Official Title: **Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY).**

NCT Number: NCT03277248

Document Date: Protocol Version 5.0: 04 September 2020

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Local Protocol #: Protocol TG1101-RMS302

TITLE:

Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects **(ULTIMATE II STUDY).**

Sponsor: TG Therapeutics, Inc.
2 Gansevoort St; 9th Floor
New York, NY 10014
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IND Number: 127265
EudraCT Number: 2017-000639-15

Study Chair: [redacted], MD

Medical Monitor: [redacted], MD
Tel: [redacted]

Study Coordination: TG Therapeutics, Inc.
2 Gansevoort St; 9th Floor
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Version: 1.0	**Date:** 14 April 2017
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Version: 3.1	**Date:** 20 October 2017
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Version: 5.0	**Date:** 04 September 2020

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol TG1101-RMS302 for issuance.

Protocol Title:	Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects **(ULTIMATE II STUDY).**
Protocol Number:	TG1101-RMS302
Trial Drug:	Ublituximab (TG-1101)
IND Number:	127265
EudraCT Number:	2017-000639-15
Date FINAL:	04 September 2020

MEDICAL MONITOR [redacted]

[redacted] MD _____ _____ 17Sep2020

Print Name Signature Date

STUDY CHAIR

[redacted] MD _____ _____

Print Name Signature Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted] PhD _____ _____

Print Name Signature Date

STATISTICIAN, TG Therapeutics, Inc.

[redacted] _____ _____

Print Name Signature Date

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol TG1101-RMS302 for issuance.

Protocol Title:	Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects **(ULTIMATE II STUDY).**
Protocol Number:	TG1101-RMS302
Trial Drug:	Ublituximab (TG-1101)
IND Number:	127265
EudraCT Number:	2017-000639-15
Date FINAL:	04 September 2020

MEDICAL MONITOR, [redacted]

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STUDY CHAIR

[redacted], MD	[redacted]	September 15, 2020
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SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted], PhD		
Print Name	Signature	Date

STATISTICIAN, TG Therapeutics, Inc.

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Print Name	Signature	Date

SPONSOR APPROVAL

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Protocol Title:	Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects **(ULTIMATE II STUDY).**
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Trial Drug:	Ublituximab (TG-1101)
IND Number:	127265
EudraCT Number:	2017-000639-15
Date FINAL:	04 September 2020

MEDICAL MONITOR, [redacted]

[redacted], MD		
Print Name	Signature	Date

STUDY CHAIR

[redacted], MD		
Print Name	Signature	Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted], PhD	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 15-Sep-2020 | 1:12:21 PM EDT [redacted]	15-Sep-2020
Print Name	Signature	Date

STATISTICIAN, TG Therapeutics, Inc.

[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 15-Sep-2020 | 10:30:47 AM PDT [redacted]	15-Sep-2020
Print Name	Signature	Date

PROTOCOL ACCEPTANCE FORM

Protocol Title:	Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects **(ULTIMATE II STUDY)**.
Protocol Number:	TG1101-RMS302
Trial Drug:	Ublituximab (TG-1101)
IND Number:	127265
EudraCT Number:	2017-000639-15
Date FINAL:	04 September 2020

I have read the attached protocol and agree that it contains all the necessary details for performing TG1101-RMS302.

I will provide copies of the protocol and of the ublituximab and teriflunomide Investigator Brochures, which were furnished to me by TG Therapeutics (Sponsor) or its representative, to all members of the study team for whom I am responsible and who participate in the study. I will discuss this material with them to ensure that they are fully informed regarding ublituximab, teriflunomide and the conduct of the study.

Once the protocol has been approved by the IRB/EC, I will not modify this protocol without obtaining the prior approval of TG Therapeutics and of the IRB/EC. I will submit the protocol modifications and/or any informed consent modifications to TG Therapeutics and the IRB/EC, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (2013) including all amendments.

Print Name	Signature	Date

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol TG1101-RMS302 for issuance.

Protocol Title:	Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects **(ULTIMATE II STUDY).**
Protocol Number:	TG1101-RMS302
Trial Drug:	Ublituximab (TG-1101)
IND Number:	127265
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Date FINAL:	04 September 2020

MEDICAL MONITOR, [redacted]

[redacted], MD		
Print Name	Signature	Date

STUDY CHAIR

[redacted], MD		
Print Name	Signature	Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted], PhD	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 15-Sep-2020 | 1:12:21 PM EDT [redacted]	15-Sep-2020
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STATISTICIAN, TG Therapeutics, Inc.

[redacted]	DocuSigned by: [redacted] Signer Name [redacted] Signing Reason: I approve this document Signing Time: 15-Sep-2020 | 10:30:47 AM PDT [redacted]	15-Sep-2020
Print Name	Signature	Date

Study Title	Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects **(ULTIMATE II STUDY)**
Study Rationale	Over the past decade, the understanding of the role of B and/or T cells in autoimmune diseases has been of great priority in both pre-clinical and clinical research in autoimmune diseases, especially in multiple sclerosis. In multiple sclerosis, B cells can form autoantibodies, which can result in pathological immune complex depositions that can activate the complement system as well as initiate acute inflammatory cascade by producing pro-inflammatory cytokines and chemokines. Further, B cells have been shown to regulate the formation and function of T cells, which can aid in the demyelinating events seen with multiple sclerosis. Ublituximab (also known as TG-1101) is a monoclonal antibody that specifically binds to the trans-membrane antigen CD20 found on B-lymphocytes. The binding of ublituximab induces an immune response that causes lysis of B cells. Ublituximab has a unique protein sequence, and targets epitopes on CD20 not targeted by rituximab, ofatumumab, or ocrelizumab; anti-CD20 antibodies approved or in development for oncologic diseases and autoimmune disorders. The CD20 molecule is expressed on pre-B cells and throughout the lifecycle of both naïve and memory B cells. It is not expressed on stem cells or pro-B cells at the earliest stages of B cell differentiation. Further, it is not expressed on plasmablasts or terminally differentiated plasma cells. [8] Thus, CD20 is an ideal target for B cell targeted immunotherapy. Rituximab was the first anti-CD20 monoclonal antibody (mAb) tested in relapsing forms of Multiple Sclerosis (RMS) subjects. More recently, ocrelizumab, a humanized anti-CD20 monoclonal antibody has shown promising results in its two Phase III trials (OPERA I and OPERA II) [20]. In OPERA I and II, subjects treated with ocrelizumab had significantly lower Annualized Relapse Rates (0.156 and 0.155, respectively) compared to subjects treated with IFNβ-1a 44µg (0.292 and 0.29, respectively). Further, in OPERA I and II, subjects treated with ocrelizumab had approximately 46% reduction in ARR as compared to those treated with IFNβ-1a 44µg; TG Therapeutics is powering this study for a 40% reduction in ARR. TG Therapeutics has performed a Phase 2a clinical trial using ublituximab as a single agent to examine the level of B cell depletion by ublituximab as well as determine the optimal dose and infusion time for ublituximab in subjects with RMS. Based on the results of the Phase 2a study with a dosing of 150 mg (infused for 4 hours) on Week 1 Day 1 and a dosing of 450 mg (infused for 1 hour) on Week 3 Day 15, a median of >99% B cell depletion was achieved on Week 4 and sustained until Week 24. The dosing regimen was well tolerated by the subjects with Infusion Related Reactions (grade 1 and 2) being the commonly reported adverse event. TG Therapeutics also performed a Phase 1 clinical study using ublituximab as a single agent to examine the safety and tolerability of a single dose ublituximab at 450 mg in subjects diagnosed with acute Neuromyelitis Optica (NMO) relapse. Although the single dose of 450 mg ublituximab infused for 4 hours was safe and well tolerated, the

	study demonstrated that after 3 months, B cells started to replete after being deplete for >99% upon the initial administration of ublituximab on Week 1 Day 1. In examining the results from both the Phase 2a RMS and Phase 1 acute NMO clinical studies, it is believed that a higher dose of ublituximab will be needed during the initial 6 months of treatment in RMS subjects. The ULTIMATE II study will test the efficacy and safety of ublituximab in RMS, in comparison to teriflunomide, an orally administered pyrimidine synthesis inhibitor. The teriflunomide registered as Aubagio® is currently approved for the treatment of RMS. A bioequivalent form of teriflunomide will be used in the study as an active comparator. The goal is to demonstrate that ublituximab is a safe and effective treatment that will markedly improve health outcomes in those living with RMS.
Products	Ublituximab is a recombinant chimeric monoclonal antibody against the CD20 antigen, available as a 10 mg/mL or 25 mg/mL concentrate for solution for infusion, supplied by TG Therapeutics, Inc. Teriflunomide is a pyrimidine synthesis inhibitor indicated for the treatment of subjects with relapsing forms of Multiple Sclerosis. It available in 14 mg tablets.
Phase	Phase III
Study Sponsor	TG Therapeutics, Inc. (New York, NY, USA)
Study Chair	**RMS Group Study Chair** [redacted], MD
Study Objectives	**Primary Objective** 1. To determine the Annualized Relapse Rate (ARR) in subjects with RMS after 96 weeks (approximately 2 years with a year equal to 365.25 days) treatment with IV infusion of ublituximab/oral placebo compared to 14 mg oral teriflunomide/IV placebo. **Secondary Objectives** The secondary objectives are to examine the effects of ublituximab/oral placebo as compared to teriflunomide/IV placebo as follows: 1. On MRI parameters, 2. Confirmed Disability Progression (CDP), 3. No Evidence of Disease Activity (NEDA), 4. Symbol Digit Modality Test (SDMT), 5. To evaluate the safety of ublituximab/oral placebo, as determined by adverse events (AEs) and serious adverse event (SAEs), including MS worsening.
Efficacy Endpoints	**Primary endpoints** 1. The primary efficacy endpoint is ARR defined as the number of IRAP-confirmed relapses per subject year. The estimate of ARR for a treatment group will be the total number of relapses for subjects in the respective treatment group divided by the sum of treatment duration for subjects in that specific treatment group. Subjects will be treated up to 96 weeks. **Secondary endpoints** Key secondary efficacy endpoints are as follows: 1. Total number of gadolinium enhancing (Gd-enhancing) T1-lesions per MRI scan by Week 96.

