PROTOCOL

STUDY TITLE:	Evaluating the Tolerability and Safety Profile of Switching from Rituximab to Ocrelizumab: A Real World Evaluation of Patients with Relapsing Forms of Multiple Sclerosis
STUDY DRUG:	OCREVUS (ocrelizumab)
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1. INTRODUCTION

Studies of rituximab, a chimeric monoclonal antibody against CD20 have shown that B-cell depletion is of significant clinical benefit as a treatment of relapsing forms of multiple sclerosis (MS).[1] Ocrelizumab is a humanized monoclonal antibody that targets CD20 and selectively depletes CD20 expressing cells, while preserving the capacity for B cell reconstitution. When compared with rituximab, ocrelizumab is associated with increased antibody-dependent cell-mediated cytotoxic effects, and reduced complement-dependent cytotoxic effects in vitro.[2] By increasing antibody-dependent cell mediated cytotoxic effects, ocrelizumab might modulate tissue-dependent mechanisms of pathogenic response more effectively compared to rituximab. As a humanized molecule, ocrelizumab is expected to be less immunogenic with repeated infusions and might thus present a more favorable safety profile when compared to rituximab.[2]

Despite rituximab's current off label use in the treatment of MS, currently there is only data available from phase 2 trials and open label trials. The HERMES group conducted a phase 2, double-blind, 48-week trial involving 104 patients with relapsing forms of MS; 69 patients received 1000 mg of intravenous rituximab and 35 patients received placebo on days 1 and 15.[3] A significantly higher number of patients in the rituximab group (78.3%) versus the placebo group (40.0%) had an infusion related reaction (IRR) events within 24 hours after the first infusion. Within 24 hours after the second infusion, fewer patients in the rituximab group (20.3%) than in the placebo group (40%) had similar events. A majority of the rituximab group with IRR events (92.6%) were classified as mild to moderate (grade 1 or 2) in severity.

Safety data from the Investigators Brochure on the OPERA I and II phase 3 trials comparing ocrelizumab to interferon β-1a on relapsing MS patients showed that IRRs were the most common adverse events experienced by patients treated with 600 mg of ocrelizumab.[4] The percentage of patients experiencing IRRs was higher in the ocrelizumab group (relapsing forms of MS: 34.3%; primary progressive forms of MS 39.9%) compared with the interferon β-1a (active control) group who received placebo infusions (relapsing forms of MS: 9.7%; primary progressive forms of MS: 25.5%). The rate of IRRs was highest during the first infusion or Dose 1 (27.5% on Day 1; 4.71% on Day 15 of Dose 1) and decreased over time (13.7%; 9.6% and 7.8% following Dose 2, 3, and 4 respectively) for the ocrelizumab treated group. Comparatively, interferon β-1a users experienced 6.5% of IRRs on Day 1, 2.58% on Day 15, $\leq$ 2.00% after doses 2, 3 and 4 respectively. The reported IRRs were primarily mild-to-moderate in severity (Grades 1 and 2). Serious IRRs occurred in 0.1% and 1.0% respectively of relapsing and progressive patients and treated with ocrelizumab.

Clinical data describing the efficacy and tolerability profile of rituximab and ocrelizumab has utilized populations with different prior treatment characteristics. In the phase 2 HERMES trials, a majority (78.5%) of rituximab patients had been **previously been treated** with a disease modifying therapy in the last 2 years.[3] In contrast, the OPERA I and II phase 3 clinical trials, a majority of ocrelizumab

patients (72.9% in OPERA I and 73.8% in OPERA II) represented a **treatment naïve population**.[4] Examining IRRs in patients who have switched from rituximab to ocrelizumab versus those continuing on rituximab will evaluate the magnitude of the IRRs and subsequent tolerability of ocrelizumab in a real world population of MS patients previously been exposed to rituximab.

Earlier concepts of MS disease pathology have suggested that pathogenic T cells are sufficient for the full expression of MS. However, it is now evident that full autoimmune B cells and humoral immune mechanisms also play key roles. [5] Ocrelizumab is a humanized monoclonal antibody that targets CD20 and selectively depleted CD-20 expressing B cells. CD20 is a B cell surface molecule that is expressed on pre B cells and mature B cells, but not expressed earlier in the development of B cells or on mature plasma cells. In all three ocrelizumab studies (with relapsing and progressive populations), treatment with 600 mg of ocrelizumab led to rapid and complete depletion of circulating $CD19^+$ B cells within 14 days post treatment. [4] B cell depletion was sustained throughout treatment period. The median time to repletion of B cells was 72 weeks (range 27-175 weeks). We hypothesize that in switching rituximab treated patients to ocrelizumab, the proportion of patients with B cell depletion (CD19+ and CD20+$\leq$ 1%) 6 months after the first and third infusion of ocrelizumab will be the same as the baseline assessment which will be 6 months after the last dose of rituximab and similar to findings in OPERA I and II.

Immunogenicity results from the OPERA I and II trials examined the number of patients who had treatment induced anti-drug antibodies (ADA) to ocrelizumab. [4] Of the 807 patients who received ocrelizumab and had an ADA assay from a post baseline sample during the controlled treatment period, 3 patients (0.4%) showed treatment induced ADA to ocrelizumab. Of these, 1 patient tested positive for neutralizing antibodies (NAB) to ocrelizumab. During the open label extension phase, the prevalence of ADA continued to remain low with post baseline incidence of 1.9% (2/103 with treatment induced ADA). Currently there is little evidence examining the prevalence of treatment induced ADAs to both rituximab and ocrelizumab in patients that switch from the former to the latter in comparison to continuing rituximab patients. Therefore, we will perform assays to detect ADAs to both rituximab and ocrelizumab in all patients switching from rituximab to ocrelizumab at Day 1, 6 months and between 12 and 18 months on ocrelizumab.

Finally, IRRs have been hypothesized to be a reaction by autoantibodies to the treatment drug or possibly from the release of cytokines from CD20 expressing cells as they are destroyed by ocrelizumab causing a “cytokine storm”. Understanding this process may lead to mechanisms that may aid in ameliorating these infusion reactions. If they are associated with ADA, then it might be possible to predictively premedicate these patients only. Alternatively, if they are associated with cytokine release, it may be possible to eliminate premedication in patients who are already CD20+cell depleted in subsequent infusions. Therefore, we will assay the profile of certain cytokines in the serum 4 hours after start of ocrelizumab infusion.

