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

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Statistical Analysis Plan (SAP) Initial /Final Sign-Off Sheet

Study title:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE HAD A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**		
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* The Biostatistics approver has ensured that key te[redacted]volved, contributed and reviewed the content of the List of Planned Outputs as described in the SAP Module guideline.

STATISTICAL ANALYSIS PLAN

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

PROTOCOL NUMBER: MN30035

STUDY DRUG: Ocrelizumab (RO4964913)

VERSION NUMBER: 2

IND NUMBER: 100,593

EUDRACT NUMBER: Not applicable

SPONSOR: Genentech, Inc.

PLAN PREPARED BY: [redacted], PhD

DATE FINAL: Version 1: May 31, 2016

DATE(S) AMENDED: Version 2: Apr 30, 2019

STATISTICAL ANALYSIS PLAN AENDMENT APPROVAL

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

April 2019

In this version of Statistical Analysis Plan (SAP), updates have been made following the approval of version 1 of the SAP:

- Study design section has been updated to reflect the protocol version 5 updates including removing the B cell monitoring after Week 96, and the shorter infusion substudy.
- Analysis plan of the shorter infusion substudy was added in Appendix 6.
- Sensitivity analysis plan of the primary endpoint has been specified including per protocol analysis and sensitivity analysis for missing data.
- Preferred terms of the AESIs (AE of Special Interest) have been updated per MedDRA coding latest version.

Additional minor changes have been made to improve clarity and consistency.

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1. BACKGROUND

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 400,000 people in the United States (U.S.) and 2.3 million worldwide (National Multiple Sclerosis Society). MS is clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression. These include relapsing remitting MS (RRMS), primary progressive MS (PPMS), progressive relapsing MS (PRMS), and secondary progressive MS (SPMS) (Lublin et al. 1996). Accumulated disability is the fate of most patients with MS when a 20- to 25-year perspective is considered (Trojano et al. 2003). Approximately 85% of MS patients initially present with RRMS (Confavreaux et al. 2000; Leray et al. 2015).

Over the past two decades, there has been a substantial increase in the number and type of available treatments for RRMS. Yet, despite suboptimal response to an adequate course of treatment with a disease-modifying treatment (DMT) that is defined as the same DMT administered for at least 6 months, a significant proportion of treated patients with RRMS will show signs of disease activity. Suboptimal responses, defined in this protocol as one or more clinically reported relapse(s), one or more T1 gadolinium (Gd)-enhanced lesion(s), or two or more new or enlarging T2 lesions on brain magnetic resonance imaging (MRI) despite being on a stable dose of the same DMT for at least 6 months, are reported in approximately one-third of patients receiving interferon beta (IFN-β) therapy (Bergvall et al. 2014; Durelli et al. 2008; Fernández et al. 2005; Waubant et al. 2003). Disease activity while receiving a DMT is associated with worse long-term outcomes (Bermel et al. 2013), thus subsequent treatment with a more effective therapy may be warranted in patients with breakthrough signs and symptoms. Consequently, reported rates of treatment switching for suboptimal responses range from 20% – 35% of patients (Rio et al. 2012; Gajofatto et al. 2009; Teter et al. 2014).

While clinical experience and retrospective studies suggest that better disease control is obtained by escalating to a higher-efficacy therapy, few prospective studies have been conducted. A prospective, observational study evaluated the outcomes of patients who failed first-line treatment with IFN-β or glatiramer acetate (GA) who were subsequently treated with a different IFN-β formulation or GA, or were escalated to natalizumab (Prosperini et al. 2012). At 1 year, no significant differences in disease activity were observed between the two groups. However, after 2 years, significantly greater proportions of patients escalated to natalizumab were free from relapse, disability progression, MRI activity, and combined activity than patients who were treated with IFN-β or GA. In the Phase III trial (CARE-MS II) published by Coles and colleagues, patients who had one or more relapses while receiving IFN-β or GA therapy were randomized to receive either IFN-β or alemtuzumab. Significant reductions in relapse rates and the accumulation of disabilities were reported with alemtuzumab compared to

IFN-β at 1 year (Coles et al. 2012). However, more data from large-scale, prospective studies assessing patients who are subsequently treated with higher-efficacy therapies following suboptimal control with first-line treatment are needed.

A Phase II study provided initial evidence that ocrelizumab could be effective at further reducing MS disease activity (i.e., annual relapse rate [ARR] and MRI activity) following initial IFN-β therapy. Additional data will also be available on previously treated patients in two completed Phase III studies (Studies WA21092 [OPERA I] and WA21093 [OPERA II]), but only in a subgroup of patients. Therefore, this prospective study was designed to specifically evaluate the effectiveness and safety of using ocrelizumab in patients who show a suboptimal response to an adequate course of a DMT.

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

2. STUDY DESIGN

This study is a prospective, multicenter, open-label, effectiveness and safety study in patients with RRMS who have had a suboptimal response to an adequate course of a DMT. This study will be conducted in North America.

An adequate course of prior DMT is defined as the same DMT administered for at least 6 months. Ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion every 24 weeks for the study duration.

Patients will be assessed for effectiveness and safety every 24 weeks as described in the schedule of assessment in Appendix 2.

The study will consist of the following periods, described in detail below:

1. Screening period: up to 4 weeks.

2. Treatment period: open-label treatment period of 96 weeks (4 doses).

3. Safety follow-up period (additional B cell monitoring not applicable to protocol v5 patients): observation after the last infusion of study drug for patients who discontinue or who chose not to continue with commercially available ocrelizumab (if approved) at the end of study.

4. Eligible patients can be enrolled into an optional shorter infusion substudy to explore the effect of a shorter infusion of ocrelizumab on the rate and severity of IRRs.

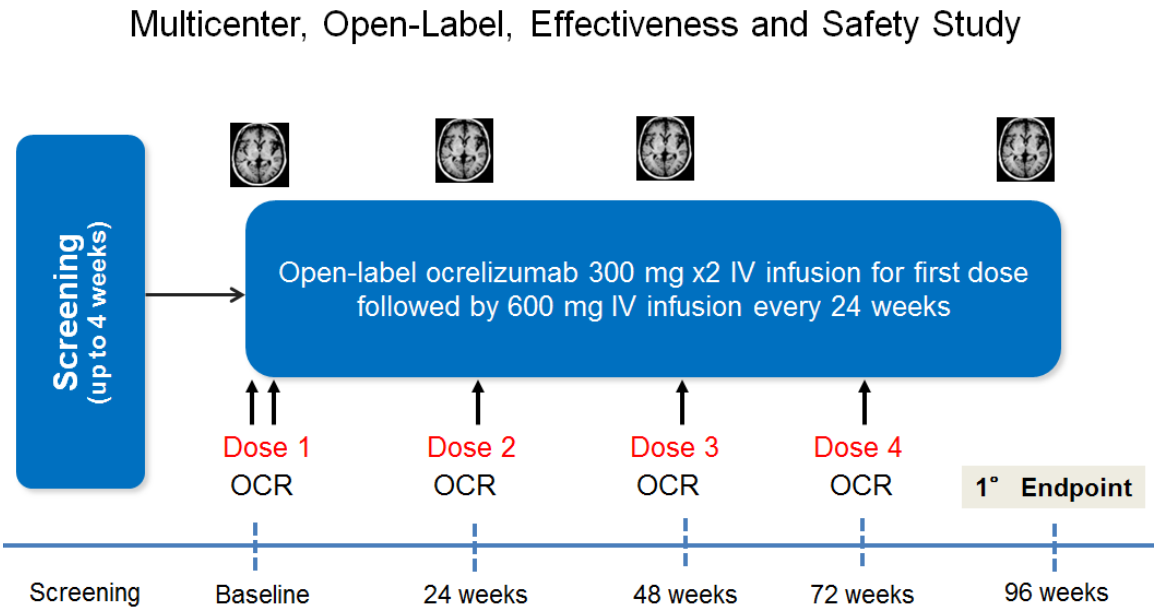
Detailed study design, outcome measures and statistical analysis plan of the shorter infusion substudy will be described in Appendix 6.

2.1 PROTOCOL SYNOPSIS

Please refer to the Protocol for study synopsis and schedule of activities (Protocol Section 6.1).

Figure 1 below presents an overview of the study procedures of the main study.

Figure 1 Overview of Study Procedures



IV = intravenous; OCR = ocrelizumab.

Note: The screening period will last up to 4 weeks, but it may be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons. Baseline MRI results must be available prior to the first infusion.

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

TITLE:	An Open-Label Study To Evaluate the Effectiveness and Safety of Ocrelizumab in Patients With Relapsing Remitting Multiple Sclerosis Who Have Had A Suboptimal Response to an Adequate Course of Disease-Modifying Treatment
PROTOCOL NUMBER:	MN30035
VERSION NUMBER:	5
Eudract Number:	Not applicable

IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	IIIb
INDICATION:	Relapsing remitting multiple sclerosis
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

Primary Objective

The primary objective of this study is to assess the effectiveness of ocrelizumab 600 mg intravenously (IV) every 24 weeks over 96 weeks in patients with relapsing remitting multiple sclerosis (RRMS) who have had a suboptimal response to an adequate course of a disease-modifying treatment (DMT).

A suboptimal response is defined by having one or more clinically reported relapse(s), OR one or more T1 gadolinium (Gd)-enhanced lesion(s), OR two or more new or enlarging T2 lesions on magnetic resonance image (MRI) despite being on a stable dose of the same DMT for at least 6 months. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event must have occurred within the last 12 months of treatment with this DMT.

Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of ocrelizumab 600 mg IV given every 24 weeks in patients with RRMS who have had a suboptimal response to an adequate course of a DMT as measured by the nature and incidence of adverse events.

Exploratory Objective

The exploratory objective of this study is to further assess the effectiveness of ocrelizumab by monitoring patient-reported outcomes (PROs) related to quality of life and treatment satisfaction.

Study Design

Description of the Study

This study is a prospective, multicenter, open-label, effectiveness, and safety study in patients with RRMS who have had a suboptimal response to an adequate course of a DMT. This study will be conducted in North America. An adequate course of prior DMT is defined as the same DMT administered for at least 6 months. Ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion every 24 weeks for the study duration.

Patients will be assessed for effectiveness and safety every 24 weeks. The study will consist of the following periods, described in detail below:

- Screening Period: Up to 4 weeks
- Treatment Period: Open-label treatment period of 72 weeks (4 doses)
- Safety Follow-up Period: Observation 24 weeks after the last infusion of study drug for patients who discontinue or who chose not to continue with commercially available ocrelizumab at the end of study

Eligible patients may choose to participate in an optional shorter infusion substudy at the Week 96 visit, during which they will receive ocrelizumab infused over a shorter time period than the approved administration rate (Appendix 2).

Number of Patients

This study will enroll approximately 600 patients with RRMS who have had a suboptimal response to an adequate course of a DMT.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Age 18□55 years, inclusive
- Have a definite diagnosis of multiple sclerosis (MS), confirmed per the revised 2010 McDonald criteria (Polman et al. 2011; Appendix 4), and have the relapsing remitting form of MS
- Have a length of disease duration, from first symptom, of □ 12 years
- Have been treated with an adequate course of treatment with no more than three prior DMTs
  - Adequate treatment is defined as □ 6 months on a DMT.
  - Discontinuation of the most recent adequately used DMT must have been due to suboptimal response as defined below.
- Suboptimal response while on his/her last adequately used DMT (for □ 6 months); a suboptimal response is defined by having one of the following qualifying events despite being on a stable dose of the same DMT for at least 6 months:
  - One or more clinically reported relapse(s)
  - OR one or more T1 Gd-enhanced lesion(s)
  - OR two or more new or enlarging T2 lesions on MRI

  These qualifying events must have occurred while on the last adequately used DMT. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event must have occurred within the last 12 months of treatment with this DMT from the date of screening.
- Expanded Disability Status Scale (EDSS) of 0 to 5.5, inclusive, at screening
- For women of childbearing potential: agreement to use an acceptable birth control method:
  - Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
  - Male or female condom with or without spermicide
  - Cap, diaphragm, or sponge with spermicide
  - A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods are also considered acceptable, but not highly effective, birth control methods)

Exclusion Criteria

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

- History of primary progressive multiple sclerosis (PPMS), progressive relapsing multiple sclerosis (PRMS), or secondary progressive multiple sclerosis (SPMS)
- Inability to complete an MRI (contraindications for MRI include but are not restricted to claustrophobia, weight, pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, inability to tolerate Gd-enhancing ligands, etc.).

- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of central nervous system (CNS) or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 [HTLV-1], herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
  - History of progressive multifocal leukoencephalopathy (PML)
- Pregnancy or lactation, or intention to become pregnant during the study
  - Women of childbearing potential must have a negative serum or urine pregnancy test result within 14 days prior to initiation of study drug.
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- Lack of peripheral venous access
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine, and gastrointestinal or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (New York Heart Association [NYHA] Class III/IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection (including tuberculosis [TB] or atypical mycobacterial disease but excluding fungal infection of nail beds) or any severe 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
- History of or currently active primary or secondary immunodeficiency
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, TB)
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- History of malignancy, including solid tumors and hematological malignancies, except basal cell, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been excised with clear margins
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of coagulation disorders
- History of alcohol or drug abuse within 24 weeks prior to screening

- Previous treatment with natalizumab within 12 months prior to screening unless failure was due to confirmed, persistent anti-drug antibodies
  - Patients previously treated with natalizumab will be eligible for this study only if duration of treatment with natalizumab was < 1 year and natalizumab was not used in the 12 months prior to screening. Anti-JCV antibody status (positive or negative) and titer (both assessed within the year of screening) must be documented prior to enrollment. When assessed, anti-JCV antibody status should be determined using an analytically and clinically validated immunoassay (e.g., ELISA).
- Previous treatment with systemic cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, or methotrexate
- Treatment with IV immunoglobulin within 12 weeks prior to baseline
- Treatment with dalfampridine (Ampyra□) unless on stable dose for □ 30 days prior to screening
  - Wherever possible, patients should remain on stable doses throughout the treatment period.
- Receipt of a live vaccine within 6 weeks prior to baseline; in rare cases when patient requires vaccination with a live vaccine, the screening period may need to be extended but cannot exceed 8 weeks
- Systemic corticosteroid therapy within 4 weeks prior to screening
  - The screening period may be extended (but cannot exceed 8 weeks) for patients who have used systemic corticosteroids for their MS before screening.
  - There should be 4 weeks from last dose of systemic corticosteroid therapy prior to first infusion.
- Previous treatment with fingolimod (Gilenya®) or dimethyl fumarate (Tecfidera□) in patients whose lymphocyte count is below the lower limit of normal (LLN)
- Contraindications to or intolerance of oral or IV corticosteroids, including IV methylprednisolone (or equivalent steroid) administered according to the country label, including:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the constituents preceding
- Treatment with alemtuzumab (Lemtrada□)
- Treatment with a B-cell targeted therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Treatment with a drug that is experimental (Exception: treatment with an experimental drug that was subsequently approved in the patient's country is allowed.)
- Laboratory test results as follows:
  - Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C antibody (HepCAb)
  - Lymphocyte count below LLN
  - CD4 count < 300/□L
  - AST or ALT ≥ 3.0 × the upper limit of normal (ULN)
  - Platelet count < 100,000/□L (< 100 × 109/L)
  - Total neutrophil 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 enrollment must meet study criteria. In such circumstances, the screening period may need to be prolonged but should not exceed 8 weeks.

End of Study

The end of the treatment period is defined as the date when the last patient, last visit (LPLV) at 96 weeks occurs (or at Week 100 in the substudy).

Length of Study

The total length of the study is expected to be approximately 4 years from the first patient enrolled to LPLV.

The end of study is defined as the LPLV of the safety follow-up.

Investigational Medicinal Products

Test Product (Investigational Drug)

Dose 1 of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15). Subsequent doses will be administered as one 600-mg IV infusion every 24 weeks, for a maximum of 4 doses.

Non-Investigational Medicinal Products

Premedicate with 100-mg methylprednisolone (or equivalent) completed approximately 30 minutes prior to each ocrelizumab infusion and with an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of infusion-related reactions (IRRs).

The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered to further reduce the frequency and severity of IRRs.

Statistical Methods

Primary Efficacy Outcome Measures

The primary efficacy assessment will be the proportion of patients who are free of any protocol-defined events during a 96-week period. The definition of a protocol-defined event is the occurrence of at least one of the following while on treatment with ocrelizumab:

- A protocol-defined relapse
- A T1 Gd-enhanced lesion on brain MRI
- A new and/or enlarging T2 lesion on brain MRI
- Confirmed disability progression (24 weeks)

Determination of Sample Size

Assuming a) the expected proportion of patients who will be event free during 96 weeks is 45%; b) the type one error rate is 5% and the half-width of 95% confidence interval (CI) for the proportion is 4%; c) the probability that half-width of 95% CI is at most 4% is 80%, then the required sample size will be n = 600.

Interim Analyses

It is estimated that two to three interim analyses will be performed during the course of the study, according to patient enrollment and availability of data of interest. Interim analyses may be used for internal decision making, hypothesis generation, abstraction/publication for major MS conferences, or other purposes, as applicable. Details on the timing and scope of interim analyses will be described in the Statistical Analysis Plan

Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Outcome Measures

The primary efficacy assessment is defined as the proportion of patients who are free of any protocol-defined events during a 96-week period. The definition of a protocol-defined event is the occurrence of at least one of the following while on treatment with ocrelizumab:

1. A protocol-defined relapse (an adjudication of protocol-defined relapses will be performed by the sponsor based on pre-specified criteria, applied to data collected by the investigator)
2. A T1 Gd-enhanced lesion on brain MRI
3. A new and/or enlarging T2 lesion on brain MRI
4. Confirmed disability progression (24 weeks)

The evaluation of T1 Gd-enhanced lesions and new and/or enlarging T2 lesions will be performed by NeuroRx and detailed in protocol MN30035 imaging review charter.

2.2.2 Secondary Efficacy Outcome Measures

- The proportion of patients free from a protocol-defined event during a 24-week period and a 48-week period
- Time to protocol-defined event (as defined in Section 2.2.1 above)
- The time to onset of first relapse
- Time to onset of first T1 Gd-enhanced lesion
- Time to onset of first new and/or enlarging T2 lesion
- Time to onset of confirmed disability progression for at least 24 weeks during the study period
- Annualized relapse rate at week 96
- Total number of T1 Gd-enhanced lesions detected by brain MRI at weeks 24, 48, and 96
- Total number of new and/or enlarging T2 lesions detected by brain MRI at weeks 24, 48, and 96

- Change in total T2 lesion volume detected by brain MRI from baseline to weeks 24, 48, and 96

2.2.3 Exploratory Efficacy Outcome Measures

- Change in neurological exam score (EDSS) at Weeks 24, 48 and 96 from baseline
- Percent change in brain volume at Weeks 24, 48, and 96 from baseline
- Change in Patients Reported Outcome Scales from baseline:
    - MSIS-29 - The Multiple Sclerosis Impact Scale
    - SATMED-q - The Treatment Satisfaction with Medicines Questionnaire
    - TSQM II - The Treatment Satisfaction Questionnaire for Medication Version II

2.2.4 Pharmacokinetic Efficacy Outcome Measures

Not Applicable to this study.