	2. Total number of new and enlarging T2 hyperintense lesions (NELs) per MRI scan by Week 96. 3. Time to Confirmed Disability Progression (CDP) for at least 12 weeks occurring during the 96-week double-blind treatment period. * 4. Proportion of subjects with No Evidence of Disease Activity (NEDA) from Week 24 to Week 96. 5. Proportion of subjects reaching impaired SDMT (Symbol Digit Modalities Test) from baseline to Week 96. 6. Percentage change in Brain Volume from baseline to Week 96. * Confirmed Disability Progression for at least 12 weeks during the 96-week treatment period will be analyzed using pooled data from the two identical studies TG1101-RMS301 and TG1101-RMS302.
Safety Endpoints	All AEs will be reported and evaluated during the treatment period using National Cancer Institute (NCI) version 4.03 grading system; the number and severity of infusion-associated events, Infusion Related Reactions, defined as infusion related AEs reported during or within 24 hours after the end of an infusion; the number and severity of infectious AEs; any clinically significant changes in laboratory or vital sign measurements; the incidence of Anti-Drug Antibodies (antibodies developed against ublituximab) to assess safety over the 96-week trial.
Study Design	This is a 120-week, Phase III, randomized, multi-center, double-blinded, double-dummy, active-controlled study that is primarily designed to assess the ARR and safety/tolerability of ublituximab (TG-1101; UTX)/oral placebo as compared to teriflunomide/IV placebo in subjects with RMS. Subjects may be screened up to 4 weeks (28 days) before the first dosing date of study medication (ublituximab/oral placebo and teriflunomide/IV placebo). Qualified subjects will be randomized in a [1:1] ratio to receive either ublituximab/oral placebo on Week 1 Day 1, Week 3 Day 15, and Weeks 24, 48, and 72 or teriflunomide/IV placebo (14 mg, QD starting on Week 1 Day 1 until the last day of Week 95). There will be two treatment groups (approximately 220 subjects treated with teriflunomide/IV placebo and approximately 220 subjects treated with ublituximab/oral placebo; please see treatment schema). Subjects within each group will receive either active treatment (ublituximab/oral placebo or teriflunomide/IV placebo) (please see table below). Upon cessation of study medication, the subjects will be followed for another 20 weeks to enable teriflunomide elimination monitoring. During this Follow-up Period all adverse events will be documented. Once a subject is qualified, the Site will use an Interactive Web Response System (IWRS) to assign subjects to either one of the two treatment groups. The Principal Investigator and/or Treating Neurologist (please see definition and roles/responsibility in Section 4.1) will be responsible for subject eligibility evaluation, supervision of study medication administration, recording and treating of adverse events and assessing relapses, and monitoring of safety assessments, including routine laboratory results and concomitant medications.

An independent Data Safety Monitoring Board (DSMB) will be established to advise the Sponsor on safety and ethical issues of the study. The DSMB and Study Chair, Medical Monitor and Sponsor Representative will be in charge of reviewing safety data. The independent DSMB will be comprised of a total of five members with at least three MDs, a biostatistician and the DSMB chair. The DSMB will meet periodically to discuss procedures and review unblinded data related to study status and enrollment, adverse events, previous/concomitant medications, hematology, blood pressure, relapses and the EDSS scores. All other serious and non-serious adverse events will be documented, managed for each subject including review of the safety data by the DSMB and possible study participation termination at the investigator's discretion. Information on these meetings will be provided per the DSMB Charter. Statistical analyses required for planned DSMB meetings will be prepared and disseminated to the DSMB members. The committee will receive unblinded safety data to allow review and assessment by treatment group. In addition, the committee will receive unblinded efficacy data to perform benefit/risk ratio assessment. Based on their reviews and analyses of safety and efficacy data, the committee shall have the right to advise the sponsor to stop the study after any meeting.

MS Relapses During the Study

Subjects enrolled into the study will be closely monitored through the study course by the Site and Sponsor's personnel as well as by an external independent Data Safety Monitoring Board (DSMB) to ensure subjects' welfare.

Relapses that occur after study drugs are withdrawn will be assessed over the remainder of the study period and this data will be utilized as part of additional sensitivity analysis (described in the statistical plan) as long as the subject has not withdrawn their consent to be in the trial.

The confirmation of a protocol-defined relapse will be determined by the Independent Relapse Adjudication Committee (IRAP). The steps for confirming a relapse are as follows:

1. **Subject Reported Relapse**

Subjects who experience new or worsening neurologic symptoms are instructed to contact the Treating Neurologist within 48 hours of symptom onset. All new or worsening neurological events, reported at a visit or over the phone, consistent with MS representing a clinical relapse as assessed by the subject will be initially reported to the Treating Neurologist. In parallel, the Examining Neurologist will also be notified to perform additional assessments. Upon the notification to the Treating Neurologist, the time and date of suspected subject reported relapse will be documented in the dedicated page eCRF (subject reported) by the Treating Neurologist or designee.

The following should be recorded in the eCRF (subject reported) by the Treating Neurologist or designee:

- Date and time of symptom onset as reported by the subject
- Symptoms and events reported by the subject (both neurological and non-neurological)
- Date of initial contact by subject
- Time of initial contact by subject

Within 7 days of the subject reporting the suspected relapse to the Treating Neurologist, the subject will be scheduled and assessed by both the Treating and Examining Neurologist independently.

2. **Initial Assessment of Relapse by Treating Neurologist and Examining Neurologist**

The Treating Neurologist will perform a neurological and physical examination and safety assessment. The Treating Neurologist or designee will document in the eCRF the following:

- Time and date of neurological and physical examination
- Clinical findings of neurological and physical examination
- Review of previously documented concomitant medications and medical history
- Safety assessment, including vital signs, CBC, B-cell count, lymphocyte counts, fibrinogen, quantitative immunoglobulin

Subjects with suspected clinical relapses reported to the Treating Neurologist or designee will be referred to the blinded Examining Neurologist who will use Neurostatus to assess the EDSS independently of the Treating Neurologist.

The Examining Neurologist or designee will document in the eCRF the following:

- Date and time of assessment
- EDSS score
- FS Scores

In addition, subjects may not begin IV methylprednisolone (IVMP) treatment of a relapse until the Examining Neurologist has completed his/her examination.

Treatment of relapses may proceed at the discretion of the Treating Neurologist only after the Examining Neurologist has completed his/her exam. The Treating Neurologist will not know the results of the EDSS assessment. When making determination to treat a potential acute relapse the Treating Neurologist can use IVMP (1.0 g/day for at least 3 days and can be extended to 5 days) and will not affect the subject eligibility to continue in the study.

The subject must re-consent at the time of each IRAP-confirmed or Treating Neurologist medically confirmed relapse to continue.

The findings from either the Treating Neurologist and Examining Neurologist will not be shared. The Examining Neurologist must be blinded to the Treating Neurologist's assessment and vice versa.

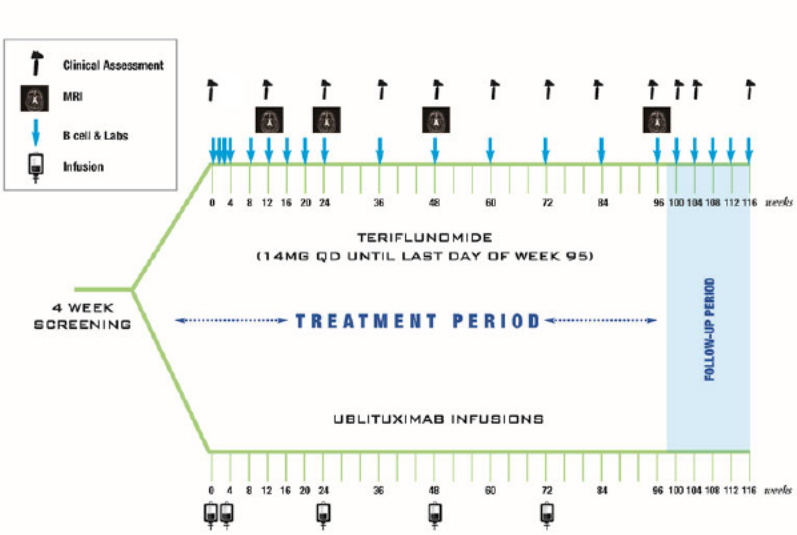
Following the completion of assessments by the Treating and Examining Neurologists these results will be sent independently to the IRAP.