Since ocrelizumab has entered the market, third party payers within and outside the US have required that the FDA or EMA approved versions of anti-CD20 monoclonal antibodies be used in the treatment of MS, namely ocrelizumab. Currently, we estimate several thousand MS patients in the US and Sweden are taking rituximab currently. Thus, it will be important to demonstrate that switching from a chimeric anti-CD20 to a more fully humanized anti-CD20 does not lead to unexpected infusion reactions and does not increase the probability of development of anti-drug antibodies.

The Rocky Mountain MS Center (RMMSC) at the University of Colorado Anschutz Medical Campus prescribed rituximab infusions for 533 MS patients in the last 12 months, of which 323 patients received their infusion at the University of Colorado Hospital's Outpatient Infusion Center between September, 2015-March, 2016. The RMMSC is one of the few sites nationwide with large numbers of MS patients treated with rituximab. On March 28, 2017, Ocrevus (ocrelizumab) was approved by the FDA for the treatment of primary progressive and relapsing multiple sclerosis. With the approval of ocrelizumab, current rituximab users are being counselled by their MS providers at RMMSC to consider switching to ocrelizumab it it is the only anti-CD20 MAB covered by their insurance.

2. OBJECTIVES

2.1 Primary Objectives

Primary objective: Our primary objective is to assess the frequency and severity of IRRs in MS patients with sustained use rituximab ($\geq$ 2 infusions) at least six months apart who switch to ocrelizumab **(switching group)**. IRRs will be compared to: a) patients continuing to receive rituximab **(comparator group)** at each infusion cycle**,** and b) with rates observed in the OPERA I and II randomized clinical trials after the first and second infusion of ocrelizumab. Grading criteria for IRR will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institutes and utilized in the OPERA I and II trials.[6] We will also compare the rates of IRRs between the first, second and third dose of ocrelizumab. In addition, patient reported outcomes of their experience with IRRs will also be captured at all infusions of ocrelizumab..

2.2 Secondary Objectives

Secondary Objective: Our secondary objective is to assess the impact of switching from rituximab to ocrelizumab **(only in the switching group)** on the incidence and prevalence of anti-drug antibodies to ocrelizumab. The presence of anti-drug binding antibodies will be assessed prior to the first and third ocrelizumab infusion and six to twelve months after the last ocrelizumab infusion. The serum drawn before the first infusion of ocrelizumab will be the baseline comparator since these patients will only have been exposed to at least two rituximab infusions over 6 months with no prior exposure to ocrelizumab. This means we will have 100 serum samples prior to ocrelizumab exposure and 200 after ocrelizumab exposure. These assays will be performed by PPD Bio A

Laboratories (in Richmond, VA) who will assess the anti-drug antibodies to ocrelizumab", and "QPS (Netherlands) who will assess the anti-drug antibodies to rituximab as a single batch once all samples have been collected and cryopreserved.

Other secondary objectives that will be assessed in **the switching group** only include the following:

a. We will assess the percent of ocrelizumab treated patients that exhibit early recovery of CD19+ and/or CD20+B cells (>1%) prior to each ocrelizumab infusion and at month 12 or 18 which is 12 or 18 months following the first infusion of ocrelizumab. We will compare this to the percent of patients with evidence of early recovery from rituximab as assessed by the baseline B cell panel. Our test will also identify CD19 antigen expression to confirm depeletion since presence of anti-CD 20 MAB in patients blood may confound the CD-20 expression assay.

b. We will assess cytokines to evaluate for possible contribution of a cytokine storm to infusion reactions. Cytokines will be assessed using the MesoScale platform. These blood samples will be collected before the start of each ocrelizumab infusion and following infusion completion. Blood samples will also be collected during a moderate or serious IRR.

c. We will describe all adverse events and serious adverse events in addition to IRRs (for example infections) as described in the investigator's brochure.

3. STUDY DESIGN

3.1 Description of the Study

This is a prospective *between and within group* observational study to determine differences in tolerability, immunogenicity and safety related outcomes for MS patients who have been administered at least two infusions of rituximab, with the last dose of rituximab within 12 months of screening and are willing to be switched to ocrelizumab, compared to patients who are continuing on rituximab as a comparison cohort from the clinic population treated as part of routine clinical care in our program.

The comparator arm is an observational arm only. In addition to prospective data collection, we will collect infusion-related reaction data retrospectively for infusions done after August 1, 2016 (when we began collecting infusion reactions in a standardized way as part of standard of care at the infusion center).

Retrospective data will be collected only after consent is obtained.

In a prospective evaluation with patients at RMMSC who are currently on sustained rituximab treatment for their MS, we will examine the frequency and

severity of IRRs for 100 patients who switch to ocrelizumab **(switching group)** compared to 200 patients continuing rituximab as our primary outcome **(comparator group).** Our secondary outcome is to examine anti-drug antibody formation post switching from rituximab to ocrelizumab **(switching group)**. Comparisons for the both outcomes will also be made to findings from the OPERA I and II randomized clinical trials. Other exploratory outcomes including the measurement of B cell reconstitution, cytokine reactions and adverse event profiles will also be examined.

For patients who are switching to ocrelizumab, the first dose of ocrelizumab will be a split dose of 300 mg on day 1 and day 15 followed by 600 mg, six months later as approved by the FDA. The timing of 12 month dose may be delayed due to vagaries in the approval of biologics by third payors. Therefore, we will include data from patients at the T3 visit between the month 12 and 18 after starting ocrelizumab. Standard of care rituximab doses are 1000 mg given as first dose followed by 500mg (or 1000 mg if evidence of early B cell recovery) every 6 months thereafter. Study patients will be current patients of the RMMSC who meet the inclusion criteria and are currently receiving rituximab infusions from the University of Colorado Hospital's Outpatient Infusion Center. Analysis of IRRs will be conducted by the research team at RMMSC. Anti-drug antibody analysis will be conducted by two external vendors: PPD Bio A Laboratories, Richmond, VA will conduct the anti-drug antibodies assays for ocrelizumab, QPS Netherlands, Netherlands will conduct the anti-drug antibodies assays for rituximab using cryopreserved blood samples sent by the RMMSC research team as a single batch at the end of the study. Cytokine analysis will be conducted by personnel at the biobank repository at RMMSC. Study duration, including the recruitment (estimated to take 6 months), data analysis and manuscript development is anticipated to be 24 months.