2.2.5 Safety Outcome Measures

- Frequency of patients with the following events:
    - Treatment emergent adverse events
    - Serious treatment emergent adverse events
    - Adverse events leading to treatment discontinuation (dose withdrawal)
    - Serious adverse events leading to treatment discontinuation (dose withdrawal)
    - Adverse events leading to infusion dose modification/interruption
    - Serious adverse events leading to infusion dose modification/interruption
    - Treatment-related adverse events
    - Treatment-related serious adverse events
    - Adverse events with fatal outcome
    - MS Relapses

- MS relapses classified as serious
- Infusion-related reactions (IRR):
  - IRR by infusion (dose 1 day 1, dose 1 day 15, dose 2, dose 3, dose 4, overall)
  - IRR by CTCAE grades
  - Infusion related reactions by infusion, grade, and by pre-medication (Methylprednisolone only, Methylprednisolone and analgesics/antipyretics, Methylprednisolone and antihistaminics, Methylprednisolone and analgesics/antipyretics and antihistaminics)
- Time to withdrawal from the study due to an adverse event

- Changes from baseline and select laboratory abnormalities for the following assessments:
  - Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent, and absolute differential count [neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells])
  - Serum Chemistries (AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin, urea, uric acid, creatinine, potassium, sodium, calcium, phosphorus)Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
  - B-cell depletion and recovery (CD19+) and T-cell counts (CD4+, CD8+)
  - HBV DNA
  - Vital signs (infusion and non-infusion visit)
- Exposure duration and dose
- Summary of previous DMTs and last DMT before switching to ocrelizumab

2.3 DETERMINATION OF SAMPLE SIZE

Assuming a) the expected proportion of patients who will be event free during 96 weeks is 45%; b) the type one error rate is 5% and the half-width of 95% confidence interval for the proportion is 4%; c) the probability that half-width of 95% confidence interval is at most 4% is 80%, the required sample size for this study is n=600. The shorter infusion

substudy will enroll approximately 100 patients. Please refer to protocol for further details.

2.4 ANALYSIS TIMING

The final analysis will be conducted after all patients completed the study visits including safety follow-up visit and the optional substudy visits. Database lock will occur several weeks after the last patient last visit to clarify all outstanding queries. In addition to the final analysis, two interim analyses were performed: 1) when 20% of patients completed their 48-week visit, and 2) when all patients completed their 48-week visit.

3. STUDY CONDUCT

3.1 RANDOMIZATION

No randomization is planned. All patients will receive ocrelizumab.

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

Not applicable.

4. STATISTICAL METHODS

For continuous variables, descriptive statistics (e.g., mean, median, standard deviation [SD], n, 25th and 75th percentiles, minimum, maximum) will be calculated and summarized. For categorical variables, the number and percentage in each category will be displayed. Statistical methods for analysis of efficacy variables are detailed in the Efficacy Analyses section below.

Planned analyses for the shorter infusion sub-study will be described in Appendix 6.

4.1 ANALYSIS POPULATIONS

The efficacy analyses will be performed using the intent-to-treat (ITT) or modified ITT (mITT) population. The per-protocol (PP) population will be used for sensitivity efficacy analyses for the primary endpoint only) in order to evaluate the influence of major protocol violators on efficacy of ocrelizumab. The safety analyses will be performed using the safety population.

4.1.1 Intent-to-Treat Population

All enrolled patients who received any ocrelizumab will be included in the ITT population. Patients who prematurely withdrew from the study for any reason and who did not have any assessments for any reason will still be included in the ITT population as long as patient received ocrelizumab.

4.1.2 Modified Intent-to-Treat Population

The modified ITT (mITT) population is a subset of the ITT population which excludes patients who discontinued ocrelizumab treatment early without any protocol-defined events for reasons other than death and lack of efficacy.

4.1.3 Per Protocol Population

The per-protocol (PP) population will include all patients in the ITT population without key major protocol violations. Key major violations includes key inclusion/exclusion criteria or violations of study conduct that are deemed to potentially affect the efficacy of study treatment. The list of key major protocol violations is finalized prior to final database lock for the study and listed in Appendix 5.

4.1.4 Pharmacokinetic-Evaluable Population

Not applicable.

4.1.5 Safety Population

The Safety Population will include all enrolled patients who received any ocrelizumab. All safety analyses will use this population.

4.2 ANALYSIS OF STUDY CONDUCT

The following will be summarized:

- Numbers of patients in each of the ITT, mITT, PP, and safety populations, and protocol deviations leading to exclusion from the PP population
- Number of patients who complete study treatment
- Reasons for study treatment discontinuation (separate summary of number and percentage of patients who continued onto commercial OCR for patients under protocol version 5 and patients under previous versions)
- Reasons for study discontinuation (separate summary of number and percentage of patients who continued onto commercial OCR for patients under protocol version 5 and patients under previous versions)
- Number of patients who complete 1, 2, 3, and 4 doses (dose 1 is split to two infusions and will be counted as 1 dose)
- Summary and Kaplan-Meier plots of time to discontinuation of study treatment (patients did not reach week 96)

4.3 ANALYSIS OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The following demographic and baseline characteristics will be summarized:

- Age at first dose (< 40, ≥ 40, also < 18, 18- 40, 40-55, > 55, and continuous)
- Sex
- Self-reported race and ethnicity
- Female and male reproductive statuses
- Country (USA, Canada)
- Height, weight, and BMI

History of MS summaries will include:

- Duration since MS first symptoms (in years): continuous and categorical (≤ 3 years, >3 - 5 years, >5 - 10 years, >10-≤12 years, >12 years)
- Duration since RRMS diagnosis (in years): continuous and categorical (≤ 2 years, >2 - 5 years, >5 - 10 years, >10-≤12 years, >12 years)
- Baseline EDSS: continuous and categorical (<4 years, ≥4 years, and <2.5 years, ≥2.5 years)
- Time since first MS relapse: continuous and categorical (≤3 months,>3 to ≤6 months, >6 months)
- Qualifying events for enrollment (relapse, T1 Gd-enhanced lesion or new and/or enlarging T2 lesion)

History of prior MS treatment summaries will include:

- Number and percent of patients taking previous unique DMTs, by number and by name of DMT
- Number and percent of patients switching previous DMTs
- Duration of previous DMT (months) by name of DMT
- Reason for discontinuation from each previous DMT by name of DMT
- Number and percent of patients taking last DMT before study enrollment by name of DMT

- Duration between end of last DMT to initiation of ocrelizumab treatment: continuous (months) and categorical (≤1 months,>1 to ≤3 months, >3 months), and by name of DMT.

- Baseline MRI results: number of Gd-enhancing T1 lesions (0, 1, 2, 3, ≥4) and normalized brain volume

General non-MS medical history and baseline conditions

- Study sites (number and percent of patients)

4.4 EFFICACY ANALYSIS

Efficacy endpoints will be evaluated for the mITT or ITT population as specified. Sensitivity for primary endpoint will be conducted for the PP population.

For all change from baseline analyses, except for EDSS, baseline will be defined as the last non-missing value on or before the first infusion. Unless otherwise specified, the baseline EDSS will be defined as (1) the last non-missing value on or before the first infusion, for patients who were administered only one EDSS evaluation before the first infusion, or (2) the average of the 2 EDSS results pre infusion, for patients who were administered an additional evaluation in cases where the screening EDSS was more than 14 days prior to the first infusion.

The baseline EDSS will be rounded to the second decimal point. For analyses that stratify by analysis baseline EDSS i.e. (< 2.5 vs. ≥ 2.5), the EDSS values will be rounded to the nearest one decimal value.

Per protocol, unscheduled MRI evaluations conducted for suspected PML will not be included in the analysis of efficacy endpoints.

Visit windows (defined in Module 2) will be applied to key efficacy assessments to accurately capture the timing of assessment.

4.4.1 Primary Efficacy Endpoint

The proportion of patients who are free from a protocol-defined event during a 96-week period will be calculated and presented along with a two-sided 95% Clopper-Pearson exact confidence interval. Data from unscheduled visits within each respective 24-week interval will be included in the evaluation of the endpoint. Analyses will be performed for the mITT population. Patients are considered to have a protocol-defined event during the 96-week period if they discontinue due to lack of efficacy or death despite without a protocol-defined event as defined below.

Event definition and Handling of Missing Data

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

- A protocol-defined relapse defined as an occurrence of new or worsening neurological symptoms attributable to MS. Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications), and immediately be preceded by a stable or improving neurological state for least 30 days.

- A T1 Gd-enhanced lesion on brain MRI

- A new and/or enlarging T2 lesion on brain MRI

- Confirmed disability progression (24 weeks)

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 two points on one of the appropriate Functional Systems Score (FSS), or one point on two or more of the appropriate FSS. The change must affect the selected FSS (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.

Progression is defined a ≥ 1−point increase in EDSS score from a baseline EDSS score of 0.0−5.5 inclusive, and a 0.5-increase from a baseline EDSS score higher than 5.5.