3. **Confirmation of Relapse by IRAP**

All assessments entered into the eCRF from both the Treating Neurologist and the blinded Examining Neurologist, will be sent to an Independent Relapse Adjudication Panel (IRAP). IRAP adjudicates each case based on all available data provided for that case and members are not permitted to contact the site or the sponsor for additional

	information. The IRAP will, in turn, make the final determination of whether the neurological events meet the criteria for a protocol-defined relapse. Each episode of relapse must be confirmed by the IRAP, based on the neurological assessments performed independently by the Treating and/or Examining Neurologist by documenting either of the following: • ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory or visual). Note, the change in FS scores should correspond to the patient's symptoms (e.g., patient reported change in visual acuity should correspond to a change in the vision FS score). Episodic spasm, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse; • An increase of ≥0.5 points in the EDSS score (unless EDSS score = 0, then an increase of at least 1.0 points is required) from the previous clinically stable assessment. MS relapses are defined as a new or worsening neurological symptoms lasting ≥24 hours with the absence of fever, injury, infection or adverse reactions to medications and accompanied by new neurological findings upon examination by the Examining Neurologist. The symptoms are attributed to MS and are preceded by 30 days of stability or improvement in neurological state. The change in EDSS score as assessed by the Examining Neurologist is ≥ 0.5 increase or ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory or visual). Note, the change in FS scale scores should correspond to the patient's symptoms (e.g., patient reported change in visual acuity should correspond to a change in the vision FS score). Episodic spasm, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Please note: sexual dysfunction and fatigue will not be scored. If the symptoms occur less than 30 days following the onset of a protocol-defined relapse, it should be considered part of the same relapse and would not be treated with IVMP within the protocol. New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse and should not be treated with steroids. The suspected relapse must be reviewed and confirmed by the IRAP; Appendix D. The IRAP will then notify the CRO and Treating Neurologist of the results of its review. Treating Neurologist/designee will enter into the eCRF whether the neurological symptoms identified were a result of an IRAP-confirmed relapse. IRAP-confirmed relapses are the sole confirmation of a protocol-defined relapse. However, for instances where IRAP-confirmed relapses may not be feasible, provisions are provided within Section 4.4.2 (Treating Neurologist medically confirmed relapse). **The subject must re-consent at the time of each IRAP-confirmed or Treating Neurologist medically confirmed relapse to continue.** Signing the informed consent form for re-consent (if the subject has a confirmed relapse), to proceed with the study at the next scheduled office visit should be within 6 weeks after first reporting of relapse.

	<u>Re-consent criteria after relapse</u> In case of an IRAP-confirmed MS relapse (as defined in the protocol, Appendix C) or Treating Neurologist medically confirmed relapse during the study, the following actions will be taken: • The subject will be reminded of the current approved MS medications/treatments and the opportunity to terminate the study and be treated with an approved MS medication. • The subject will be requested to re-sign an informed consent form within 6 weeks after first reporting of the suspected relapse if he/she chooses to continue to participate in the study, in the same treatment assignment. **Disability Progression** The method of disability progression calculation will be different than that of the relapse confirmation. The EDSS score will be used to assess disability progression. EDSS assessment will be performed by the Examining Neurologist. The Examining Neurologist must not share the EDSS score with the Treating Neurologist. The EDSS assessment for disability progression will be performed at screening and on Week 1 Day 1 (prior to randomization) and Weeks 12, 24, 36, 48, 60, 72, 84 and 96. To clarify, disability progression is not calculated by the Examining Neurologist (disability progression is a post hoc analysis based on the EDSS scores). Disability progression is defined as an increase of ≥1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥0.5 when the baseline score is above 5.5. Disability progression is considered confirmed when the increase in the EDSS is confirmed at regularly scheduled visits at least 12 or 24 weeks after the initial documentation of neurological worsening.

Treatment Study Visits	**<u>Ublituximab/oral placebo vs Teriflunomide/IV placebo Regimen (please see dosing regimen below)</u>**  • Ublituximab or IV placebo: Infusions on Week 1 Day 1 and Week 3 Day 15 and Weeks 24, 48, and 72 • Teriflunomide or oral placebo: Daily starting at Week 1 Day 1 until the last day of Week 95 **<u>Abbreviated Blood Sample Assessment Schedule (for further details see Section 6):</u>** • For all subjects treated: o Blood collection for CBC and serum chemistry at screening, and Week 1 Day 1 (pre-dose), Week 1 Day 2, Week 2 Day 8, Week 3 Day 15 (pre-dose), and Weeks 4, 8, 12, 16, 20, 24 (pre-dose), 36, 48 (pre-dose), 60, 72 (pre-dose), 84 and 96 o Blood collection for B lymphocyte cell counts (% $CD19^+$ B cells) at screening, and Week 1 Day 1 (pre-dose), Week 1 Day 2, Week 2, Week 3 Day 15 (pre-dose), and Weeks 4, 8, 12, 16, 20, 24 (pre-dose), 48 (pre-dose), and 72 (pre-dose), 84 and 96 (or Early Withdrawal from Treatment), 100 and 104. Also, at any Unscheduled Relapse Visits. **<u>MRI Schedule:</u>** Screening, Weeks 12, 24 (pre-dose) and 48 (pre-dose) and 96 **<u>Clinical Assessment Schedule:</u>** Screening, Week 1 Day 1 (pre-dose) Weeks 12, 24 (pre-dose), 36, 48 (pre-dose), 60, 72 (pre-dose), 84 and 96 For further information on the scheduled events for each study visit see Tables 5, 6 and 7 in Section 6 and Appendix F.
Screening Lab Evaluation (Central Lab)	• CBC with differential • Varicella titer • Serology to rule out active Hep B/C and HIV • Serum chemistry • Serum pregnancy test • B lymphocyte cell counts (% $CD19^+$ B cells) • See Section 6 for complete listing of laboratory assessments

ADA Assessment:

All subjects will have six serum samples taken to assess for the presence of ADA prior to the infusions on Week 1 Day 1, Week 3 Day 15 and Weeks 24, 48, and 72. In addition, a serum sample will be taken at Week 96.

Pharmacokinetic (PK):

Serum samples will be drawn from all subjects pre-infusion on infusion days of ublituximab or IV placebo and at 30 minutes +/- 15 minutes post-infusion on infusion days (Week 1 Day 1, Week 3 Day 15, Weeks 24, 48, and 72). One additional serum sample will be taken on Week 96. [redacted]

Only serum samples from subjects treated with ublituximab will be analyzed for serum ublituximab concentrations. See the Laboratory Manual for PK collection and processing instructions.

[redacted]

Plasma Concentration for Teriflunomide

In order to assess teriflunomide compliance, four plasma samples will be taken from all subjects. The first sample will be taken prior to oral administration of teriflunomide or oral placebo on Week 1 Day 1. The second sample will be taken prior to infusion of ublituximab or IV placebo on Week 48. The third sample will be taken Week 96. The last plasma sample for teriflunomide will be taken at Week 116.

Only plasma samples from subjects treated with teriflunomide will be analyzed for plasma teriflunomide concentrations. See the Laboratory Manual for PK collection and processing instructions.

Instrumental Tests

- MRI (≥1.5T; closed MRI only)

Dosing Regimen

	Week 1 Day 1	Week 3 Day 15	Week 24	Week 48	Week 72	Week 96
Ublituximab plus oral placebo	UTX (150 mg/ 4h)	UTX (450 mg/ 1h)	UTX (450 mg/ 1h)	UTX (450 mg/ 1h)	UTX (450 mg/ 1 h)	
	Oral Placebo QD* starting on Week 1 Day 1 until last day of Week 95					
Teriflunomide plus placebo infusion	Teriflunomide (14 mg) QD* starting on Week 1 Day 1until last day of Week 95					
	Infusion Placebo	Infusion Placebo	Infusion Placebo	Infusion Placebo	Infusion Placebo	

*May be taken in the morning daily. Alternative dosing times are allowed if necessary.

Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for participation in this study:

1. 18-55 age
2. Diagnosis of RMS (McDonald criteria 2010; Appendix C)
3. ≥ 2 relapses in prior 2 years or 1 relapse in the year prior to screening and/or ≥1 Gd enhancing lesion

	4. Documented MRI of brain with abnormalities consistent with MS 5. Active disease 6. EDSS 0-5.5 (inclusive) at screening 7. B cell counts ≥5% of total lymphocytes 8. Neurologic stability ≥ 30 days prior to screening and baseline 9. Female subjects who are not of child-bearing potential, have documented surgical sterilization (see Appendix A), and female subjects of child-bearing potential who have a negative serum pregnancy test at baseline. Female subjects of child-bearing potential (see Appendix A), and all male partners must consent to use a medically/clinically acceptable method of contraception throughout the treatment period and for 20 weeks after the cessation of active treatment. Female subjects of child-bearing potential (see Appendix A) must agree to undertake urine pregnancy tests every 4 weeks during active treatment and the follow up period. 10. Fertile male subjects participating in the study who are sexually active with women of child bearing potential, must agree to use a condom during the treatment period and for an additional 20 weeks after cessation of active treatment. Agree to use an accelerated elimination procedure after the last dose of study medications or early termination from the study (see Section 6.10.1) 11. Willingness and ability to comply with trial and follow-up procedures, give written consent
Exclusion Criteria	Subjects who meet any of the following exclusion criteria are not to be enrolled to this study: 1. Treatment with Anti-CD20 or other B cell directed treatment 2. Treatment with the following therapies at any time prior to randomization: • Alemtuzumab • Natalizumab, • Teriflunomide, • Leflunomide, and • Stem cell transplantation 3. Contraindications to teriflunomide or incompatibility with use of teriflunomide. 4. Therapies that are disallowed (minimum of 4 weeks prior to randomization): phenytoin, warfarin, tolbutamide, St John's Wort or cholestyramine 5. Prior DMT exposure within months of screening: a. 24 months with cladribine b. 6 months with daclizumab, azathioprine, methotrexate, or cyclophosphamide c. 90 days with fingolimod, or experimental S1P modulators, IV immunoglobulin, and plasmapheresis d. 30 days with glatiramer acetate, interferons, dimethyl fumarate, laquinimod or glucocorticoids 6. Diagnosed with Primary Progressive MS (PPMS) 7. Pregnant or nursing 8. ≥ 10 years disease duration from onset with subjects EDSS ≤ 2.0 9. Contraindication for MRI and/or gadolinium 10. Known presence of other neurologic disorders that may mimic MS 11. Current evidence or known history of clinically significant infection including: a. Chronic or ongoing active viral, bacterial, or fungal infectious disease requiring long term systemic treatment such as, but not limited to: PML, chronic renal

infection, chronic chest infection with bronchiectasis, tuberculosis (TB), or active hepatitis C

b. Previous serious opportunistic or atypical infections

c. History of positive serology for hepatitis B or hepatitis C or HIV

12. History of clinically significant CNS trauma (e.g., traumatic brain injury, cerebral contusion, spinal cord compression)

13. History of liver disease, including but not limited to:

    a. Known history of active hepatitis B or C any time prior to randomization or known history of active hepatitis A within 3 years prior to randomization
    b. Presence of clinically significant chronic liver or biliary disease
    c. Moderate or severe hepatic impairment defined as Child Pugh Score B or C, respectively, based on measurement of total bilirubin, serum albumin, International Normalized Ratio (INR) and as well as on presence /absence and severity of ascites and hepatic encephalopathy
    d. Any of the following abnormal laboratory values at screening or first infusion:

- ALT/SGPT>2X the Upper Limit of Normal (ULN)
- AST/SGOT>2X ULN

14. Previous diagnosis with a congenital or acquired immunodeficiency (AIDS)
15. History of renal impairment, including, but not limited to:
    a. Hypoproteinemia (e.g., in case of severe renal disease or nephrotic syndrome) with serum albumin <3.0 g/dL
    b. Severe renal insufficiency requiring renal dialysis

16. Past or current history of medically significant adverse effects (including allergic reactions) from:

    a. Corticosteroids

    b. Diphenhydramine

    c. Murine or mouse/human chimeric antibodies

17. Subjects with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia

    a. Hematocrit <24% and/or

    b. Absolute white blood cell count <4,000 cells/mm^3 and/or
    c. Platelet count <150,000 cells/mm^3 and/or
    d. Absolute neutrophil ≤ 1,500 cells/mm^3

18. Absolute lymphocyte counts less than 1000/microliter
19. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

    a. Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV [see Appendix B]

    b. QTcF: Female >450 msec; male > 430 msec Angina not well-controlled by medication

    c. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months prior to screening

	20. Other significant concurrent, uncontrolled medical condition including, but not limited to, cardiac, renal, hepatic, hematological, gastrointestinal, endocrine, immunodeficiency syndrome, pulmonary, cerebral, psychiatric, or neurological disease which could affect the subject's safety, impair the subject's reliable participation in the trial, impair the evaluation of endpoints, or necessitate the use of medication not allowed by the protocol, as determined by the PI of the trial 21. Current participation in any other interventional clinical trial. Participation in non-interventional trial requires approval by the Sponsor 22. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol 23. Lack of immunity to varicella as determined by screening based on the level of VZV IgG. Subject may receive vaccine and be rescreened 24. Vaccination with live virus within 2 months of randomization 25. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation or bone marrow transplantation
Populations	The **Intention-to-Treat (ITT) population** will consist of all randomized subjects. Subjects will be analyzed by randomized treatment group. **Modified Intention to Treat (mITT) Population** – all subjects in the ITT population who received at least one dose of study medication and have one baseline and post-baseline efficacy assessment. For analysis of MRI endpoints, the subgroup of mITT subjects who have baseline and post-baseline MRI will be used. The Safety Population will include all subjects who receive at least one dose of study drug (ublituximab or teriflunomide, with corresponding placebos).
Statistical Considerations	All efficacy analyses will be performed on the mITT population. The ARR will be analyzed using a Negative Binomial regression testing for treatment differences between UTX and teriflunomide, adjusted by region and baseline EDSS score as covariates. A significant result at a two-sided alpha=0.05 will demonstrate a superior effect of UTX in reducing ARR compared with teriflunomide. Further details on the planned statistical analysis and hypothesis to be test will be provided in the Statistical Analysis Plan.
Estimated Sample Size	The proposed sample size for this clinical trial is approximately 440 subjects (approximately 220 subjects in the teriflunomide/IV placebo group (N1) and 220 subjects in the ublituximab/oral placebo group (N2) [redacted], this required sample size is increased to 220 per group or a total randomized of 440.
Estimated Study Duration	Approximately 120 weeks for any enrolled subject, with approximately 4 weeks allocated for screening, approximately 96 weeks for treatment with study medication followed by a 20-week Follow-up Period including the accelerated teriflunomide elimination procedure.

	The full study duration is anticipated to be approximately two to three years based on the following: approximately 6 to 10 months allocated for enrolling subjects and enrollment of the last subject being randomized and treated for approximately 96 weeks with study medication followed by a 20-week Follow-up Period including the accelerated teriflunomide elimination procedure (total of 116 weeks). A subject will participate in the study for approximately 120 weeks, 4 weeks for screening, 96 weeks for treatment, and 20 weeks for follow-up, unless subject consents to participation in the Open Label Extension study.
Open Label Extension (OLE): TG1101-RMS303	TG1101-RMS303 is a 172-week open label extension (OLE) trial. Subjects completing 96-weeks of treatment in TG1101-RMS301 or TG1101-RMS302 trials in United States, Croatia, Ukraine, Russia, Republic of Belarus, Serbia, Poland, and Georgia may be eligible to participate. Regardless of which treatment group the subject was assigned to in the core study, all subjects enrolled in the OLE will receive ublituximab on the following schedule: Week 1 Day 1, Week 3 Day 15, and Weeks 24, 48, 72, 96, 120, 144 and 168 or until physician or subject decision to withdraw prior to this time. Subjects will have final assessments done at Week 172. TG1101-RMS302 is considered a core study protocol for OLE. The TG1101-RMS303 subjects, sponsor and investigators will not know TG1101-RMS301 and TG1101-RMS302 treatment assignments until these studies are unblinded.

Phase III

Table 1: Ublituximab/oral placebo and Teriflunomide (14 mg)/IV placebo

	Week 1 Day 1	Week 3 Day 15	Week 24	Week 48	Week 72	Week 96
Ublituximab plus oral placebo	UTX (150 mg/ 4h)	UTX (450 mg/ 1h)	UTX (450 mg/1h)	UTX (450 mg/ 1h)	UTX (450 mg/ 1h)	
	Oral Placebo QD* from Week 1 Day 1 until last day of Week 95					
Teriflunomide plus placebo infusion	Teriflunomide (14 mg) QD* from Week 1 Day 1 until last day of Week 95					
	Infusion Placebo	Infusion Placebo	Infusion Placebo	Infusion Placebo	Infusion Placebo	

*May be taken in the morning daily. Alternative dosing times are allowed if necessary.