The study design is represented in **Figure 1** below and described in further detail in section 4.5.1

3.2 Rationale for Study Design

Ocrelizumab and rituximab are among the most effective disease modifying therapies studied to date. Also, their safety profile to date (in terms of serious adverse events) is better than the other highly effective therapies including natalizumab, fingolimod, alemtuzumab, daclizumab and dimethyl fumurate. Several centers including the RRMSC and the Swedish Coalition of MS Clinics have large MS populations on rituximab, some for more than 6 years. However, rituximab does not have a patient assistance program, will remain off label for MS and will have significant uncertainty about access for the seeable future. Also, Ocrelizumab has been positioned to possibly be superior to rituximab in terms of IRRs, ADA and efficiency of B cell depletion. Although, these statements have not been proved, they will be influential to some MS patients, rituximab prescribers and third party payers. Thus a significant amount of

switching from rituximab to ocrelizumab is likely to occur. We know of no data describing the consequence of such switching in terms of IRRs, formation of ADAs and efficiency of B cell depletion. The proposed study has good power to address these 3 issues. It is not powered to look at any efficacy outcomes and none are included. We will monitor for safety per standard operating procedures for our study team.

3.3 Outcome Measures

3.3.1. Primary Outcome Measure

Primary endpoint:

a. Primary endpoint: The primary end point will be proportion of infusions with ≥ 1 IRR between the switching and comparator groups.

b. Secondary IRR assessments:
   a. We will also report the difference in the total number of IRRs after each infusion of ocrelizumab in the switching group compared to similar rituximab infusions in the comparator group.

   b. The difference in proportion of patients with ≥ 1 IRR across any of their infusions between the switching and comparator groups

   c. We will also compare the proportion of patients with an IRR following day 1 infusion versus the proportion of patients with an IRR at day 15 and month 6 infusions of ocrelizumab in the switching group.

   d. The severity of IRRs will be assessed following each infusion of ocrelizumab in the switching and comparator group using the National Cancer Institute's Common Terminology for Adverse Events Scale.[6] The frequency of each severity grade of IRR will be compared in a similar fashion.

Nursing staff at the University of Colorado's Outpatient Infusion Center will be responsible for classifying the severity of an IRR for each patient at the end of every ocrelizumab and rituximab infusion using the scale below. Nursing staff will be asked to record the highest grade of an IRR that they observed or intervened upon for each patient after completion of their infusion.

Severity of IRR:

Grade 0: No infusion reaction

Grade 1: Mild reaction (transient flushing or rash drug fever < 38 degrees C); infusion interruption not indicated; intervention not indicated

Grade 2: Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for 24 hours.

Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death

3.3.2 Secondary Outcome Measures

a. Anti-drug antibodies (ADAs): We will measure the number of patients who have treatment induced ADAs against rituximab and ocrelizumab prior to every ocrelizumab infusion (T_0, T_1, T_2) and at the research termination visit (T_3=between month 12 and 18) in **ONLY** the switching group. This analysis will be performed by PPD Bio A Laboratories (in Richmond, VA) who will assess the anti-drug antibodies to ocrelizumab", and "QPS (Netherlands) who will assess the anti-drug antibodies to rituximab a single batch at end of study for the switching group.

b. Treatment efficiency: We will be measure B cell depletion before each ocrelizumab infusion (T_0, T_1 and T_2), by the clinical laboratories (T cell and B cell panel) at the University of Colorado Hospital. We will measure the proportion of patients who are B cell depleted (CD-19+ and CD-20+) by the time of the next infusion and 6 to 12 months after the last infusion in the switching group.

c. Cytokine profile: To better characterize infusion reactions and evaluate the contribution by either hypersensitivity reactions to ocrelizumab directly and/or by release of cytokines from dyeing CD20 positive cells, serum levels of cytokines will be evaluated. Cytokines will be measured using the MesoScale platform before the start of each ocrelizumab infusion, and after the infusion is completed (T_0,T_1,T_2,T_3). In addition, blood samples will be collected for those who experience a moderate to severe IRR to further examine cytokine profiles during an IRR. Plasma samples will be analyzed using the V-PLEX Human Biomarker 40-Plex Kit which assays for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, GM-CSF, IL-5, IL-16, IL-7, IL-12/IL-23p40, IL-1α, VEGF-A, IL-17A, IL-15, TNF-β, IL-8 (HA), MCP-1, MCP-4, Eotaxin, IP-10, MDC, Eotaxin-3, TARC, MIP-1α, MIP-1β, VEGF-C, VEGF-D, Tie-2, Flt-1/VEGFR-1, PlGF, FGF (basic), SAA, CRP, VCAM-1, ICAM-1 per manufacturer's recommendation on a MesoScale SECTOR Imager 2400. This array of cytokines will provide information on the levels of cytokines being released during the infusion to determine if they are limited to those released by B cells. Patients will be categorized as either not having had an IRR (Grade 0), having had a mild

reaction (Grades 1-2), or a moderate/severe reaction (Grades 3-5). These patient groups will also be evaluated for difference before and after their infusions for changes in each of the above cytokines. These groups of patients will also be evaluated for the presence of antibodies to ocrelizumab as described above.

d. Patient reported infusion tolerance: A short patient reported outcome scale describing the patient's experience to any IRR during the ocrelizumab infusion developed by the research team at RMMSC. will be administered by the study coordinators at the end of each infusion. Scale items will measure patient responses to their perception and experience of IRRs.

3.3.3 Ancillary Safety Outcome Measures

We will report all adverse and serious adverse events for both study groups as described in the investigators brochure guide.[4] In addition, we will run an immunoglobulin panel in the switching group as well.

3.4 Safety Plan

Patients will be evaluated at each study visit for the duration of their participation in the study (see Table 1 under section 4.5 for schedule of events conducted on the switching group; comparator group is standard of care). Patients will be interviewed by the study coordinator at each visit to determine additional safety issues**.** See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

3.5 Compliance with Laws and Regulations

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements. An investigator held IND has been granted (IND number 132705).

4. MATERIALS AND METHODS

4.1 Subjects

We plan to enroll 100 patients in the switching group and between 100 and 200 patients in the comparator group (to study 200 infusions) for a total of up to 200-300 patients which would provide adequate power (90%) for the study. To account for screen failures and withdrawals, we are seeking to enroll an additional 50 patients for a total of 250-350 patients. Patients are not confined to only one of the 2 groups. For example, data may be collected from a patient as part of the rituximab arm and then at a later point the patient decides to switch to ocrelizumab. This patient could then be consented into the switching group. Enrollment will occur over a 3-month period at RMMSC.. Dropouts in the switching group that occur prior to the 6 month infusion will be replaced. All patients will be included in the analyses (Intent to Treat Analysis).