For example, for a patient with a baseline EDSS score of 5.25 or 5.5, the progression is defined as an EDSS score of at least 6.5. For a patient with a baseline EDSS score of 5.75 or 6.0, the progression is defined as an EDSS score of at least 6.5.

Confirmation of the 24-week disability progression must occur at the regularly scheduled visit that is at least 24 weeks (168 days ± 14 days) after initial progression.

If a patient has a missing EDSS at the scheduled visit occurring at least 168 days after an initial progression, the next immediate scheduled or unscheduled EDSS will be used to confirm disability progression. In cases where confirmation of disability progression during the study is not possible due to missing 24-week assessments, such that establishment of the occurrence of a protocol-defined event is not possible, the patient will be considered as not having an event.

4.4.2 Secondary Efficacy Endpoints

The mITT population will be used for secondary efficacy endpoints of the proportion of patients free from a protocol-defined event during the first 24-week and 48-week period.

Analyses of all other secondary efficacy endpoints will be performed using the ITT population.

The proportion of patients free from a protocol-defined event during the first 24-week and 48-week will be presented along with a two-sided 95% Clopper-Pearson exact confidence interval. Same analysis method of the primary efficacy endpoint will be applied to the 24-week and 48-week outcomes. Note that event during the first 24-weeks will not include CDP events due to no confirmatory EDSS score can be observed within the first 24-weeks. A histogram of the percent of patients who are event free at weeks 24, 48, and 96 will be produced.

Time-to-event endpoints

The Kaplan–Meier method (i.e., the product limit estimator) will be used to estimate the time to onset of the 5 parameters listed below. Kaplan-Meier plots will be produced. The event-free probability at Week 96 will be calculated based on Kaplan-Meier method as sensitivity analyses of the primary endpoint, proportion of patients without a protocol-defined event.

Time to protocol-defined event

For patient with an event, it will be defined as the earliest onset time of the following: a protocol-defined relapse, T1 Gd-enhanced lesion, new and/or enlarging T2 lesion, or confirmed disability progression (see below for the determination of the time to onset of confirmed disability progression)

Patients without an event (either during the complete 96-week study period, or before early withdrawal from treatment) will be censored at the last evaluation of a protocol defined event, i.e. the maximum time of last MRI or EDSS evaluation

Time to onset of first relapse

For patients with an event, it will be determined as the first relapse time reported by the patient.

Patients without any relapse will be censored at the last study visit.

Time to onset of first T1 Gd-enhanced lesion

For patient with event, it will be defined as the first time a T1 Gd-enhanced lesion was detected post baseline.

Patients without an event will be censored at the last performed MRI evaluation.

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

For patient with event, it will be defined as the first time, including at unscheduled visits, a new and/or an enlarging T2 lesion was detected.

Patients without an event will be censored at the last performed MRI evaluation.

Time to onset of confirmed disability progression determination for at least 24 weeks during the study period

For patient with an event, it will be defined as the initial disability progression time.

Patients without an event will be censored at the last available EDSS evaluation.

The adjusted annualized relapse rate at Week 96 will be estimated using a negative binomial model, adjusting for the number of previous DMTs (1 or >1), baseline EDSS (< 2.5 vs ≥ 2.5), and including the log-transformed years of drug exposure time as an "offset" variable. The adjusted rates along with the two-sided 95% confidence interval will be presented. SAS proc GENMOD will be applied. Years of drug exposure will be defined as ((earlier of date of Week 96 visit or date of treatment early termination) − date of first infusion + 1)/365.25

The unadjusted annualized relapse rate at Week 96 will be presented. It is defined as the total number of relapses for all patients divided by the total years of drug exposure.

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

The analyses will include patients who have an interpretable MRI at the time point of interest. The following analyses will be presented:

- Number and percentage of patients having 0, 1, 2, 3, and greater than 3 lesions at weeks 24, 48, and 96.
- The unadjusted and adjusted rates of lesion occurrence at weeks 24, 48, and 96 combined will be calculated:
    - The unadjusted rate will be the ratio of the total number of T1 Gd-enhanced lesions to the total number of interpretable MRI scans.
    - The adjusted rate will be derived using a negative binomial model. The dependent variable in the model will be the total number of T1-Gd-enhanced lesions. The model will be adjusted for the following baseline covariates: Gd lesion (present or not), EDSS score (< 2.5 vs. ≥ 2.5), and number of previous DMTs (1 vs. >1). In order to account for patients potentially receiving varying numbers of brain MRI scans during the study, the log-transformed number of brain MRI scans received will be included in the model as an "offset".

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

Total number of new and/or enlarging T2 lesions detected by brain MRI at weeks 24, 48, and 96

The analyses of this outcome will be similar to the analyses of total T1 Gd-enhanced lesions as described above.

The mean change in total T2 lesion volume detected by brain MRI from baseline to Weeks 24, 48, and 96 will be analyzed using a longitudinal mixed effects model repeated measure (MMRM). The model's fixed effects will include visit along with the following baseline covariates: baseline T2 lesion volume, number of previous DMTs (1 vs. >1), baseline T2 lesion volume by visit interaction, and baseline EDSS score (< 2.5 vs. ≥ 2.5). Visit will be treated as a repeated variable within a patient. Patient and visit will be treated as factor variables. An unstructured variance−covariance structure will be applied to model the within-patient errors. The model will be fitted using the Restricted Maximum Likelihood method (REML). Denominator degrees of freedom will be estimated using Satterthwaite's approximation. Any patient with an interpretable post baseline MRI will be included in the model.

A plot of T2 lesion volume least squares mean changes from baseline over time and corresponding 95% confidence intervals will be presented.

4.4.3 Exploratory Efficacy Endpoints

The ITT population will be used for exploratory efficacy endpoints.

Changes from baseline in EDSS scores at Weeks 24, 48, and 96 will be estimated using a longitudinal mixed effects model repeated measure (MMRM). The model's fixed effects will include visit along with the following baseline covariates: baseline EDSS score and number of previous DMTs (1 vs. >1), baseline EDSS score by visit interaction. Visit will be treated as a repeated variable within a patient. Patient and visit will be treated as factor variables. An unstructured variance−covariance structure will be applied to model the within-patient errors. The model will be fitted using the Restricted Maximum Likelihood method (REML). Denominator degrees of freedom will be estimated using Satterthwaite's approximation.

A plot of the adjusted mean EDSS changes form baseline will be produced.

Percent changes from baseline in brain volume at Weeks 24, 48, and 96 will be estimated using the same model as the T2 lesion volume in section 4.4.2.

Change in below PROs from baseline will be estimated using MMRM adjusting for visit along with following baseline covariates: baseline score and number of previous DMTs

(1 vs. >1), baseline EDSS score (<2.5 vs. >=2.5) and baseline PRO score by visit interaction. Visit will be treated as a repeated variable within a patient. Patient and visit will be treated as factor variables.

- MSIS-29 - The Multiple Sclerosis Impact Scale
- SATMED-q - The Treatment Satisfaction with Medicines Questionnaire
- TSQM II - The Treatment Satisfaction Questionnaire for Medication Version II

Detailed analysis method for the PRO endpoints will be described in Section 4.6.

4.4.4 Sensitivity Analyses

The analysis of primary efficacy endpoint described in Section 4.4.1 will be performed for the PP population as a sensitivity analysis. Per study schedule, the last EDSS assessment is at Week 96, such that no subsequent visit with EDSS measurement can be used to confirm an initial disability progression at Week 96. A Sensitivity analysis will be performed for the mITT population to impute 50% of the patients with an initial disability progression at Week 96 as having an event of CDP; the other 50% of these patients as having no event of CDP.

4.4.5 Subgroup Analyses

The primary and all secondary outcomes will be analyzed for the following subgroup for the mITT population:

Last DMT before enrollment: Fingolimod vs. Other

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not Applicable.

4.6 PATIENT REPORTED OUTCOME ANALYSES

All analyses on the patient reported outcomes (PROs) will be based on the ITT population.

4.6.1 MSIS-29

The Multiple Sclerosis Impact Scale (MSIS-29) is a 29-item questionnaire designed to measure the physical and psychological impact of MS from the patient's perspective.

Dimension	Items	Item Scores
Physical Scale	1-20	1 = Not at all 2 = A little 3 = Moderately 4 = Extremely
Psychological Scale	21-29	1 = Not at all 2 = A little

		3 = Moderately 4 = Extremely

Score for the physical scale is calculated as follows:

- Items 1-20 are added
- A transformed score = 100 x (observed score - 20) /(80-20) is derived

Score for the psychological scale is calculated as follows:

- Items 21-29 are added
- A transformed score = 100 x (observed score - 9) /(36-9) is derived

Higher scale values indicate higher impact of MS disability on the patient. Missing scores in the specific scale are not imputed.

MSIS-29 results by dimension will be summarized for baseline and weeks 24, 48, 72, and 96 visits. The mean change in each MSIS-29 dimension score from baseline to weeks 24, 48, and 96 will be analyzed using a longitudinal mixed effects model repeated measure (MMRM). The fixed effects will include visit along with the following baseline covariates: baseline MSIS-29 score, number of previous DMTs (1 vs >1), baseline MSIS-29 score by visit interaction, and baseline EDSS score (< 2.5 vs. ≥ 2.5). Visit will be treated as a repeated variable within a patient. Patient and visit will be treated as factor variables. An unstructured variance−covariance structure will be applied to model the within-patient errors. The model will be fitted using the Restricted Maximum Likelihood method (REML). Denominator degrees of freedom will be estimated using Satterthwaite's approximation.