LIST OF ABBREVIATIONS

Abbreviations and Definition of Terms	
Ab	Antibody
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Class
AUC	Area Under the Curve
BBB	Blood Brain Barrier
BM	Bone Marrow
Ca	Calcium
CAEPRS	Comprehensive Adverse Events and Potential Risks
CBC	Complete Blood cell Count
CD	Cluster of Differentiation
CDC	Complement-Dependent Cytotoxicity
CDI	Confirmed Disability Improvement
CDP	Confirmed Disability Progression
Cl	Clearance
CIS	Clinically Isolated Syndrome
CLL	Chronic Lymphocytic Leukemia
Cmax	Maximum Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
CVA	Cerebrovascular Accident
D, d	Day
DLT	Dose Limiting Toxicity
DMT	Disease Modifying Therapy
DOR	Duration of Response
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
Fc	Fragment crystallizable (region)
FIS	Fatigue Impact Scale
FL	Follicular Lymphoma
FS	Functional System
FU	Follow-up
GCP	Good Clinical Practice

Abbreviations and Definition of Terms	
GCSF	Granulocyte Colony Stimulating Factor
Gd	Gadolinium
GLP	Good Laboratory Practice
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Ig	Immunoglobulin
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL	Interleukin
IRAP	Independent Relapse Adjudication Panel
IRR	Infusion Related Reactions
ITT	Intent to Treat
IV	Intravenous
IVMP	Intravenous methylprednisolone
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
MCL	Mantle Cell Lymphoma
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSQoL-54	Multiple Sclerosis Quality of Life-54
NCI	National Cancer Institute
NCI-WG	National Cancer Institute – Working Group
NEDA	No Evidence of Disease Activity
NEL	New and enlarging T2-hyperintense lesions
NK	Natural Killer
OLE	Open Label Extension
NHL	Non-Hodgkin's Lymphoma
NMO	Neuromyelitis Optica
OLE	Open Label Extension
OS	Overall survival
PASAT	Paced Auditory Serial Addition Test
PCD	Programmed cell death
PCR	Polymerase Chain Reaction
PFS	Progression-Free Survival
PD	Pharmacodynamic or Progressive Disease
PHI	Subject Health Information
PI	Principal Investigator
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
PR	Partial Response
PRMS	Progressive Relapsing Multiple Sclerosis
PT	Preferred Term
R-FC	Rituximab-Fludarabine, Cyclophosphamide

Abbreviations and Definition of Terms	
RMS	Relapsing forms of Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
RRR	Relapse Rate Reduction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDMT	Symbol Digit Modalities Test
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
t1/2	Half-Life of Elimination
T2FW	Timed 25-Foot Walk
TB	Tuberculosis
TEAEs	Treatment Emergent Adverse Events
TIA	Transient Ischemic Attack
TMF	Trial Master File
ULN	Upper Limit of Normal
V	Visit
Vd	Volume of distribution
WHO	World Health Organization

TABLE OF CONTENTS

Summary of Changes

Version 2.0 (dated 7 June 2017) is the first amendment to this protocol and contains the following updates:

- A sentence was added to include additional analysis of relapses from a more specific timeframe. The sentence reads as follows: "Relapses that occur after study drugs are withdrawn will be assessed over the remainder of the study period and this data will be utilized as part of additional sensitivity analysis (described in the statistical plan) as long as the subject has not withdrawn their consent to be in the trial.",
- The interface between IRAP and the study sites have been updated to as follows: "IRAP adjudicates each case based on all available data provided for that case and members are not permitted to contact the site or the sponsor for additional information.",
- The change in EDSS score for defining progression of disability has been updated to state as follows: "…if a subject experiences at least 1.0 point increase on the EDSS when a baseline score is < 5.5…",
- The assessment tables now stipulates EDSS must be assessed 1 day prior to randomization,
- Intent to treat definition was updated in the body of the protocol
- Now included is a hierarchy analysis, sensitivity analysis for secondary endpoints and subjects who withdraw from study
- The timeframe of relapse assessment was further defined
- Interim sample size reassessment for relapses was further defined
- Minor typographical errors

Version 2.1 (dated 26 July 2017) is the second amendment to this protocol and contains the following updates:

- Endpoints are now numbered instead of bulleted
- Examining and Treating Neurologists will act independently. Any scores from evaluations performed by either the Examining or Treating Neurologist will not be shared.

Version 3.0 (dated 03 August 2017) is the third amendment to this protocol and contains the following updates:

- Include information regarding a new vial size for ublituximab
- Update Sections 7.2.1.3 and 7.2.1.4 to reflect changes in adverse events as reported in the revised Investigator Brochure (Version 5.0; dated 01 August 2017)
- Minor typographical errors

Version 3.1 (dated 20 October 2017) is the fourth amendment to this protocol and contains the following updates:

- Minor administrative updates and typographical errors were corrected throughout
- Adverse Events will be reported using version 4.03 of the NCI grading system
- FS scale scores should be correspond to patient's symptoms
- For relapses, patients must re-consent only if they have a confirmed relapse
- Re-consenting criteria will based on the Treating Neurologists discretions and the criteria in Appendix C
- Treatment Schema has been updated to reflect additional MRI scan at Week 12
- Malignancy has been added to the list of discontinuation reasons
- All subjects at Week 116 will be counseled by the treating team to have their teriflunomide plasma concentration re-measured prior to attempting to become pregnant or trying to impregnate their female partner.
- The Treating Neurologist will perform MSFC and SDMT assessments
- Blinded Assessment Relapse Team (BART) will reassess sample size when 210 out of 220 patients in each arm have been randomized
- The use of medical equivalents when those listed in Section 4.4 and Sections 7.5.2.1 are not available can be used at the Investigator's Discretion for Supportive Care Guidelines
- Section 5.2.1 actions taken per Grade have been updated

- EDSS scores assessed by the Examining Neurologist is not to be shared with the Treating Neurologist and the Principal Investigator, if they act as the Treating Neurologist
- Section 7.1 has been updated to provide storage conditions for the United States and Europe
- Section 7.2 has been updated to reflect the increased shelf life of ublituximab (36 months)
- Teriflunomide may be taken with or without breakfast
- Liver enzymes will be recorded using a Grading System
- Section 7.5.2.4 now describes updated information regarding second infusion interruptions
- Adverse Events, including pregnancies and medically confirmed deaths, will be following beginning from the day the consent form is signed until 20 weeks after discontinuation
- Protocol-defined events of special interest (Section 9.10.6) have been updated
- The Data Safety Monitoring Board (DSMB) will be comprised of at least addition three MDs not including the chair
- Appendix A has been updated to reflect the following: pregnancies are to be followed for 20 weeks after the last study drug was administered, women of child-bearing potential must have a negative serum pregnancy test within 5 days prior to initiating treatment, males must not donate sperm for 20 weeks following the last study drug administered, the pregnant subject/male subject's partner will be asked to provide consent to allow the pregnancy to be followed up for the full duration (or until termination) and 6 most post birth.
- Appendix F has been updated to reflect newly provided time

Version 3.2 (dated 09 February 2018) is the Ukraine specific amendment to this protocol containing the following updates:

- Clarification of the exclusion criteria to avoid potential misinterpretation
- Clarification regarding the active comparator to confirm bioequivalent teriflunomide product is used in the study
- Clarification on MRI and Pharmacokinetic (PK) windows
- Minor administrative revisions to remove inconsistencies

Version 4.0 (dated 17 January 2020) is the next amendment to this global protocol which now includes the Ukraine specific changes and additional following updates:

- Clarification of the exclusion criteria to avoid potential misinterpretation
- Clarification regarding the active comparator to confirm bioequivalent teriflunomide product is used in the study
- Clarification on MRI and Pharmacokinetic (PK) windows
- Minor administrative revisions to remove inconsistencies
- Advise subjects to seek immediate medical help and inform the investigator if they experience signs or symptoms of an infection
- Provide information on TG1101-RMS303 which is the Open Label Extension of TG1101-RMS301 and TG1101-RMS302

Version 5.0 (dated 04 September 2020) is the next amendment to this protocol and contains the following updates:

- Amended list of abbreviations
- Updated Secondary Endpoints
- Updated Tertiary Endpoints
- Provided clarification/correction for Exclusion Criteria 13b, 15, 21
- Specified timing of teriflunomide elimination procedure post discontinuation from study treatment
- Clarified subjects that early terminate can enter 20-week Follow-Up Period but must sign Early Termination ICF
- Refined procedures for pregnancy confirmation and added wording regarding counselling regarding teratogenicity