4.1.1 Subject Selection

All subjects will be MS patients receiving care at the RMMSC at the University of Colorado Hospital

4.1.2 Inclusion Criteria

Switching group:

- Current active patient of RMMSC
- 18-65 years
- Diagnosis of relapsing forms of MS
- Completed **≥ two doses** of rituximab with the last dose having been administered:

  a) within 12 months of screening

  and

  b) at least 6 months prior to first planned infusion of study drug
- Are receiving their current infusions of rituximab at the University of Colorado Outpatient Infusion Center
- Have discussed the possibility of switching to ocrelizumab with their MS provider
- Screened for Hepatitis B and C and TB within 2 years of first dose of ocrelizumab
- A negative serum pregnancy test must be available for premenopausal women and for women <12 months after the onset of menopause, unless they have undergone surgical sterilization.
- Women of childbearing potential must agree to use a “highly effective”, hormonal form of contraception or two “effective” forms of non-hormonal contraception. Contraception must continue for the duration of study treatment and for at least three months after the last dose of study treatment
- Are able to complete patient reported outcomes developed as English written scales.
- Must be able and willing to give meaningful, written informed consent prior to participation in the trial, in accordance with local regulatory requirements

Comparator group:

- Current active patient of RMMSC

- 18-65 years
- Diagnosis of relapsing forms of MS
- Completed **≥ two doses** of rituximab with the last dose having been administered within 12 months of screening as standard of care
- Are receiving their current infusions of rituximab as standard of care at the University of Colorado Outpatient Infusion Center and will continue to do so
- Are willing to be followed for subsequent rituximab infusions during the study period as standard of care, and/or allow retrospective data collection on previous rituximab infusions
- Must be able and willing to give meaningful, written informed consent prior to participation in the trial, in accordance with local regulatory requirements

4.1.3 Exclusion Criteria

Both groups:

- Pregnant or lactating women
- Hypersensitivity to trial medications
- Hepatic Dysfunction (liver enzymes are 5 times greater than normal)
- History of Congestive Heart Failure
- Any history of a positive blood assay for Hepatitis B or C
- Any history of TB or a positive Quantiferon Gold Assay
- Concurrent use of immunosuppressant medications
- Any history of immunodeficiency or other medical condition increasing risk of anti-CD 20 therapy.
- Serious infection at the time of a scheduled study infusion.
- Any medical, psychiatric or other condition that could result in the patient not being able to give fully informed consent, or to comply with the protocol requirements as determined by the investigator

4.2 Method of Treatment Assignment

The study will not be a randomized trial. Patients will not be assigned to the switching group, but rather will be enrolled after a clinical decision has been made with their provider about whether they will continue on rituximab or switch

to ocrelizumab. The following steps will be taken to minimize potential biases in sample selection.

First, in an effort to impose some degree of similarity between the treatment groups, control patients will be matched, either 1:1 or 2:1 depending on the number of control patients, with switching patients on gender and age (+/- 2 years) at recruitment. The demographic information on switching patients will be scanned to find matches for the patients in the non-switching group.

Furthermore, screening of additional patients beyond the 200 required for enrollment in the non-switching group will be also conducted to ensure the best possible matches. Second, baseline statistics will be monitored as patients enter the study, and selection of patients may be modified in order to maintain relative balance between treatment groups (if necessary using measures of disease severity other than age and gender) if we are able to overenroll the number of non-switchers. Third, demographic variables and measures of baseline disease severity, including age, gender, MS disease duration, type of MS at baseline (first infusion in both study groups), along with discontinuations, will be recorded and compared between treatment groups.

All available observations will be used. For continuous variables (age, MS disease duration), by treatment group means, standard deviations, medians, and ranges will be recorded, and differences among treatment groups will tested for with either with T-test/ANOVA methods or Wilcoxon/Kruskal Wallis tests. For categorical variables (gender, type of MS, disability, discontinuations), frequencies and proportions will be presented, and differences among treatment groups will be tested for using chi-square/Fisher's exact test. Fourth, following these measures, if treatment confounding is found to still be an issue, regression or propensity score methods, with covariates such as age, MS disease duration, and baseline EDSS score will be used post hoc to minimize confounding.

Potential study patients will be identified from RMMSC electronic medical records (EPIC) using the study inclusion and exclusion criteria. Patients will be recruited by the study coordinator through the University of Colorado's Outpatient Infusion Center. Potential patients are already being identified through their MS providers at RMMSC with whom discussions about the possibility of switching to ocrelizumab are currently underway. Study participants who complete the observation phase of the study will be offered the ability to continue to receive ocrelizumab infusions provided for free by Genentech until ocrelizumab is approved and available to them through their health insurance plan. Once ocrelizumab is available by prescription they will receive priority for assistance through the Genentech/Roche Patient Assistance Program for Ocrelizumab for out of pocket expenses. Ocrelizumab will be provided through priority placement in Genentech's patient assistance program for those patients who are not able to receive insurance coverage for it.

MS patients included in this study will have made a decision with their provider to either stay on rituximab or to switch to ocrelizumab outside of this study. The decision to switch to ocrelizumab or to stay on rituximab will be made as part of

the clinical treatment process between the patient and his/her provider based on his/her disease severity and suitability for treatment among other factors. Therefore, patients are not randomized into either treatment arm. For the group that stays on rituximab, participation in this study is purely observational. For those patients in the rituximab arm who are deemed to be appropriate candidates for switching to ocrelizumab, the option to do so will be provided as standard of care under priority access and/or patient assistance programs (contingent on their individual health insurance status).

It is important to note that because the incidence of IRRs for infusions prior to enrollment are not collected prospectively for those continuing treatment with rituximab and because adverse events including IRRs will not be collected using the same methods for each treatment group following enrollment, interpretation of any difference in the incidence of these events will be limited.

4.3 Study Treatment

Ocrelizumab will be provided free of charge by Genentech. The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (C.F.R.), Part 312.57 and 312.62 and Genentech requirements. Study drug will be managed with in the UCH research pharmacy.

4.3.1 Dosage, Preparation, Administration and Storage

Ocrelizumab Formulation Packaging, and Handling

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

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

Ocrelizumab may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter. The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of up to 0.2 micrometer).

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

Dosage, Administration, and Compliance

Ocrelizumab 600 mg will be administered as 600 mg will be administered as one 600-mg IV infusions at a scheduled interval of every 24 weeks. The first dose of ocrelizumab will be a split dose of 300 mg on day 1 and day 15 followed by 600 mg every 6 months thereafter.

Standard of care rituximab doses are 1000 mg given as first dose followed by 500mg (or 1000 mg if evidence of early B cell recovery) every 6 months thereafter. However, The B cell depletion with rituximab can last up to two years in some patients with good efficacy demonstrated after a single dose in the HERMES study for up to a year.[3] Patients are often out of window due to difficulties in obtaining insurance approval within the 6 month time window. Therefore, we will include those patients that receive rituximab infusions within a 12 month window.