A plot of the least squares mean changes from baseline in MSIS-29 scores over time and the corresponding 95% confidence intervals will be presented for each dimension of the scale.

4.6.2 SATMED-q

The Treatment Satisfaction with Medicines Questionnaire includes 17 questions scored on a 5-point Likert-type scale investigating the following dimensions. The bolded dimensions will be summarized:

Dimension	Items	Item Scores
Any Undesirable side effects	1	0=No 1=Yes
Undesirable Side effects	1-3	4 = Not at all 3 = A little bit 2 = Somewhat

		1 = Quite a bit 0 = Very much
Treatment effectiveness	4-6	0 = Not at all 1 = A little bit 2 = Somewhat 3 = Quite a bit 4 = Very much
Convenience for use	7-9	0 = Not at all 1 = A little bit 2 = Somewhat 3 = Quite a bit 4 = Very much
Impact on daily activities	10-12	0 = Not at all 1 = A little bit 2 = Somewhat 3 = Quite a bit 4 = Very much
Medical care	13-14	0 = Not at all 1 = A little bit 2 = Somewhat 3 = Quite a bit 4 = Very much
Global satisfaction	15-17	0 = Not at all 1 = A little bit 2 = Somewhat 3 = Quite a bit 4 = Very much

Items are summed to yield the dimension scores. Higher scores indicate higher satisfaction with treatment. Missing score should be substituted by the worst possible score where applicable (items 1 to 3: if question “Have you experienced any undesired effects caused by the medicine” = “Y”, then missing=”Quite a bit”, otherwise missing will not be imputed; items 4 to 17: missing=”Not at all”). If two or more answers are missing in a given dimension, the dimension should be discarded. If two contiguous response categories are selected for one item, the worst score should be selected as valid. When two non-contiguous response categories are selected, the response should be considered as missing.

Analysis of the SATMED-q scores will be based on a longitudinal MMRM similar to the planned analyses of the MSIS-29 scores as described above.

A plot of the least squares mean changes from baseline in SATMED-q scores over time and the corresponding 95% confidence intervals will be presented for each bolded dimension of the scale.

4.6.3 TSQM II

The Treatment Satisfaction Questionnaire for Medication Version II consists of 11 questions and 4 dimensions

Dimension	Cluster of	Score	Scoring

	Items that are added		
Effectiveness	1-2	1 = Extremely Dissatisfied 2 = Very Dissatisfied 3 =Dissatisfied 4 = Somewhat Satisfied 5 = Satisfied 6 = Very Satisfied 7 = Extremely Satisfied	([(item 1 + item 2) – 2]/12) * 100 If one item is missing: ([(Use the completed item)) – 1] / 6) * 100
Side Effects	4-6	1 = Extremely Dissatisfied 2 = Very Dissatisfied 3 = Somewhat Dissatisfied 4 = Slightly Dissatisfied 5 = Not at all Dissatisfied (6) = Not Applicable	([Sum(item 4 - item 6) – 3] /12) * 100 If one item is missing: ([(Sum(*the two completed items*)) – 2]/8) * 100
Convenience	7-9	1 = Extremely Dissatisfied 2 = Very Dissatisfied 3 =Dissatisfied 4 = Somewhat Satisfied 5 = Satisfied 6 = Very Satisfied 7 = Extremely Satisfied	([Sum(Item 7 - item 9) – 3]/18) * 100 If one item is missing: ([(Sum(*the two completed items*)) – 2]/12) * 100
Global Satisfaction	10-11	1 = Extremely Dissatisfied 2 = Very Dissatisfied 3 =Dissatisfied 4 = Somewhat Satisfied 5 = Satisfied 6 = Very Satisfied 7 = Extremely Satisfied	([Sum(Item 10 to Item 11) – 2] /12) * 100 If one item is missing: ([(Use the completed item)) – 1] divide by 6) * 100

All missing or 'not applicable' responses for Side Effects (relevant to item 4 – item 6) will be imputed as "Extremely Dissatisfied" if the question "As a result of taking this medication, do you experience any side effects at all?" is answered as "Yes"; otherwise will not be imputed. If two or more item is missing in a subscale, the subscale will be discarded.

Analysis of the TSQM II scores will follow the MMRM approach similar to the analysis of the MSIS-29 scores as described above.

A plot of the least squares mean changes from baseline in TSQM-II scores over time and the corresponding 95% confidence intervals will be presented for each of the four dimension scales.

4.7 SAFETY ANALYSES

All safety analyses will be based on the safety population. For all change from baseline analyses, unless noted otherwise, baseline will be defined as the last non-missing value on or before the first infusion.

Treatment emergent AEs (TEAEs) are defined as AEs that occur on or after treatment on Day 1 or existing events that worsened after first study dose. Treatment emergent serious AEs (SAEs) are defined as SAEs that occur on or after treatment on day 1 or existing events that increased in severity after first study dose. AEs will be coded using the current MedDRA Dictionary and summarized by NCI CTCAE v4.0 grade.

Relapse is part of the efficacy outcome as a component of protocol defined events and will be reported in the efficacy results section.

Visit windows will be used in analyses that summarize laboratory measurements, vital signs. Visit window specifications will be provided in the separate Module 2.

4.7.1 Exposure of Study Medication

Patients will be considered to have received a dose of treatment if they were administered at least part of one infusion of a dose (including day 1 or day 15 for the first dose).

The treatment duration (weeks) and the number of doses received (day 1 and day 15 infusions are considered as one dose) will be summarized.

The number and percent of patients with study treatment intervention and the type of intervention (slowed down, interrupted, or discontinued infusion) will be summarized. The summaries will be presented by dose (dose 1 day 1, dose 1 day 15, dose 2, dose 3, dose 4) and overall.

Kaplan-Meier plots of time to discontinuation of study treatment will be presented.

4.7.2 Adverse Events

All TEAE will be coded, summarized by NCI CTCAE v4.0 grade, and tabulated by body system and Preferred Term for individual adverse events within each body system. Grade 3 to 5 adverse events, serious adverse events, adverse events leading to treatment discontinuation, time to withdrawal from treatment due to an adverse event, adverse events leading to infusion adjustment, and treatment-related adverse events will be summarized. In addition, all adverse events leading to withdrawal from treatment and deaths will be listed if applicable.

Number of events per 100 Patient-Years along with 95% exact confidence intervals will be summarized for all AE, serious AE and serious infections.

The number and percentage of patients with at least one infusion related reaction (IRR), and the intensity (highest grade for each patient) will be summarized in total, by dose (dose 1 day 1, dose 1 day 15, dose 2, dose 3, dose 4) and by pre-medication. In

addition, the total number of IRRs will be summarized (multiple events will be counted) in total and by dose.

4.7.3 Laboratory Data

Associated laboratory parameters, such as hepatic function, renal function, and hematology values, will be grouped and presented together. A summary of the number and percentage of patients with abnormal laboratory outcomes will be produced for each parameter.

4.7.4 Vital Signs

Changes in physical findings and vital signs with onset on or after the first OCR infusion will be summarized at each scheduled visit.

4.7.5 Safety Endpoints of Special Interest

All reported AESI will be summarized overall and by NCI CTCAE v4.0 grade, and tabulated by specific MedDRA bucket terms and preferred terms. The following types of events are of special interest:

- Drug-induced liver injury
- Suspected transmission of an infectious agent via product

4.8 MISSING DATA

AEs with missing relationship to study drug will be considered as 'Related'. AEs with missing CTCAE grade will be imputed as grade 3. AE with missing seriousness will be graded as serious.

Missing and partial dates for AEs and concomitant medications will be handled according to Roche STREAM algorithm.

4.9 INTERIM ANALYSES

Two interim analyses were performed during the course of the study, according to patient enrollment and availability of data of interest. Interim analyses were used for hypothesis generation, abstraction/publication for major scientific conferences, or other purposes, as applicable. The statistical analysis plan of the interim analyses were detailed and documented in a separate *DAP Module 1 CHORDS Study_Interim_v1.0*.

Since no adjustment of the study design or course are planned as a result of the interim looks, no adjustments to the type I error will be applied.

5. REFERENCES

Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR), *Am J Epidemiol.* 1990 Feb;131(2):373-5

Appendix 1
Protocol Synopsis

TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE HAD A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**
PROTOCOL NUMBER:	MN30035
VERSION NUMBER:	5
EUDRACT NUMBER:	Not applicable
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	IIIb
INDICATION:	Relapsing remitting multiple sclerosis
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

Primary Objective

The primary objective of this study is to assess the effectiveness of ocrelizumab 600 mg intravenously (IV) every 24 weeks over 96 weeks in patients with relapsing remitting multiple sclerosis (RRMS) who have had a suboptimal response to an adequate course of a disease-modifying treatment (DMT).

A suboptimal response is defined by having one or more clinically reported relapse(s), OR one or more T1 gadolinium (Gd)-enhanced lesion(s), OR two or more new or enlarging T2 lesions on magnetic resonance image (MRI) despite being on a stable dose of the same DMT for at least 6 months. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event must have occurred within the last 12 months of treatment with this DMT.

Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of ocrelizumab 600 mg IV given every 24 weeks in patients with RRMS who have had a suboptimal response to an adequate course of a DMT as measured by the nature and incidence of adverse events.

Exploratory Objective

The exploratory objective of this study is to further assess the effectiveness of ocrelizumab by monitoring patient-reported outcomes (PROs) related to quality of life and treatment satisfaction.