- Added reference to pharmacists as site team members
- Clarified site team roles and responsibilities including Treating Neurologist, Examining Neurologist, Radiologist, and Clinical Coordinator
- Updated DSMB composition and review procedures
- Clarified teriflunomide alternative dosing times are allowed if necessary
- Clarified time window for administration of pre-medication on infusion days
- Defined Treating Neurologist Medically Confirmed relapses
- Added requirement to re-consent patients upon Treating Neurologist medically confirmed relapse
- Updated reference timepoint for patients re-consenting after confirmed relapse
- Clarified the definition of disability progression
- Clarified disability is a post-hoc analysis
- Clarified AE follow-up if subject discontinues from study
- Added guidance to assessments during dosing delay due to lab abnormalities and suspected relapse
- Further defined procedure timing in Schedule of Assessments in tables 5, 6, 7
- Clarified urine pregnancy is required in 20-week Follow-up Period
- Clarified window for PK sampling
- Clarified requirement to collect blood sample for teriflunomide concentration at Early Withdrawal from Treatment Visit
- Clarified requirement to collect urine sample at Early Withdrawal from Treatment Visit and Unscheduled Relapse Visit
- Clarified requirement to draw blood sample for B-lymphocyte cell count at Early Withdrawal from Treatment Visit and Unscheduled Relapse Visit
- Clarified MRI window if early withdrawal from study
- Clarified that MRI reports with only non-MS pathology will be provided to Treating Neurologist after randomization
- Clarified subject reported outcomes (FIS, MSQoL) are done at Early Withdrawal from Treatment Visit
- Clarified time windows for recording of ECG and vital signs pre- and post-infusion
- Clarified starting time for teriflunomide elimination procedure for subjects who withdraw from treatment
- Reiterated that no Disease Modifying Therapy is permitted during the 20-week Follow-up Period
- Clarified PK analysis
- Clarified that urine pregnancy testing is mandatory for female subjects of childbearing potential at each visit during the follow-up period
- Clarified that teriflunomide drug concentration testing is performed at Week 116 but not shared with sites and subjects
- Clarified ublituximab vial cap colors
- Updated the CAEPRS profile of teriflunomide and ublituximab
- Clarified timing of teriflunomide concentration, includes early withdrawal from treatment visit and Week 116
- Provided definition of Infusion Related Reaction and that they will be analyzed separately
- Updated ublituximab/IV placebo infusion interruption procedure
- Clarified infusion delay process due to relapse
- Updated general analysis will be presented with P values with 4 decimals
- Updated definitions of ITT, mITT, and PP populations
- Clarified definition of ublituximab/IV placebo treatment exposure
- Specified that primary statistical analysis will be done once all subjects have completed Week 96
- Listed and clarified all pooled analysis
- Provided further statistical analysis details
- Further defined Treatment Emergent Adverse Events
- Clarified that hospitalizations due to the underlying disease (MS disease progression) and due to relapse do not have to be reported as SAE
- Replaced protocol list of Adverse Events of Special Interest with reference to valid IB

- Further defined the definition of overdose
- Updated the requirement for sites to have procedures in place to ensure study conduct
- Specified pregnancy does not require a report on study medication relatedness
- Defined female patients with hysterectomy as not considered women of childbearing potential
- Administrative revisions to Per Visit Procedures in Appendix F

1 INTRODUCTION

1.1 BACKGROUND

Multiple Sclerosis (MS) is a chronic demyelinating autoimmune disease of the central nervous system (CNS). Although it can occur at any age, it is often seen in young adults between the ages of 20 to 40 with a higher incidence in females versus males. According to the Multiple Sclerosis Foundation, over 400,000 people in the United States and approximately 2.5 million people worldwide have been diagnosed with the disease.[1] Prior to 2014, MS had been classified into four clinical subtypes: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive relapsing MS (PRMS).[2] In 2014, the International Advisory Committee on Clinical Trials of MS revised the MS phenotypes to the following disease modifier phenotypes: Clinically Isolated Syndrome (CIS; not active or active), RMS (not active or active), progressive disease (active and with progression; active but without progression; not active with progression; not active and without progression).[3] The progression, severity and specific symptoms of MS vary amongst each subjects and are unpredictable. Since 1993, twelve disease modifying therapies (DMTs) have been approved by the Food and Drug Administration (FDA) to treat MS. These include 7 injectable agents, 3 orals and 3 infusions. The main target in the majority of these therapies has been T cells. Despite improvements in the available therapies in reducing relapses by up to 65% [4] and slowing the progression of the disease, subjects continue to experience disease relapses and progression. Furthermore, some of the T cell directed therapies have shown safety issues that have challenged their more widespread use. Recent immunopathologic and clinical studies have demonstrated that B cells also play a central role in the pathogenesis of the disease, perhaps upstream of the T cell mediated pathology. As such, targeting aberrant autoimmune activity in B cells in MS may represent the next leap forward in treating MS. Phase 2 and 3 studies with anti-CD20 antibodies, which selectively deplete B cells, have shown robust efficacy over both placebo and B-interferon. To date, B cell targeted therapies have not been approved for the treatment of relapsing and progressive forms of MS. Thus, there is a pressing need for new, innovative, B cell targeted therapies for the treatment of this heterogeneous disease.

1.2 UBLITUXIMAB

Ublituximab is a novel third generation chimeric anti-CD20 monoclonal antibody bioengineered for potent activity, exhibiting a unique glycosylation profile with a low fucose content, designed to introduce superior antibody-dependent cytotoxicity (ADCC). Ublituximab has maintained competitive complement-dependent cytotoxicity (CDC) and has also demonstrated to induce programmed cell death (PCD) upon binding to the CD20 antigen on B-lymphocytes. Ublituximab has a unique protein sequence, and targets epitopes on CD20 not targeted by rituximab or ofatumumab, both currently approved anti-CD20 antibodies in oncologic diseases and rheumatoid arthritis (rituximab only).

1.2.1 PRE-CLINICAL EVALUATIONS OF UBLITUXIMAB

1.2.1.1 IN VITRO ACTIVITY

In an in-vitro assay using B-CLL cells from subject donors, ublituximab demonstrated an enhanced ability to kill CLL cells compared to rituximab. Ublituximab demonstrated improved Fcγ receptor IIIA (FcγRIIIA)/CD16 binding and FcγRIIIA dependent effector functions compared to rituximab. Additionally, ublituximab induced higher ADCC against CLL cells, and a higher FcγRIIIA mediated interleukin (IL)-2 production by FcγRIIIA+ Jurkat cells (5). Ublituximab demonstrated high ADCC against both subject-derived CLL cells and NHL cell lines. Against the NHL cell line Ramos, ublituximab was observed to inhibit the constitutively active NF-κB survival pathway and induce the expression of PTEN along with inhibition of the PI3K-AKT pathway. Ublituximab also induced the expression of pro-apoptotic factors, sensitizing Ramos cells to TRAIL mediated apoptosis (6).

1.2.1.2 IN VIVO ACTIVITY

The antitumor effect of ublituximab was compared to that of rituximab with chemotherapy in follicular lymphoma (FL), and mantle cell lymphoma (MCL) xenograft murine models. Single agent ublituximab demonstrated dose-related anti-tumor activity with 100% tumor growth inhibition in the FL xenograft at a dose of 100 mg/kg, and a superior tumor growth delay (21 days) compared to rituximab. Ublituximab also demonstrated superior anti-tumor activity compared to rituximab against MCL xenografts at all dose levels (7).

1.2.1.3 TOXICOLOGY

In single-dose and repeat dose toxicology studies performed under GLP, ublituximab displayed a safety profile similar to what might be expected for anti-CD20 monoclonal antibodies. Single administration of up to 100 mg/kg ublituximab in cynomolgus monkeys was well tolerated, with no local irritation with intravenous administration. Genotoxicity studies (Ames test) showed that ublituximab was not mutagenic. Monkeys that received a single injection of 0.3 mg/kg of ublituximab developed an anti-ublituximab response, whereas anti-ublituximab antibodies were not detected in the animals which received 10 or 100 mg/kg (see Ublituximab Investigator Brochure).

1.2.2 CLINICAL DEVELOPMENT OF UBLITUXIMAB

1.2.2.1 PHARMACOKINETICS

After infusion of ublituximab (previously known as LFB-R603) at 150 mg dose followed by seven weekly infusions at 450 mg, results suggested non-linear pharmacokinetics with respect to dose (450 mg vs. 150 mg) and time (Week 4 vs. Week 8); and more than proportional increase of Cmax and AUC∞ due to a clearance decrease. The volume of distribution at steady state was small (~5 L), approximately equal to blood volume. This non-linear pharmacokinetics may be explained by binding of ublituximab to its target, with a large component of target-mediated elimination after the first dose that is decreased after subsequent infusions due to a reduction in the available target. However, limited data for each dose level cohort and considerable variability in baseline subject characteristics, particularly in terms of tumor burden, make firm conclusions difficult.

The linear mean serum concentration-times profile after the first, the fourth and the eight infusion of ublituximab are presented in Figure 1. A summary of non-compartmental PK parameters after the first, the fourth and the eighth infusion of ublituximab are presented in Table 2.