Although ocrelizumab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Ocrelizumab infusions should always be administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member. Each ocrelizumab infusion should be given as a slow IV infusion over approximately 150 minutes (2.5 hours) for the 300-mg dose. To reduce potential Infusion Related Reactions (IRRs), all patients will receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent IV steroid), administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion.

It is also strongly recommended that the infusion is accompanied by prophylactic treatment with an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) and/or an IV or oral antihistamine (such as IV diphenhydramine 50 mg or equivalent dose of alternative) 30 − 60 minutes prior to the start of an infusion to reduce potential IRRs. Patients administered a sedating antihistamine for the treatment or prevention of IRRs should be given appropriate warnings concerning drowsiness and potential impairment of ability to drive or operate machinery.

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

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

After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs intravenously, if necessary, in the event of a delayed reaction. If no adverse events occur during this period of time, the IV cannula may be removed and the patient may be discharged.
See the Ocrelizumab Investigator's Brochure for detailed instructions on drug preparation, storage, and administration.

4.3.2 Dosage Modification

Dose modification of ocrelizumab is not permitted.

4.3.3 Overdosage

There is no experience with overdosage in human clinical trials.

4.4 Concomitant and Excluded Therapy

e.g., Infusion protocol concomitant therapy: all patients will receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent IV steroid), administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion

Excluded medications are any significantly immunosuppressive medications or treatments (i.e., radiation therapy) as determined by the treating neurologist.

4.5 Study Assessments

Full protocol review and approval will be obtained from the University of Colorado's IRB board, known as the Colorado Multiple Institutional Review Board (COMIRB) including a scientific review from COMIRB's Scientific Advisory and Research Committee. Signed, IRB-approved informed consent will be obtained from patients prior to any assessments.

4.5.1 Assessments during Treatment

The following evaluations will be conducted during and post treatment:

<u>Study Visits and Procedures Summary</u>:

Study visits for the switching group include a) screening visit, b) first infusion of 300 mg of ocrelizumab (day 1 or T_0), c) 300 mg of ocrelizumab infusion on day 15 (T_1), d) 600 mg of ocrelizumab at 6 months (+/- 2 weeks) after day 1 (T_2) and, e) a research termination visit between month 12 and 18 - (+/- 2 weeks)(T3). In some cases, screening procedures may be performed on the first infusion day rather than as a separate visit. .The patient may continue on 600 mg of ocrelizumab or (if the patient prefers) 500mg rituximab at T_3, or 12 to 18 months after Day 1 (T_0). A month is defined as 28 days. Study visits for the comparator group include only standard of care infusion of rituximab, up to two infusions per patient, approximately 6 months apart. Research data on IRRs for the comparator group will be collected from the medical records.

A summary of all procedures for switching group is outlined under "Schedule of Events" in **Table 1** below. During the screening visit, patients will be consented for the study and receive both a medical and full neurological exam. Verification of their hepatitis B and C status including testing will be conducted if a patient has not been tested in the last two years. MS disease history and demographic information will also be collected. Patients will also receive an EDSS exam and take an online version of the PDDS (done as standard of care- on an IPad).

The Expanded Disability Status Scale (EDSS) is a commonly used assessment that allows clinicians to objectively measure changes in the disability status of MS patients using unbiased clinical raters.[7] The **EDSS** provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The range of main categories include (0) = *normal neurologic exam*; to (5) = *ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities*; to (10) = *death due to MS*. In addition, it also provides seven subscale measurements called Functional System (FS) scores.

The Patient-Determined Disease Steps (PDDS) is a PRO version of the clinician-reported EDSS which hones the stages of cane use and thus is more responsive to mid-range disability changes.[8] This tool asks the patient to characterize level of disability into one of nine steps (0=normal, 1=mild disability, 2=moderate disability, 3=gait disability, 4=early cane, 5=late cane, 6=bilateral support, 7=wheelchair scooter, 8=bedridden). The PDDS will be used to characterize (and to control for) disability in both study groups at all study time points.

Following the screening visit, patients in the switching group will be scheduled for their first infusion of ocrelizumab at their next regularly scheduled infusion date (no more than six months after their last rituximab infusion). Study infusion cycle T_1 will have an acceptable window of +/- 4 days since it is given 15 days apart, while infusion cycles T_2 and T_3 will have an acceptable window of +/- 14 days since it is administered 6 months later.

Prior to the start of the infusion, blood samples will be collected that will be utilized for several purposes. At infusion cycle time points, T_0, T_2 and T_3 blood samples for the following assessments will be drawn. First, patients will be

monitored through standard of care assessments for this population to include a complete metabolic panel (CMP) and complete blood counts (CBC) with differential. Second, their immune profile will be evaluated through an immunoglobulin panel and analyzing T and B cell subsets using flow cytometry by the clinical laboratories at the University of Colorado Hospital. Samples for the cytokine analysis will be drawn on a similar schedule. For the cytokine analysis, blood samples will be collected prior to and after each infusion in CPT tubes Because moderate to severe infusions reactions can delay infusions, we will plan to add an additional blood draw when these reactions are detected to keep timing of the blood draws more consistent and to capture any possible peak in cytokine levels during these reactions should they be occurring. Plasma will be derived by centrifuging at 1500g for 15 min and then will be aliquoted and stored at -80C. Cells will be reconstituted in freezing media (20% fetal bovine serum, 10% DMSO) and stored at -80C for further analysis. Additionally, plasma samples will be analyzed by MesoScale SECTOR Imager 2400 for evaluation of cytokine levels. Blood draws for the anti-drug antibody analysis will also be drawn at T_1 and sent to PPD Laboratories, Richmond, VA using cryopreserved blood samples as a single batch at the end of the study and analyzed for cytokine analysis.

Patients will receive 100 mg of methylprednisolone 30 minutes before administration of ocrelizumab at each infusion cycle (T_0-T_2). Following the infusion, nursing staff will record IRR using the National Cancer Institute's Common Terminology for Adverse Events Scale. Patient self-assessment of IRRs will also be captured. Adverse events will also be recorded as described in Section 5 by either the nursing staff or study coordinators. Finally, at the last research termination visit (T_3), only blood samples, AEs and concomitant medications will be collected from study patients. Concomitant medications include those used for the treatment for spasticity, depression, or fatigue and other prescription and non-prescription concomitant treatments that will be captured from the patient directly.

Patients will then receive ocrelizumab or rituximab, if they wish, as ongoing therapy. Ocrelizumab and infusion costs will be provided by Genentech until ocrelizumab is approved by the FDA and available to the patient through their insurance plan.