Study Design

Description of the Study

This study is a prospective, multicenter, open-label, effectiveness, and safety study in patients with RRMS who have had a suboptimal response to an adequate course of a DMT. This study will be conducted in North America. An adequate course of prior DMT is defined as the same DMT administered for at least 6 months. Ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion every 24 weeks for the study duration.

Patients will be assessed for effectiveness and safety every 24 weeks. The study will consist of the following periods, described in detail below:

- Screening Period: Up to 4 weeks
- Treatment Period: Open-label treatment period of *72* weeks (4 doses)
- Safety Follow-up Period: Observation *24* weeks after the last infusion of study drug for patients who discontinue or who chose not to continue with commercially available ocrelizumab at the end of study

Eligible patients may choose to participate in an optional shorter infusion substudy at the Week 96 visit, during which they will receive ocrelizumab infused over a shorter time period than the approved administration rate (Appendix 2).

Number of Patients

This study will enroll approximately 600 patients with RRMS who have had a suboptimal response to an adequate course of a DMT.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Age 18–55 years, inclusive
- Have a definite diagnosis of multiple sclerosis (MS), confirmed per the revised 2010 McDonald criteria (Polman et al. 2011; Appendix 4), and have the relapsing remitting form of MS
- Have a length of disease duration, from first symptom, of ≤ 12 years
- Have been treated with an adequate course of treatment with no more than three prior DMTs
  - Adequate treatment is defined as ≥ 6 months on a DMT.
  - Discontinuation of the most recent adequately used DMT must have been due to suboptimal response as defined below.
- Suboptimal response while on his/her last adequately used DMT (for ≥ 6 months); a suboptimal response is defined by having one of the following qualifying events despite being on a stable dose of the same DMT for at least 6 months:
  - One or more clinically reported relapse(s)
  - OR one or more T1 Gd-enhanced lesion(s)
  - OR two or more new or enlarging T2 lesions on MRI

  These qualifying events must have occurred while on the last adequately used DMT. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event must have occurred within the last 12 months of treatment with this DMT from the date of screening.
- Expanded Disability Status Scale (EDSS) of 0 to 5.5, inclusive, at screening
- For women of childbearing potential: agreement *to use an acceptable birth control method:*
  - *Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action*
  - *Male or female condom with or without spermicide*
  - *Cap, diaphragm, or sponge with spermicide*
  - *A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods are also considered acceptable, but not highly effective, birth control methods)*

Exclusion Criteria

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

- History of primary progressive multiple sclerosis (PPMS), progressive relapsing multiple sclerosis (PRMS), or secondary progressive multiple sclerosis (SPMS)
- Inability to complete an MRI (contraindications for MRI include but are not restricted to claustrophobia, weight, pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, inability to tolerate Gd-enhancing ligands, etc.).
- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of central nervous system (CNS) or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 [HTLV-1], herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
  - History of progressive multifocal leukoencephalopathy (PML)
- Pregnancy or lactation, or intention to become pregnant during the study
  - Women of childbearing potential must have a negative serum or urine pregnancy test result within 14 days prior to initiation of study drug.
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- Lack of peripheral venous access
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine, and gastrointestinal or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (New York Heart Association [NYHA] Class III/IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection (including tuberculosis [TB] or atypical mycobacterial disease but excluding fungal infection of nail beds) or any severe 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
- History of or currently active primary or secondary immunodeficiency
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, TB)
- History of recurrent aspiration pneumonia requiring antibiotic therapy

- History of malignancy, including solid tumors and hematological malignancies, except basal cell, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been excised with clear margins
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of coagulation disorders
- History of alcohol or drug abuse within 24 weeks prior to screening
- Previous treatment with natalizumab within 12 months prior to screening unless failure was due to confirmed, persistent anti-drug antibodies
  - Patients previously treated with natalizumab will be eligible for this study only if duration of treatment with natalizumab was < 1 year and natalizumab was not used in the 12 months prior to screening. Anti-JCV antibody status (positive or negative) and titer (both assessed within the year of screening) must be documented prior to enrollment. When assessed, anti-JCV antibody status should be determined using an analytically and clinically validated immunoassay (e.g., ELISA).
- Previous treatment with systemic cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, or methotrexate
- Treatment with IV immunoglobulin within 12 weeks prior to baseline
- Treatment with dalfampridine (Ampyra®) unless on stable dose for $\geq$ 30 days prior to screening
  - Wherever possible, patients should remain on stable doses throughout the treatment period.
- Receipt of a live vaccine within 6 weeks prior to baseline; in rare cases when patient requires vaccination with a live vaccine, the screening period may need to be extended but cannot exceed 8 weeks
- Systemic corticosteroid therapy within 4 weeks prior to screening
  - The screening period may be extended (but cannot exceed 8 weeks) for patients who have used systemic corticosteroids for their MS before screening.
  - There should be 4 weeks from last dose of systemic corticosteroid therapy prior to first infusion.
- Previous treatment with fingolimod (Gilenya®) or dimethyl fumarate (Tecfidera®) in patients whose lymphocyte count is below the lower limit of normal (LLN)
- Contraindications to or intolerance of oral or IV corticosteroids, including IV methylprednisolone (or equivalent steroid) administered according to the country label, including:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the constituents preceding
- Treatment with alemtuzumab (Lemtrada®)
- Treatment with a B-cell targeted therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Treatment with a drug that is experimental (Exception: treatment with an experimental drug that was subsequently approved in the patient's country is allowed.)
- Laboratory test results as follows:
  - Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C antibody (HepCAb)
  - Lymphocyte count below LLN
  - CD4 count $< 300/\mu L$
  - AST or ALT $\geq 3.0 \times$ the upper limit of normal (ULN)

- Platelet count $< 100{,}000/\mu L$ ($< 100 \times 10^9/L$)
- Total neutrophil 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 enrollment must meet study criteria. In such circumstances, the screening period may need to be prolonged but should not exceed 8 weeks.

End of Study

The end of the treatment period is defined as the date when the last patient, last visit (LPLV) at 96 weeks occurs *(or at Week 100 in the substudy)*.

Length of Study

The total length of the *study* is expected to be approximately 4 years from the first patient enrolled to LPLV.

The end of study is defined as the LPLV of the safety follow-up.

Investigational Medicinal Products

Test Product (Investigational Drug)

Dose 1 of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15). Subsequent doses will be administered as one 600-mg IV infusion every 24 weeks, for a maximum of 4 doses.

Non-Investigational Medicinal Products

Premedicate with 100-mg methylprednisolone (or equivalent) completed approximately 30 minutes prior to each ocrelizumab infusion and with an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of infusion-related reactions (IRRs).

The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered to further reduce the frequency and severity of IRRs.

Statistical Methods

Primary Efficacy Outcome Measures

The primary efficacy assessment will be the proportion of patients who are free of any protocol-defined events during a 96-week period. The definition of a protocol-defined event is the occurrence of at least one of the following while on treatment with ocrelizumab:

- A protocol-defined relapse
- A T1 Gd-enhanced lesion on brain MRI
- A new and/or enlarging T2 lesion on brain MRI
- Confirmed disability progression (24 weeks)

Determination of Sample Size

Assuming a) the expected proportion of patients who will be event free during 96 weeks is 45%; b) the type one error rate is 5% and the half-width of 95% confidence interval (CI) for the proportion is 4%; c) the probability that half-width of 95% CI is at most 4% is 80%, then the required sample size will be $n = 600$.

Interim Analyses

It is estimated that two to three interim analyses will be performed during the course of the study, according to patient enrollment and availability of data of interest. Interim analyses may be used for internal decision making, hypothesis generation, abstraction/publication for major MS conferences, or other purposes, as applicable. Details on the timing and scope of interim analyses will be described in the Statistical Analysis Plan

Appendix 2
Schedule of Assessments

	Screening	Treatment Period					End of Treatment/ Early With-drawal Visit [b]	Unscheduled Visit *(due to relapse)* [c]	Safety Follow-up Visit [d]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**		
Week	**–4** [a]	**–**	**2**	**24**	**48**	**72**	**96**		
Study Day (window in days)	**–28**	**1 Baseline**	**15 (± 2)**	**169 (± 14)**	**337 (± 14)**	**505 (± 14)**	**673 (± 14)**		
Informed consent [e]	x								
Medical history and demographic data [f]	x								
Review inclusion and exclusion criteria	x	x							
Physical examination [g]	x	x	x	x	x	x	x	x	*x*
Height	x								
Weight	x								
Vital signs [h]	x	x	x	x	x	x	x	x	
Laboratory Assessments [i]									
Hematology, chemistry, urinalysis [j]	x	x [k]		x	x	x	x		
Pregnancy test [l]	x	x	x	x	x	x	x		*x*
Hepatitis screening [m]	x								
Hepatitis B virus DNA test [m]	x			x	x	x	x		
Immunoglobulin levels [n]	x			x	x	x	x		*x*
Lymphocyte subtypes [o]	x			x	x	x	x		*x*

	Screening	Treatment Period					End of Treatment/ Early Withdrawal Visit [b]	Unscheduled Visit *(due to relapse)* [c]	Safety Follow-up Visit [d]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**		
Week	**–4** [a]	**–**	**2**	**24**	**48**	**72**	**96**		
Study Day (window in days)	**–28**	**1 Baseline**	**15 (± 2)**	**169 (± 14)**	**337 (± 14)**	**505 (± 14)**	**673 (± 14)**		
EDSS score	x	x [k]		x	x	x	x	*x*	
Neurological examination [p]	x	x	x	x	x	x	x	*x*	x
Patient-Reported Outcome Assessments [q]		x		x	x	x	x		
Brain MRI [r]		x [s]		x	x		x [b]		
Recording of potential relapses		x	x	x	x	x	x	x	x
Adverse event assessment [t]		x	x	x	x	x	x	x	x
Concomitant treatment review		x	x	x	x	x	x	x	*x* [u]
Methylprednisolone premedication [v]		x	x	x	x	x			
Ocrelizumab administration [w]		x	x	x	x	x			

β-hCG = beta human chorionic gonadotropin; 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; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; QC = quality control.