Figure 1: Linear mean serum concentration-times profile after the first, the fourth and the eighth infusion of ublituximab

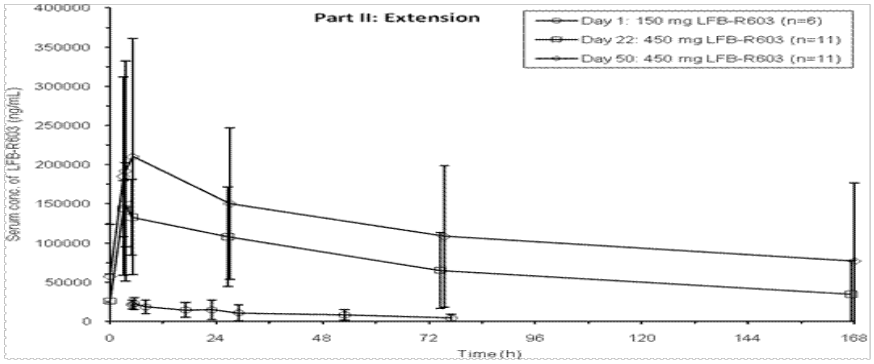


Table 2: Pharmacokinetic results after the 1st (150 mg), the 4th (450 mg) and the 8th (450 mg) infusion of ublituximab

PK Parameters [a]	1st Infusion 150 mg (Day 1)	4th Infusion 450mg (Day 22)	8th Infusion 450 mg (Day 50)
N	12	11	11
C_{max} (mg/L)	23.4 ± 11.2	168.6 ± 61.8	220.5 ± 141.9
t_{max} (h)	9.0 (5.0-30.3)	5.00 (3.1-52.0)	5.1 (3.1-23.5)
AUC∞ (mg.h/L)	732.1 ± 590	17890 ± 17730*	50760 ± 74460
$t_{1/2term}$ (h)	13.43± 10.2	80.7 ± 58.5*	147.8 ± 133.8
CL (mL/h)	424.2 ± 389.3	57.69 ± 42.91	38.62 ± 26.63
V_d/V_{dss}, (L)	4.8 ± 2.1	4.9 ± 2.3*	5.7 ± 3.3

[a] mean ± SD, t_{max}: median (range), with respect to the start of infusion *Accurate determination not possible

Concentration was still measurable in at least one subject of the cohort up to Day 169. Values for C_{max} and AUC_{∞} increased from the first to the eighth infusion whereas $t_{1/2}$ term decreased.

1.2.2.2 IMMUNE EFFECTS

Significant blood lymphocyte depletion was observed in all subjects reflecting the intended biological activity of ublituximab. [redacted] Lymphocyte depletion was sustained until 6 months after start of therapy for most subjects.

1.3 RATIONALE

1.3.1 CLINICAL STUDIES WITH RITUXIMAB AND OCRELIZUMAB

In vivo and in vitro studies have shown that B cells contribute to tissue damage in MS. B cells may enhance autoimmune processes through the presentation of autoantigens. Additionally, B cells can modulate the effector function of other autoimmune cells by producing soluble inflammatory mediators. In MS, B cells are believed to cross the blood brain barrier (BBB) and undergo stimulation, antigen-driven affinity maturation and clonal expansion within the CNS environment. [8] B cells are the source of differentiating plasma cells which secretes autoreactive antibodies, which may contribute to the demyelinating events in the CNS.

The CD20 molecule is expressed on pre-B cells and throughout the lifecycle of both naïve and memory B cells. It is not expressed on stem cells or pro-B cells at the earliest stages of B cell differentiation. Further, it is not expressed on plasmablasts or terminally differentiated plasma cells. Thus, CD20 is an ideal target for B cells targeted immunotherapy. Rituximab was the first anti-CD20 monoclonal antibody (mAb) to be tested in RRMS subjects. The rituximab Phase I trial, a 72 week open-label study consisting of 26 enrolled RRMS subjects, demonstrated that B-cell depletion was approximately 99.8% depleted by Week 2 and sustained through Week 48 when subjects were treated with rituximab (500 mg day 1; 500 mg day 15). [9] Further, rituximab showed a 96% reduction in Gd-enhancing lesions at Week 24 with 100% reduction by Week 72. Clinically, the Annualized Relapse Rate (ARR) at 48 and 72 weeks were 0.25 and 0.22, respectively, which equated to 81% and 83% reduction from baseline, respectively. The phase II (HERMES) study similarly demonstrated significant reduction in MRI and clinical activities, 91% reduction in the total number of Gd-enhancing lesions at Week 12, 16, 20 and 24 compared to placebo and 42.3% reduction in relapse rate compare to placebo at 48 weeks. [10]

The second anti-CD20 mAb tested in RRMS subject was ocrelizumab. In its phase II study, similar to rituximab, there were significant reductions in both radiological and clinical activities. [11] In subjects treated with ocrelizumab (600 mg), there was an 89% reduction in total number of Gd-enhancing lesions for Week 12, 16, 20 and 24 when compared to placebo. Clinically, ocrelizumab treated subjects achieved an 80% reduction in relapse rate when

compared to placebo at 24 weeks. More recently, ocrelizumab demonstrated promising results in its 2 Phase III trials (OPERA I and OPERA II) [20]. In OPERA I and II, subjects treated with ocrelizumab had significantly lower Annualized Relapse Rates (0.156 and 0.155, respectively) compared to subjects treated with IFNβ-1a, 44μg (0.292 and 0.29, respectively). Further, in OPERA I and II, subjects treated with ocrelizumab had approximately 46% reduction in ARR as compared to those treated with IFNβ-1a 44μg; TG Therapeutics is powering this study for a 40% reduction in ARR. [14]

1.3.2 RATIONALE FOR THE TRIAL

Ublituximab has been studied extensively in the treatment of B-cell malignancies and has been shown to be a potent B-cell depleting agent. Based on the success of other CD20s in the treatment of RMS, ublituximab is being studied in RMS.

TG Therapeutics has performed a phase 2a clinical trial using ublituximab as a single agent to examine the level of B cell depletion by ublituximab as well as determine the optimal dose and infusion time for ublituximab in subjects with RMS. Based on the results of the Phase 2a study with a dosing of 150 mg (infused for 4 hours) on Week 1 Day 1 and a dosing of 450 mg (infused for 1 hour) on Week 3 Day 15, a median of >99% B cell depletion was achieved on Week 4 and sustained until Week 24. The dosing regimen was well tolerated by the subjects with Infusion Related Reactions (grade 1 and 2) being the commonly reported adverse event.

TG Therapeutics also performed a phase 1 clinical study using ublituximab as a single agent to examine the safety and tolerability of a single dose ublituximab at 450 mg in subjects diagnosed with acute Neuromyelitis Optica relapse. Although the single dose of 450 mg ublituximab infused for 4 hours was safe and well tolerated, the study demonstrated that after 3 months, B cells started to replete after being deplete for >99% upon the initial administration of ublituximab on Week 1 Day 1.

In examining the results from both the Phase 2a RMS and Phase 1 acute NMO clinical studies, it is believed that a higher dose of ublituximab will be needed during the initial 6 months of treatment in RMS subjects. With enhanced potency over first generation anti-CD20s due to its glycoengineering, we believe we may be able to optimize the therapeutic window and/or safely decrease infusion times, offering subjects comparable efficacy with a more convenient infusion.

2 ENDPOINTS

2.1 PRIMARY ENDPOINT

The primary efficacy endpoint is ARR defined as the number of IRAP-confirmed relapsed per-subject year. The estimate of ARR for a treatment group will be the total number of relapses for subjects in the respective treatment group divided by the sum of treatment duration for subjects in that specific treatment group. Subjects will be treated up to 96 weeks.

2.2 SECONDARY ENDPOINTS

The key secondary outcomes will be tested using a hierarchical approach with the order specified below using a step-down procedure where each test is at a Type I error 0.05. If any endpoint fails to reach significance, then formal testing of significance of the subsequent secondary outcomes will not be performed. The hierarchical analyses of the key secondary endpoints are as follows:

1. Total number of gadolinium enhancing (Gd-enhancing) T1-lesions per MRI scan by Week 96.
2. Total number of new and enlarging T2 hyperintense lesions (NELs) per MRI scan by Week 96.
3. Time to Confirmed Disability Progression (CDP) for at least 12 weeks occurring during the 96-week double-blind treatment period. *
4. Proportion of subjects with No Evidence of Disease Activity (NEDA) from Week 24 to Week 96.
5. Proportion of subjects reaching impaired SDMT (Symbol Digit Modalities Test) from baseline to Week 96.
6. Percentage change in Brain Volume from baseline to Week 96.

* Confirmed Disability Progression for at least 12 weeks during the 96-week treatment period will be analyzed using pooled data from the two identical studies TG1101-RMS301 and TG1101-RMS302.