For the comparator group, they may be approached to gauge interest in the study via telephone. If they are interested, the consent can be sent to them. These patients will be given the following options: 1) complete consent process orally over the phone with coordinator (and a treating physician if patient desires), sign and date the consent form and send back to coordinator via mail, fax, or email, 2) complete consent process with coordinator (and a treating physician if patient desires) in person at their next scheduled rituximab infusion. In either case, data collection will not begin until written consent is obtained. Following each rituximab infusion, nursing staff will record IRR using scales as part of standard care.

As required by the University of Colorado's Institutional Review Board, an independent Data and Safety Monitoring Board (DSMB) will meet at initiation of the study and every 6 months thereafter until the end of the study.

Table 1. Schedule of Events (for switching group)

Data Collection Event	Screening Visit[a]	Day 1 (T_0) 300 mg of OCR[a]	Day 15 (T_1) 300 mg of OCR)	6 months (T_2) (600 mg of OCR)	12 -18 months research termination visit (T_3)
Informed Consent	X				
Medical Exam	X				
Physical Exam	X				
Demographics and MS Disease History	X				
Concomitant Meds	X	X	X	X	X*
Vital Signs		X	X	X	X
Hepatitis B and C evaluation confirmed	X				
EDSS	X				
PDDS	X				X*
Pre-infusion blood draw:					
Lab: CBC, CMP		X		X	X
Lab: B and T cell subsets by flow cytometry		X		X	X
Lab: immunoglobulin panel		X		X	X
Lab: Binding antibodies		X		X	X
Pre and post-infusion blood draw and during moderate/severe reactions:					
Lab: Cytokine levels		X	X	X	
Administration of Ocrelizumab		X	X	X	
Pre-medication of 100 mg of methylprednisolone		X	X	X	
Nurses record IRRs		X	X	X	
Nurses/Study Coordinator record AE		X	X	X	X*
Patient self-report of IRRs		X	X	X	

* may be completed over the phone

4.5.2. Follow-Up Assessments

Refer to 4.5.1. For comparator group, follow-up assessments are performed per standard of care and IRR information will be collected from the medical records.

4.6 Discontinuation of Protocol-Specified Therapy

Protocol-specified therapy may be discontinued for any of the following reasons:

- Unacceptable toxicity
- Patient election to discontinue therapy (for any reason)
- Physician's judgment

4.7 Subject Discontinuation

Patients will be withdrawn from the study if they get pregnant during the treatment period or withdraw consent. If patients discontinue ocrelizumab for any reason they will be asked to continue the study assessments per protocol until end of study for safety assessments. Patients in the switching group who withdraw from the study before their first infusion at 6 months will be replaced.

The reason for premature discontinuation of a subject will be recorded on the Case Report Form.

4.8 Study Discontinuation

Genentech Study Center, and the Principal Investigator has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording are inaccurate or incomplete
- Study protocol not followed

4.9 STATISTICAL METHODS

4.9.1 Analysis of the Conduct of the Study

The study will consist of a convenience sample of eligible MS patients at the Rocky Mountain MS Center who are currently active patients and are taking rituximab for the treatment of their MS.

We will keep track of the number enrolled in each study group and log any protocol deviations, lack of compliance, no shows or drop outs. Frequencies and proportions will be presented and compared between treatment groups.

4.9.2. Analysis of Treatment Group Comparability

As described in section 4.2, demographic variables and measures of baseline disease severity, including age, gender, MS disease duration, baseline PDDS, type of MS at baseline (first infusion in both study groups), along with discontinuations, will be recorded and compared between treatment groups. All available observations will be used. For continuous variables (age, MS disease duration), by treatment group means, standard deviations, medians, and ranges will be recorded, and differences among treatment groups will tested for with either with T-test/ANOVA methods or Wilcoxon/Kruskal Wallis tests. For categorical variables (gender, type of MS, disability, discontinuations), frequencies and proportions will be presented, and differences among treatment groups will be tested for using chi-square/Fisher's exact test.

4.9.3 Efficacy Analysis –Not Applicable

a. Primary Endpoint: NA

b. Secondary Endpoints: NA

4.9.4 Safety Analysis

The default analysis will be available case for all eligible participants on an intent to treat basis. Alpha = 0.05 for all tests. As in the OPERA I and II randomized clinical trials, the primary and secondary end points will be descriptively presented. Frequencies and percentages for the severity of IRR grades (Grades 0-5) will be presented for both study groups following each infusion time point and overall between groups. 95% confidence intervals for the proportions will be calculated. Differences in the distribution of IRR severity grades between independent samples (i.e. comparison between groups at a common time point) will be tested with the chi-square or Fisher's exact association test, and additionally with ordinal or multinomial logistic regression. If sample sizes are small among some levels of IRR severity grades, they may be collapsed or dichotomized (i.e. Grade 3 or higher, any reaction or no reaction, severe reaction or none as examples) and methods described for binary outcomes under secondary endpoints will be utilized. Dichotomization may be used to make analysis and presentation of results more manageable as well.

The primary endpoint will be the proportion of whether any IRR occurred (yes or no) per infusion cycle per patient in each study group. The secondary endpoints include the proportion per infusion per patient of severe infusion reaction (grade 3 or greater), the proportion of infusion reactions and severe infusion reaction per patient across all infusions, the proportion patients with anti-drug antibodies, and the proportion of patients with depleted B cells. The primary outcome, binary occurrence of IRR per infusion per patient, could be analyzed with logistic or relative risk models, with GEE (generalized estimating equations) and/or GLMM

(generalized linear mixed models) methods to incorporate correlation on repeated infusions on a patient. The same method will apply to other longitudinal binary outcomes. Poisson or negative binomial models with exposure terms could calculate rates of IRR per infusion per patient as a counting process. Similar methods will be used to compare IRR rates between the switching group and OPERA I and II phase 3 clinical trials. The total number of IRRs experienced in each patient, will be analyzed with Poisson or negative binomial models. Paired T tests will be used to assess differences in specific cytokine markers between pre and post infusion at each infusion cycle. Patient reported outcomes will also be reported descriptively. Frequencies and proportions will be reported for adverse and serious events and loss to follow up

As contingency methodology, exact tests and confidence intervals for measures of association between categorical variables can be utilized when necessary, if the sample sizes for some of the cells are small. Transforms or rank based methods, such as Wilcoxon sign rank, can be used in place of the T-test if deviation for normality is severe. Otherwise the T-test is a robust test of mean differences for medium to large sample sizes. If matching leads to good balance between the treatment groups on the demographic and disease variables, including age, MS disease duration, and baseline PDDS score, then confounding will not be an issue and the proposed unadjusted tests should be adequate. Alternatively, if the demographic and disease variables are not balanced, then regression or propensity score methods will be used to adjust for potential confounding. Sensitivity analysis comparing unadjusted and adjusted results will be used to determine the extent of the confounding effect. Adjustment for covariates can sometimes improve the precision of the estimated treatment difference by reducing random noise in the outcome.

