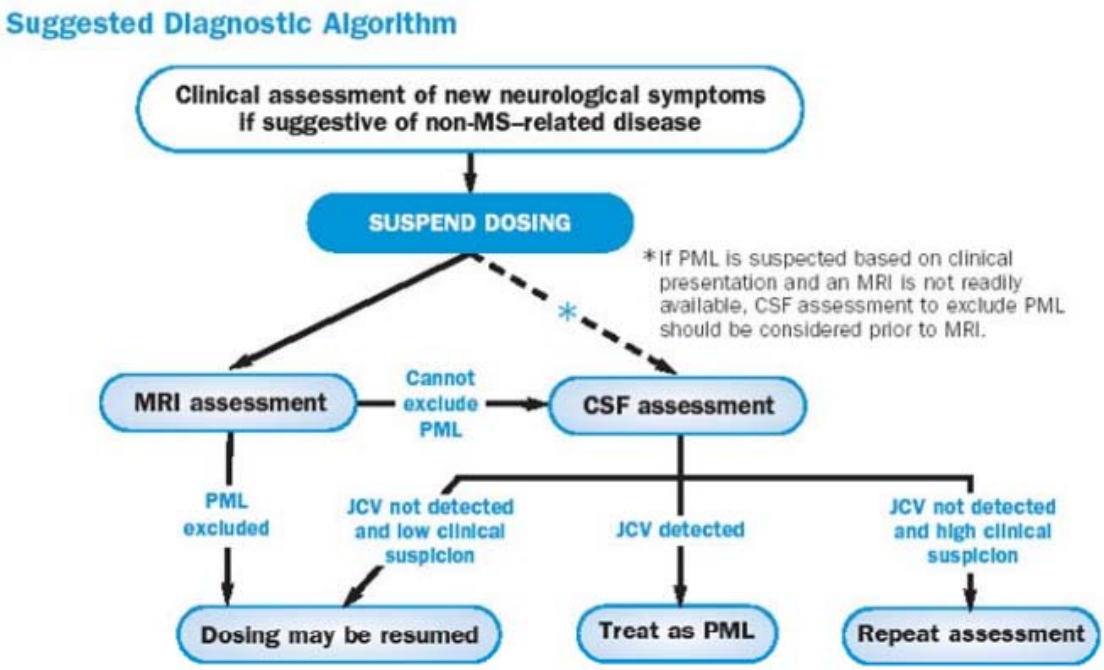
- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurological changes suggestive of PML (see Figure 1).
- Comparison with a baseline scan may assist with interpretation of the findings on the newly acquired MRI (see Table 2 for differences in lesion characteristics that may help differentiate between PML and multiple sclerosis [MS]).

CSF ASSESSMENT

- The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Appendix 6
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

Figure 1 Diagnostic Algorithm for PML



CSF = cerebrospinal fluid; JCV = JC virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Appendix 6
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

TABLE 1

Clinical Signs and Symptoms Typical of MS and PML*		
Onset	**MS** **Acute**	**PML** **Subacute**
Evolution	➢ Over hours to days ➢ Normally stabilized ➢ Resolve spontaneously even without therapy	➢ Over weeks ➢ Progressive
Clinical presentation	➢ Diplopia ➢ Paresthesia ➢ Paraparesis ➢ Optic neuritis ➢ Myelopathy	➢ Cortical symptoms/signs ➢ Behavioral and neuropsychological alteration ➢ Retrochiasmal visual defects ➢ Hemiparesis ➢ Cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination)

Source: Kappos et al. 2007.

Appendix 6
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

TABLE 2 MRI LESION CHARACTERISTICS TYPICAL OF PML AND MS

Feature	MS (relapse)	PML
Location of new lesions	Mostly focal; affect entire brain and spinal chord, in white and possibly gray matter	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; irregular in shape; confined to white matter; sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed.
Mode of extension	Initially focal; lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T2-weighted sequence	• Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure • Subacute and chronic lesions: hyperintense with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions.
On T1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious; true extension of abnormality more clearly visible than in T2-weighted images
With enhancement	• Acute lesions: dense homogeneous enhancement, sharp edges • Subacute lesions: ring enhancement • Chronic lesions: no enhancement	Usually no enhancement, even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy.
Atrophy	Focal atrophy possible due to focal white-matter degeneration; no progression	No focal atrophy

Source: Yousry et al. 2006.

Appendix 7
2010 Revised McDonald Diagnostic Criteria for Multiple Sclerosis

Clinical (attacks)	Lesions	Additional Criteria to Make Diagnosis
2 or more	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1 T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratorial, spinal cord); OR • Await further clinical attack implicating a different CNS site
1	Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by • Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR • A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; OR • Await a second clinical attack
1	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1 T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR • Await further clinical attack implicating a different CNS site AND Dissemination in time, demonstrated by • Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR • A new T2 and/or contrast-enhancing lesions(s) on follow-up MIR, irrespective of its timing; OR • Await a second clinical attack

Appendix 7
2010 Revised McDonald Diagnostic Criteria for Multiple Sclerosis (cont.)

Clinical (attacks)	Lesions	Additional Criteria to Make Diagnosis
0 (progression from onset)		One year of disease progression (retrospective or prospective) AND at least 2 out of 3 criteria: • Dissemination in space in the brain based on ≥1 T2 lesion in periventricular, juxtacortical or infratentorial regions; • Dissemination in space in the spinal cord based on ≥2 T2 lesions; OR • Positive CSF
2 or more	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS

CNS = central nervous system; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MS = multiple sclerosis.

Sources:
http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Paper-TipSheet_-2010-Revisions-to-the-McDonald-Criteria-for-the-Diagnosis-of-MS.pdf
Polman et al. 2011.

Appendix 8
B-Cell Monitoring Schedule of Activities

	Prolonged B-Cell Monitoring [a]
Assessment	*Visits Every 24 Weeks (± 7 days)* [b]
Physical examination	*x*
Neurological examination	*x*
Vital signs	*x*
Routine safety laboratory tests [c]	*x*
Urine pregnancy test	*x*
Hepatitis B virus DNA test [d]	*x*
Total Ig, IgA, IgG, and IgM levels	*x*
Blood TBNK/B-cell subset panel [e]	*x*
Recording of potential relapses	*x*
Adverse event assessments	*x*
Concomitant treatment review	*x*

HBcAb =hepatitis B core antibody; HBsAg =hepatitis B surface antigen; HBV =hepatitis B virus; PCR =polymerase chain reaction; TBNK =T cells, B cells, and natural killer cells.

[a] *Patients whose B-cells have not been repleted after 48 weeks of Safety Follow-up period will continue with visits every 24 weeks (±7 days) until B-cell repletion (prolonged B-cell monitoring).*

[b] *Visits will be performed at 24-week intervals counting from the date of last infusion of ocrelizumab.*

[c] *Routine safety laboratory tests: hematology, chemistry, and urinalysis.*

[d] *For enrolled patients with negative HBsAg and positive total HBcAb, HBV DNA (by PCR) must be repeated every 12 weeks.*

[e] *Includes CD19 and other circulating B-cell subsets, T cells, natural killer cells, and other leukocytes.*