[a] *The screening period will last up to 4 weeks, but it may be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons.*

[b] When a patient *discontinues* treatment, all assessments must be completed/obtained, except for MRI if done within *the past* 8 weeks unless clinically indicated.

[c] Additional assessments may be conducted, as determined by the investigator, in order to investigate adverse events.

[d] The Safety Follow-up Period will begin when the patient completes *the study* and *does* not continue with commercially available ocrelizumab, or discontinues from treatment early. *Patients will be assessed in Safety Follow-up 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. During the Safety Follow-up Period, patients who receive other B-cell targeted therapies will only be followed for an additional period of approximately 48 weeks from the start of the alternative MS treatment; they will not be entered into the prolonged B-cell monitoring period thereafter.*

[e] Written informed consent will be obtained from all patients during screening in order to be eligible for the study.

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

[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] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and temperature. Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone 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.

[i] *Needs to* be available prior to dosing (*to* be taken up to 14 days prior to dosing). *In rare cases in which the result is not assessable (e.g., indeterminate) or is 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.*

[j] 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*. Urinalysis *or urine dipstick* will *be used to assess kidney function*.

[k] If the screening assessments have been conducted/obtained *within* 14 days prior to dosing, *respective baseline assessments* do not need to be *repeated* prior to dosing.

[l] 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.

[m] All patients must have negative HBsAg result and negative HepCAb screening tests prior to enrollment in the study. If the 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.

[n] *Immunoglobulin* levels collected only *and stored for further analysis upon request.*

[o] *Whole-blood samples will be collected to determine the duration of B-cell depletion and recovery (CD19+) and T-cell counts (CD4+, CD8+).*

[p] 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* neurological *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.

[q] PRO assessments will consist of the following: Multiple Sclerosis Impact Scale 29 (MSIS-29), the Treatment Satisfaction Questionnaire for Medication (TSQM II), and the Treatment Satisfaction with Medicines Questionnaire (SATMED-Q). *Please note that all PROs are required to be administered prior to administration of study drug and prior to any other study assessment(s) to ensure the validity of the instruments is not compromised.*

[r] Should only be done at scheduled visits unless PML is suspected.

[s] *MRI has to be conducted before the baseline visit, and results must be available prior to treatment. Prior to initiation of treatment on Day 1/Baseline, a QC report for the baseline MRI scan must have been received from the centralized reading center confirming scan passed QC.*

[t] 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. After initiation of study drug, *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. Unrelated serious adverse events must be collected and reported during the study through the end of the Safety Follow-up period, which is at least 48 weeks after the last infusion but may be extended in patients whose B cells take longer to replete. Non-serious adverse events have to be reported until the end of the Safety Follow-up Period.*

[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. Prophylactic treatment with an analgesic/antipyretic (e.g., 1 g acetaminophen) and/or an IV or oral antihistamine (e.g., IV diphenhydramine 50 mg or equivalent dose of alternative) is strongly recommended 30–60 minutes prior to the start of ocrelizumab infusion to reduce the risk of IRRs.

[w] Dose 1 of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15). Subsequent doses will be administered as one 600-mg IV infusion every 24 weeks for a maximum of 4 doses.

Appendix 3
Data Handling Rules

Assessment of clinical relapse:

1. Check whether the following eCRF question is answered 'yes': "Did suspected MS relapse symptoms persist for > 24 hours and were not being attributable to confounding clinical factors? (e.g. fever, infection, injury, adverse reactions to concomitant medication"

2. Check whether the first EDSS assessment at a visit (unscheduled or scheduled) on or after the onset date of the relapse is increased by ≥ 0.5 steps from the previous EDSS; OR SELECTED FSS domains relevant to the relapse event (pyramidal, ambulation, cerebellar, brainstem, sensory, or converted visual) are increased by ≥ 2 points on one domain or ≥ 1 point on two or more domains. When deriving this step do the following:

    - Select the last EDSS/FSS score before each clinical relapse onset date
    - Select the first EDSS/FSS score on or after each clinical relapse onset date
    - Calculate the difference between the two scores above

3. Select clinical relapses where there is an increase of ≥ 0.5 in EDSS OR ≥2 on one appropriate FSS domain OR ≥ 1 on two or more appropriate FSS domains

For each relapse that satisfies the 3 criteria above, check if the following relapses are within 30 days (i.e., the onset dates are ≤ 30 days apart). If they are within 30 days, then the later relapses are not protocol-defined relapses

Additional data handling rules are specified throughout the document and in DAP Module 2.

Appendix 4
Programming Codes for Statistical Analyses

Kaplan-Meier method

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

Appendix 5
Reasons for Exclusion from the Per-Protocol Population

1. Select study inclusion criteria
   - Had more than 3 adequate prior DMTs (IC06)
   - No suboptimal response on the most recent adequately used DMT (IC07)
   - Suboptimal response while on last DMT that is less than 6 months (IC06)
   - Disease duration from first symptom of more than 12 years (Due to previous protocol versions has ≤10 years as inclusion criteria, deviation code includes a mixture of deviations of >10 years and >12 years of duration. Thus for this criteria, program on clinical data will be used to identify patients with deviation.)

2. Select study exclusion criteria
   - History of PPMS, PRMS, or SPMS (EC01)
   - Previous treatment with natalizumab within 12 months prior to screening unless failure was due to confirmed, persistent ADAs (EC22)
   - Systemic corticosteroid therapy within 4 weeks prior to screening (EC24)

Appendix 6
Statistical Analysis Plan for Shorter Infusion Substudy

Background

Ocrevus (ocrelizumab) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with primary progressive multiple sclerosis (PPMS) and relapsing multiple sclerosis (RMS). According to the currently approved U.S. label, ocrelizumab must be administered at a 600-mg dose through slow intravenous (IV) infusion. The first dose is given as two doses, separated by 14 days, and administered as two 300-mg infusions over the course of 2.5 hours, while subsequent doses are given as a single 600-mg infusion over 3.5 hours. This substudy will explore the effect of a shorter infusion of ocrelizumab on the rate and severity of infusion-related reactions (IRRs).

The most common safety events reported with ocrelizumab are IRRs. IRRs occur more frequently during the first infusion of the first dose. The majority of IRRs (>90% of patients reporting IRRs) were of mild to moderate intensity, and the intensity of IRRs decreased with subsequent dosing. The most frequently reported IRR symptoms during infusion in the ocrelizumab group were pruritus, rash, throat irritation, and flushing (33.0%, 29.2%, 29.8%, and 16.8% of patients with IRR, respectively) (see the Ocrelizumab Investigator's Brochure).

A Phase II, parallel-group, dose-finding trial (WA21493) evaluated ocrelizumab compared with placebo and Avonex (interferon-β1a) in patients with RRMS for up to 96 weeks. In this study, both the 600-mg and 1000-mg dose were administered over 4 cycles. After the first cycle, during which only the 600-mg dose was divided in half and given over a 15-day interval, subsequent cycles involved administration as a single, undivided dose. Doses were administered over approximately 240 minutes. The infusion schedule in this study shows that, both for the 600- and 1000-mg dose, approximately 400 mg of ocrelizumab were infused within 2 to 2.5 hours. However, in the remaining 1.5 to 2 hours of the infusion, only 200 mg remained to be infused for the lower dose, while in the 1000-mg dose, 600 mg were given within the same timeframe. Based on this infusion schedule, a dose/infusion rate/IRR relationship was not clearly observed.

The lack of dose/infusion rate/IRR relationship based on the current clinical data is supportive of the hypothesis that administration of ocrelizumab over a shorter infusion time should not pose a potential additional risk to patients in terms of increased risk of IRRs, but would help convenience of use and compliance for both patients and

healthcare practices. In addition, procedures are in place to further mitigate risk of IRR, such as a pre-treatment schedule and guidance around infusion adjustment, if required.

After the infusion, patients will be followed for safety, per the substudy schedule of activities, to monitor for any effects of the shorter administration.

Substudy Design

This is an open-label, non-randomized substudy to MN30035 designed to evaluate the safety and tolerability of ocrelizumab infused over a shorter time period than the approved administration rate. Patients who complete their Week 72 ocrelizumab infusion and do not experience any serious IRR (see Section protocol 5.2.2 for seriousness criteria) throughout the main study will be eligible to enroll in this optional substudy and receive one additional shorter infusion of ocrelizumab at the Week 96 visit.

Premedication in the substudy will be administered per the main study methods (protocol Section 4.3.3). Ocrelizumab will then be administered as a single 600-mg dose at a shorter infusion rate (i.e., over the course of approximately 2 hours instead of 3.5 hours) than in the main study.

Ocrelizumab infusion rate will be slowed and/or stopped if a patient experiences a Grade 3 or higher IRR or other serious adverse event.

Patients who received ocrelizumab at a shorter infusion rate at the Week 96 visit will return for a substudy follow-up visit approximately 30 days after treatment.