Separate descriptive statistics will be presented for relapsing and progressive MS patients. Similar descriptive analysis will be conducted for subgroups according to age (in tertiles) and baseline disability (mild, moderate, severe) as measured by baseline PDDS score. However, the study is not powered for subgroup analyses and no inferences for subgroups or interactions are planned. As the sample is one of convenience, the study is generalizable to the extent patients at the Rocky Mountain MS center who are willing to participate are representative of MS patients.

With only one primary endpoint, adjustment for multiple comparisons will not be much of an issue. Secondary endpoints will be tested univariately. The study is not powered for multiple tests with control of the family-wise error rate. Bonferroni, iterative Bonferroni, false discovery rates, and, in some cases, protective overall tests could also be used if adjustment for multiple tests is desired.

All adverse events, lack of compliance, protocol violations, and drop outs will be logged, and frequencies and proportions will be presented. Safety will be assessed at each infusion.

4.9.5 Missing Data

Descriptive statistics will be run on missing data and checked for patterns. We anticipate few missing data issues other than possibly a few data points missing completely at random, as patients who enroll in the switching are choosing to receive their only course of MS treatment at no cost to them. Treatment is administered in clinic once every 24 weeks and is important to the patient, so patient compliance should not be much of an issue, unless they drop out of the study. Patients who miss a treatment will be followed up. Mixed models and GLMM (generalized linear mixed models) for longitudinal data can take into account missingness at random.

4.9.6 Determination of Sample Size

The sample size will be a convenience sample. It is anticipated a minimum of 100 patients will qualify for each cohort (200 total) resulting in studying 300 infusions with ocrelizumab and 200 infusions with rituximab. This is an observational study not designed to demonstrate superiority of ocrelizumab over rituximab in efficacy but instead indicate the magnitude of the relative tolerability and immunogenicity. The primary endpoint is the difference in the percentage of IRRs between the two study groups. In addition, both study groups will include treatment experienced patients on rituximab who have experienced a minimum of two infusions and either continue to stay on rituximab or switch to ocrelizumab.

To estimate study power with the proposed sample size of 100 infusions in each group, we conducted a chart review of 50 patients at the Rocky Mountain MS Center who are currently taking rituximab and examined their IRRs using the proposed IRR grading scale (see section 3.3.1) from Grade 0-5. The number and severity of IRRs were captured following their third rituximab infusion. The highest grade of an IRR that occurred during the infusion was recorded. Our pilot data revealed that following the third rituximab infusion, 14.3% of patients had an IRR of which 85.71% were Grade 0, 12.24% were grade 2 and 2.05% were Grade 3. Hauser et al., found that following the second infusion of rituximab in patients, the majority of whom (60%) were not taking a DMT for 6 months prior to initiating rituximab only 20.3% experienced in an IRR. [3]

Using IRR estimates from our pilot data and establishing a clinically meaningful difference of 20% increase in IRRs, we conducted the following power analysis for a sample of 95 patients (assuming a 5% attrition rate after recruiting 100 patients in each study group). An IRR proportion for ocrelizumab users at 34.3% compared with 14.3% for rituximab (obtained from our pilot data) for a two sided (alpha = 0.05) two sample proportion test for the null hypothesis of no difference between rituximab and ocrelizumab in proportion of IRRs would result in 90% power for 95 patients per group.

In response to the FDA IND letter, “the power analysis in Section 4.9.6 of the protocol appears to compare the infusion-related reaction (IRR) rate at the third rituximab infusion (14.3%) to that of the first infusion of OCR (34.3%). Because

the incidence of an IRR for most monoclonal antibodies is highest with the first infusion and declines with subsequent infusions, we recommend that you revise your sample size and power calculations using the IRR incidence for a comparable number of infusions; for example, the first, second, or third infusion":

Our response is that neither the switching and comparison groups are receiving their very first infusion of any anti-CD 20 monoclonal antibody (rituximab or ocrelizumab) following enrollment in the study. Both study groups have received a minimum of at least two infusions of rituximab prior to enrollment in the study. The first study related infusion for ocrelizumab in the switching group represents (at minimum) their third infusion for an anti-CD monoclonal antibody which will be compared to their third standard of care infusion for rituximab (at minimum) following study enrollment. As a result, we believe both groups represent those patients who have experienced at least three infusions of an anti-CD monoclonal antibody agent. Thereby our power calculations were based on the IRRs observed following the third infusion of rituximab in our pilot sample (at 14.3%) and using a clinically meaningful difference of 20% increase in IRRs for the ocrelizumab group (34.3%) to provide 90% power for 95 patients per study group (assuming a 5% attrition rate after recruiting 100 patients in each study group).

As there is only one primary outcome to power the study on, there is no need to reduce the alpha level of the univariate test as part of multiple testing adjustment. Adjustment for interim analysis is not an issue as there are no early stopping rules.

4.10 Data Quality Assurance

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

5. REPORTING OF ADVERSE EVENTS

5.1 Assessment of Safety

Safety Review

All AEs and SAEs will be reviewed by the project Steering Committee at their monthly project management meetings. This Committee will be composed of Drs. Vollmer, Nair and Alvarez supported by Stefan Sillau PhD and the lead study coordinator, Shane Curran-Hays. We will also establish an external DSMB as required by UCD that will meet at baseline, then every 6 months and at the time of any SAE. This committee will consist of two neurologists and Dr. Stefan Sillau PhD biostatistics.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other

protocol-imposed intervention, regardless of attribution. For the patients on Ocrelizumab, all AEs occurring between the time of consent and the study termination visit will be recorded.

For the comparator group, IRRs are the only AEs that will be collected. In addition, clinical relapses documented during the clinical process will also be collected.

Serious Adverse Events
An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

All SAEs reported or observed in either group will be recorded and reported as necessary.

5.2 Methods and Timing for Assessing and Recording Safety Variables
The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period
The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment or "initiation of any study procedures" and ends at T_3 which is 6 months after last dose of study medication. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events
AEs and SAEs may be collected from medical record review, or elicited by asking non-directive questions at each study visit both before and after the infusion. Infusion-related AEs will be captured by the infusion nurses as well as self-reported by the patient as described in Outcome Measures. Patients will also be reminded to alert the study team about any concerning health issues between study visits. Each recorded AE or SAE will be described by its duration (i.e., start and end dates) and will include, and actions taken.

For all recorded AEs, a study investigator will make an assessment of seriousness, and causality. To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes
There is a plausible temporal relationship between the onset of the AE and administration of the ocrelizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the ocrelizumab; and/or the AE abates or resolves upon discontinuation of the ocrelizumab or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the AE has an etiology other than the ocrelizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to ocrelizumab administration (e.g., event diagnosed 2 days after first dose of ocrelizumab).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

5.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

Eliciting Adverse Events
A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new/changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events
Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information

that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving ocrelizumab or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the ocrelizumab should be reported as an SAE.

Additional information on any ocrelizumab-exposed pregnancy and infant will be requested by Genentech Drug Safety at specific time points (i.e. after having

received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior ocrelizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct safety reconciliation for the safety events reported on ocrelizumab. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

h. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product. The AEs of special interest listed below will also be recorded and must be reported to Genentech as described in Section i.

Hys and Stiamp:

1. Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law
2. Suspected transmission of an infectious agent by the study drug, as defined below:

   Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

i. Adverse Event Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225--4630

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

Serious AE reports and AEs of Special Interest, whether related or unrelated to ocrelizumab, will be transmitted to Genentech within one (1) business day of the Awareness Date.

Additional reporting requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with ocrelizumab and within the follow-up period (for female patients within 90 days after the last dose of ocrelizumab will be transmitted to Genentech within one (1) business day of the Awareness Date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.
- All non-serious ocrelizumab AEs originating from the study will be forwarded to Genentech quarterly.

In addition to SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech/Roche even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
- Lack of therapeutic efficacy

In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

j. Aggregate Reports

The University of Colorado will forward a copy of the Final Study Report to Roche upon completion of the Study.

Note: Investigators should also report events to their IRB as required.

5.4 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/medwatch/getforms.html

5.5 Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of ocrelizumab. An unexpected adverse event is one that is not already described in the ocrelizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of ocrelizumab. An unexpected adverse event is one that is not already described in the ocrelizumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

And to the Site IRB:

Colorado Multiple Institutional Review Board (COMIRB) office at 303-724-1055 or COMIRB@ucdenver.edu.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 OR (650) 225-4630

IND Annual Reports

Copies to Genentech:

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech when available:

ocrelizumab-iis-d@gene.com and ctvist_drugsafety@gene.com

Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study: ocrelizumab-iis-d@gene.com and your Genentech MSL

6. Investigator Requirements

6.1 Study Initiation

Before the start of this study, the following documents must be on file with Genentech or a Genentech representative:

- Original U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current *curriculum vitae* of the Principal Investigator
- Written documentation of IRB approval of protocol and informed consent document
- A copy of the IRB-approved informed consent document
- A signed Clinical Research Agreement

6.2 Study Completion

The following materials are requested by Genentech when a study is considered complete or terminated:

- Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:
- Email : ocrelizumab-iis-d@gene.com

6.3 Informed Consent

The informed consent document will be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject will document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms will remain in each subject's study file and will be available for verification by study monitors at any time.

6.4 Institutional Review Board or Ethics Committee Approval

This protocol, the informed consent document, and relevant supporting information will be submitted to COMIRB for review and approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator will be responsible for keeping COMIRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific adverse event requirements that investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 Study Monitoring Requirements

NA

6.6 Data Collection

See section 4.5.1.

6.7 Study Medication Accountability (if applicable)

If study drug will be provided by Genentech, accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log.

All expired, partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

6.8 Disclosure and publication of Data

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, Genentech, and the IRB for each study site, if appropriate.

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for the publication of study results.

Additionally, Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) (PDF) requires Responsible Parties to register and submit summary results of clinical trials with ClinicalTrials.gov. The law applies to certain clinical trials of drugs (including biological products) and medical devices. (Refer to FDAAA 801 Requirements to learn about Responsible Party, Applicable Clinical Trials, and deadlines for registration and results submission)

6.9 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified. Genentech will notify the Principal Investigator of these events.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with U.S. FDA IND regulations and with the record retention policies of the relevant national and local health authorities.

REFERENCES

1. Palanichamy A, Jahn S, Nickles D, Rituximab efficiently depletes increased CD20 expressing T cells in multiple sclerosis patients. *J Immunol*. 2014 July 15; 193(2): 580–586. doi:10.4049/jimmunol.1400118
2. Ludwig Kappos, David Li, Peter A Calabresi, Paul O'Connor, Amit Bar-Or, Frederik Barkhof, Ming Yin, David Leppert, Robert Glanzman, Jeroen Tinbergen, Stephen L Hauser; Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial: Lancet 2011; 378: 1779–87
3. Hauser SL, Waubant E, Arnold DL, et al, for the HERMES Trial Group. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008; 358: 676–88
4. F. HOFFMANN-LA ROCHE LTD. INVESTIGATOR'S BROCHURE RO4964913 Ocrelizumab Fourteenth Version, November 2015 Addendum No. 1 (February 2016).
5. Owens, GP; Bennet, JL. Gilden, DH, Burgeon, MP. The B cell response in multiple sclerosis. Neurol Res 2006;28;236-44.
6. National Cancer Institute, Common Terminology Criteria for Adverse Events V 4.0 (available ahttp://www.oncology.tv/SymptomManagement/NationalCancerInstituteUpdatesCTCAEtov403.aspx)
7. Schwartz CE, Vollmer T, Lee H, North American Research Consortium on Multiple Sclerosis Outcomes Study Group. Reliability and validity of two self-report measures of impairment and disability for MS Neurology 1999; 52: 63–71
8. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, November 1983;33(11). 1444. doi: 10.1212/WNL.33.11.1444

APPENDIX B: SAFETY REPORTING FAX COVER SHEET

Genentech
A Member of the Roche Group

Genentech Supported Research

6.1.1.1.1.1.1 AE / SAE FAX No: (650) 225-4682

6.1.1.1.1.1.2 Alternate Fax No: (650) 225-5288

Genentech Study Number	
6.1.1.1.1.1.3 Principal Investigator	
6.1.1.1.1.1.4 Site Name	
6.1.1.1.1.1.5 Reporter name	
6.1.1.1.1.1.6 Reporter Telephone #	
6.1.1.1.1.1.7 Reporter Fax #	

6.1.1.1.1.1.8 Initial Report Date	6.1.1.1.1.1.9 [DD] / [MON] / [YY]
6.1.1.1.1.1.10 Follow-up Report Date	6.1.1.1.1.1.11 [DD] / [MON] / [YY]

6.1.1.1.1.1.12

6.1.1.1.1.1.13 Subject Initials 6.1.1.1.1.1.14 (Enter a dash if patient has no middle name)	6.1.1.1.1.1.15 [ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555