The end of the treatment period in the substudy is defined as the date when the last patient in the substudy completes the substudy follow-up visit (Week 100).

Protocol Synopsis

Refer to the main study protocol synopsis. For additional details, see the Schedule of Assessments in Appendix A and Rate of Shorter Infusion in Appendix B.

Outcome Measures

The primary objective of the substudy is to evaluate the rate and severity of IRRs of the ocrelizumab 600-mg infusion administered over the course of approximately 2 hours, instead of the currently approved duration of 3.5 hours, in patients with MS who have had prior treatment with ocrelizumab in study MN30035 (CHORDS), as measured by the rate and frequency of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) Grade 3 and 4 IRRs. Specifically, the safety outcome measures are listed below.

- Rate and frequency of Grade 3 or 4 IRRs with onset on or after the shorter ocrelizumab infusion at Week 96 and at the substudy follow-up
- Changes in physical findings and vital signs with onset on or after the shorter ocrelizumab infusion at Week 96 and at the substudy follow-up

Determination of Sample Size

This substudy will enroll approximately 100 patients from MN30035 who did not experience any serious IRR throughout the main study. Based on the sample size of 100 patients used for analysis, the 95% CIs for some assumed Grade 3 or 4 IRRs are provided in Table 1.

Table 1: Determination of Substudy Sample Size

Number of Patients with Grade 3 or 4 IRRs	Grade 3 or 4 IRRs (%) (N=100)	95% CIs for Grade 3 or 4 IRRs (%)
1	1.00	(0.03, 5.45)
2	2.00	(0.24, 7.04)
3	3.00	(0.62, 8.52)
4	4.00	(1.10, 9.93)
5	5.00	(1.64, 11.28)
6	6.00	(2.23, 12.60)
7	7.00	(2.86, 13.89)

The 95% CIs for the IRR (%) are calculated based on the Clopper and Pearson method.

Analysis Timing

The final analysis will be conducted when all patients enrolled in the substudy have received the shorter infusion and completed the 30-day safety follow-up assessments. Interim look for safety monitoring purpose can be conducted when deemed necessary.

Study Conduct

Randomization Issues

Not applicable.

Statistical Methods

Safety analyses will include all patients who received any dose of study treatment through shorter infusion in the substudy.

Safety will be summarized using descriptive statistics. Continuous variables will be summarized using n (sample size), mean, standard deviation, median, minimum, and maximum. Frequency distributions (patient counts and associated percentages) will be used to summarize categorical variables. When applicable, 95% confidence intervals (CIs) will be provided for the mean and proportion. The Clopper and Pearson method will be used to calculate exact CIs for proportion when applicable.

Analysis of Study Conduct

Patient disposition including the number of patients enrolled, discontinued, and completed the shorter infusion substudy will be summarized. Reasons for treatment and substudy discontinuations will also be summarized. Major protocol deviations that happened during the substudy period will also be summarized when applicable.

Demographics and Baseline Characteristics

Patients' demographics, neurological examination, MS disease history (e.g., duration since MS first symptom, duration since MS diagnosis) at enrollment of the main study and previous DMTs before receiving any ocrelizumab in the main study will be summarized.

Safety Analyses

Safety analyses of the substudy will include all patients who enrolled into the substudy and received >0 dose of the Week 96 shorter infusion.

Summary of IRRs

The number and proportion of patients in the substudy who experienced Grade 3 or 4 IRRs with onset on or after the shorter infusion (including the safety follow-up period) will be summarized with the associated 95% exact confidence interval. The 2-sided 95% exact confidence interval will be calculated using the Clopper and Pearson method.

The incidence rate and the 2-sided 95% exact confidence interval will also be calculated for all Grade 1-4 IRRs.

The number and proportion of patients in the substudy who experienced local IRR and systemic IRR will also be summarized with 95% exact confidence interval.

Listings of Grade 3 or 4 IRRs, and IRRs that led to interruption of the shorter infusion or treatment withdrawal will be provided, if applicable, on the symptom of the IRR, CTCAE grade, infusion rate at the onset of IRR, action taken on ocrelizumab administration following the IRR, and the history of IRR events during the long infusion study period (e.g., highest CTCAE grade, frequency)

Adverse Events

All adverse events occurring on or after the shorter infusion (including the safety follow-up period) will be coded, summarized by NCI CTCAE v4.0 grade, and tabulated by body system and Preferred Term for individual adverse events within each body system. All adverse events, Grade 3 to 5 adverse events, serious adverse events, adverse events leading to treatment discontinuation, time to withdrawal from the study due to an adverse event, adverse events leading to infusion adjustment, and treatment-related adverse events will be summarized. In addition, all serious adverse events and deaths will be listed if applicable.

Exposure of Study Medication

Ocrelizumab exposure will be summarized including duration of the shorter-infusion drug administration, actual volume and dosage of ocrelizumab administered.

Number and percentage of patients who experienced shorter infusion interventions (slowing, interruption or stopping) will be summarized.

Duration of the shorter infusion will also be summarized for patients who experienced each type of interventions and for patients who did not experience any intervention separately.

Laboratory Data

A summary of the number and percentage of patients with abnormal laboratory outcomes will be produced for each laboratory parameter.

Vital Signs

Changes in physical findings and vital signs with onset on or after the shorter infusion at Week 96 and at the substudy follow-up visit will be summarized.

Missing Data

Missing and partial dates for AEs will be handled according to Roche STREAM algorithm.

For partial or missing shorter infusion administration start/end time, data will not be imputed considering the potential impact of imputed time points on the duration of the shorter infusion (about 2 hours).

Missing assessments for continuous variables, such as physical examinations and vital signs, will not be imputed.

Interim Analyses

No formal interim analysis is planned for the substudy. Interim looks may be performed for safety monitoring or publication purpose.

Scope of Planned Analyses

The final substudy analysis will include all patients and all data collected during the shorter infusion study period (including Week 96 and the safety follow up period). Specific list of planned outputs will be available in DAP Module 2.

Appendix A
Schedule of Assessments

	Week 96 Treatment Visit (±14 days)	Substudy Follow-up Visit (30±14 days later) [a]
Informed consent [b]	x	
Review inclusion and exclusion criteria	x	
Physical examination [c]	x	x
Weight	x	
Vital signs [d]	x	x
Brain MRI [e]	x	
Pregnancy test [f]	x	
Adverse event assessment [g]	x	x
Concomitant treatment review	x	x [h]
Methylprednisolone and antihistamine premedication [i]	x	
Ocrelizumab administration	x	

eCRF=electronic case report form; IRR=infusion-related reaction; IV=intravenous; MRI=magnetic resonance imaging; PML=progressive multifocal leukoencephalopathy.

[a] Conducted 30 days after the shorter infusion with ocrelizumab.

[b] Written informed consent will be obtained from all patients in order to be eligible for the study and prior to any study procedures.

[c] A limited physical examination may be conducted. Any abnormality identified should be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate

[d] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and temperature. Vital signs should be taken approximately 45 minutes prior to the premedication methylprednisolone infusion. In addition, vital signs should be obtained prior to the ocrelizumab infusion then approximately every 15 minutes for the first hour, followed by approximately every 30 minutes until 1 hour after the end of the infusion.

[e] Should only be done if PML is suspected, and should not be done in addition to an MRI at Week 96 conducted in the main study. If needed, should be done pre-dose.

[f] Pregnancy test should not be done in addition to the pregnancy test at Week 96 conducted in the main study. If needed, should be done pre-dose.

[g] 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. After initiation of study drug, related serious adverse events must be collected and reported regardless of the time elapsed from the study drug administration, even if the substudy has been closed. Unrelated serious adverse events must be collected and reported during the substudy and substudy follow-up. Non-serious adverse events have to be reported until the end of substudy follow-up.

[h] Medications used after treatment discontinuation should be recorded during substudy follow-up.

[i] All patients must receive prophylactic treatment with 100 mg methylprednisolone (or equivalent), to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and with an antihistaminic drug (e.g., diphenhydramine) approximately 30–60 minutes before each infusion of ocrelizumab. Prophylactic treatment with an analgesic/antipyretic

(e.g., 1 g acetaminophen) is strongly recommended 30–60 minutes prior to the start of ocrelizumab infusion to reduce the risk of IRRs.

Appendix B
Infusion rates for 600-mg ocrelizumab Shorter Dose

Time (min)	Infusion rate (mL/hr)	Infusion rate (mg/hr)	Max Dose per Interval (mg)	Cumulative Dose (mg)
0–15	100	120	30	30
15–30	200	240	60	90
30–60	250	300	150	240
60–90	300	360	180	420
90–120	300	360	180	600

Infusion time: 120 min.

Preparation per U.S. label: 600 mg ocrelizumab/500 mL normal saline toward a drug concentration of approximately 1.2 mg/mL.

Statistical Analysis Plan (SAP) Initial /Final Sign-Off Sheet

Study title:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE HAD A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**		
Protocol #:	MN30035	**SAP Version:**	**2.0**
Authors: [redacted]			
Study Statistician: [redacted]		**Signature**	**Date**
Reviewers:			
Study Medical Director: [redacted]		**Signature**	**Date**
Study Statistical Programmer: [redacted]		**Signature**	**Date**
[redacted]: [redacted]		**Signature**	**Date**
Approvers:			
[redacted]: [redacted]		**Signature**	**Date**

* The Biostatistics approver has ensured that key team members have been involved, contributed and reviewed the content of the List of Planned Outputs as described in the SAP Module guideline.