2.3 TERTIARY ENDPOINTS

1. Change in MSFC score from baseline to Week 96
2. Time to Confirmed Disability Progression (CDP) for at least 24 weeks
3. Time to Confirmed Disability Improvement (CDI) for at least 12 weeks
4. Time to Confirmed Disability Improvement (CDI) for at least 24 weeks
5. Health outcomes (MSQoL-54 (inclusive of SF36); FIS, hospitalization, steroid use, time out of work)
6. Total volume of Gd enhancing T1 lesions per MRI scan over the treatment period
7. Volume of T2 lesions
8. Volume of hypointense T1 lesion component (black holes)
9. Proportion of subjects free of disability progression at 24 weeks, 48 weeks, and 96 weeks
10. Proportion of subjects with a relapse
11. Time to first confirmed relapse

3 STUDY POPULATION

3.1 INCLUSION CRITERIA

Subjects must meet the following inclusion criteria to be eligible for participation in this study:

1. 18-55 age
2. Diagnosis of RMS (McDonald criteria 2010; Appendix C)
3. ≥ 2 relapses in prior 2 years or 1 relapse in the year prior to screening and/or ≥1 Gd enhancing lesion
4. Documented MRI of brain with abnormalities consistent with MS
5. Active disease
6. EDSS 0-5.5 (inclusive) at screening
7. B cell counts ≥5% of total lymphocytes
8. Neurologic stability ≥ 30 days prior to screening and baseline
9. Female subjects who are not of child-bearing potential, have documented surgical sterilization (see Appendix A), and female subjects of child-bearing potential who have a negative serum pregnancy test at baseline. Female subjects of child-bearing potential (see Appendix A), and all male partners must consent to use a medically/clinically acceptable method of contraception throughout the treatment period and for 20 weeks after the cessation of active treatment. Female subjects of child-bearing potential (see Appendix A) must agree to undertake urine pregnancy tests every 4 weeks during active treatment and the follow up period.
10. Fertile male subjects participating in the study who are sexually active with women of child bearing potential, must agree to use a condom during the treatment period and for an additional 20 weeks after cessation of active treatment. Agree to use an accelerated elimination procedure after the last dose of study medications or early termination from the study (see Section 6.10.1)
11. Willingness and ability to comply with trial and follow-up procedures, give written consent

3.2 EXCLUSION CRITERIA

Subjects who meet any of the following exclusion criteria are not to be enrolled to this study:

1. Treatment with Anti-CD20 or other B cell directed treatment
2. Treatment with the following therapies at any time prior to randomization:

    - Alemtuzumab
    - Natalizumab,
    - Teriflunomide,
    - Leflunomide, and
    - Stem cell transplantation

3. Contraindications to teriflunomide or incompatibility with use of teriflunomide.
4. Therapies that are disallowed (minimum of 4 weeks prior to randomization): phenytoin, warfarin, tolbutamide, St John's Wort or cholestyramine
5. Prior DMT exposure within months of screening:
    a. 24 months with cladribine
    b. 6 months with daclizumab, azathioprine, methotrexate, or cyclophosphamide
    c. 90 days with fingolimod, or experimental S1P modulators, IV immunoglobulin, and plasmapheresis
    d. 30 days with glatiramer acetate, interferons, dimethyl fumarate, laquinimod or glucocorticoids
6. Diagnosed with Primary Progressive MS (PPMS)
7. Pregnant or nursing
8. ≥ 10 years disease duration from onset with subjects EDSS ≤ 2.0
9. Contraindication for MRI and/or gadolinium

10. Known presence of other neurologic disorders that may mimic MS
11. Current evidence or known history of clinically significant infection including:
    a. Chronic or ongoing active viral, bacterial, or fungal infectious disease requiring long term systemic treatment such as, but not limited to: PML, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis (TB), or active hepatitis C
    b. Previous serious opportunistic or atypical infections
    c. History of positive serology for hepatitis B or hepatitis C or HIV
12. History of clinically significant CNS trauma (e.g., traumatic brain injury, cerebral contusion, spinal cord compression)
13. History of liver disease, including but not limited to:
    a. Known history of active hepatitis B or C any time prior to randomization or known history of active hepatitis A within 3 years prior to randomization
    b. Presence of clinically significant chronic liver or biliary disease
    c. Moderate or severe hepatic impairment defined as Child Pugh Score B or C, respectively, based on measurement of total bilirubin, serum albumin, International Normalized Ratio (INR) and as well as on presence /absence and severity of ascites and hepatic encephalopathy
    d. Any of the following abnormal laboratory values at screening or first infusion:
    - ALT/SGPT>2X the Upper Limit of Normal (ULN)
    - AST/SGOT>2X ULN
14. Previous diagnosis with a congenital or acquired immunodeficiency (AIDS)
15. History of renal impairment, including, but not limited to:
    a. Hypoproteinemia (e.g., in case of severe renal disease or nephrotic syndrome) with serum albumin <3.0 g/dL
    b. Severe renal insufficiency requiring renal dialysis
16. Past or current history of medically significant adverse effects (including allergic reactions) from:
    a. Corticosteroids
    b. Diphenhydramine
    c. Murine or mouse/human chimeric antibodies
17. Subjects with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia
    a. Hematocrit <24% and/or
    b. Absolute white blood cell count <4,000 cells/mm^3 and/or
    c. Platelet count <150,000 cells/mm^3 and/or
    d. Absolute neutrophil ≤ 1,500 cells/mm^3
18. Absolute lymphocyte counts less than 1000/microliter
19. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    a. Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV [see Appendix B]
    b. QTcF: Female >450 msec; male > 430 msec Angina not well-controlled by medication
    c. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months prior to screening
20. Other significant concurrent, uncontrolled medical condition including, but not limited to, cardiac, renal, hepatic, hematological, gastrointestinal, endocrine, immunodeficiency syndrome, pulmonary, cerebral,

psychiatric, or neurological disease which could affect the subject's safety, impair the subject's reliable participation in the trial, impair the evaluation of endpoints, or necessitate the use of medication not allowed by the protocol, as determined by the PI of the trial

21. Current participation in any other interventional clinical trial. Participation in non-interventional trial requires approval by the Sponsor
22. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol
23. Lack of immunity to varicella as determined by screening based on the level of VZV IgG. Subject may receive vaccine and be rescreened
24. Vaccination with live virus within 2 months of randomization
25. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation or bone marrow transplantation

3.3 DISCONTINUATION FROM STUDY TREATMENT

Subjects will be discontinued from trial treatment or withdrawn from the study for any of the following reasons:

- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Subject requests to withdraw consent or discontinue treatment
- Pregnancy (see Section 3.3.1)
- Inability of the subject to comply with trial requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Inter-current illness (this will be at the Principal Investigator and/or Treating Neurologist discretion)
- Malignancy
- Discontinuation of the study by the Sponsor

After discontinuation from protocol treatment all subjects (other than those who withdraw consent and refuse to enter into the 20 week Follow-up Period) should undergo an accelerated teriflunomide elimination procedure with either oral cholestyramine or oral activated charcoal and be followed for safety for 20 weeks after their last dose of ublituximab/oral placebo or teriflunomide/IV placebo. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the PI and/or Treating Neurologist, these values are not likely to improve because of the underlying disease. In this case the PI and/or Treating Neurologist must record his or her reasoning for this decision in the subjects' medical records and as a comment on the electronic Case Report Form (eCRF).

All subjects who have Common Terminology Criteria for Adverse Events (CTCAE; Ver 4.03) grade 3 or 4 laboratory abnormalities at the time of discontinuation from protocol treatment must be followed until the laboratory values have returned to grade 1 or 2, unless it is, in the opinion of the PI and/or Treating Neurologist, not likely that these values are to improve because of the underlying disease. In this case, the PI or Treating Neurologist must record his or her reasoning for making this decision in the subjects' medical records and as a comment on the eCRF.

Any subject that withdraws their consent to participate in the study will have all data collection stop on that day and will not be followed-up on. These subjects, however, could be followed further if they agree to sign the Early Termination ICF and enter the 20 week Follow-up Period.

3.3.1 PREGNANCY

During the course of the trial, all female subjects of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix A) must contact the PI and/or Treating Neurologist immediately if they suspect that they may be pregnant (a missed or late menstrual period should also be reported to the PI and/or Treating Neurologist).

If an investigator suspects that a subject may be pregnant during the study, the trial drugs must be withheld immediately, until the result of the pregnancy test is confirmed. Subjects will proceed with a urine pregnancy test immediately. If the urine pregnancy test is positive, the subject should be informed of the potential teratogenic effects, therefore consideration to withhold further teriflunomide/oral placebo dosing should be made and follow-up appointment should be scheduled as soon as possible where a serum pregnancy test will be performed for confirmation.

If a pregnancy is confirmed via serum pregnancy test, the trial drugs must be stopped immediately and permanently. The subject will complete the Withdrawal from Treatment Visit as soon as possible and will then enter the 20-week Follow-up Period inclusive of accelerated teriflunomide elimination procedure with either oral cholestyramine or oral activated charcoal. The subject will be expected to complete the full Follow-up Period regardless of the outcome of the pregnancy. The investigator must record the pregnancy on a Pregnancy Report Form within 24 hours of learning of its occurrence (see Section 9.10.6 for more details on pregnancy reporting).

Additionally, if a pregnancy is confirmed, the subject will be asked to sign an informed consent form to allow the collection of medical information of both the subject and her baby throughout the pregnancy and until 6 months after the baby is born, as permitted by local regulations. Where required by local regulations, the consent of the father will also be obtained.

If a male subject's female partner becomes pregnant and the male subject has taken at least one dose of study medications (ublituximab/oral placebo or teriflunomide/IV placebo), the pregnancy and newborn will also be followed. In this case, the subject's partner will be asked to sign an informed consent form to allow the collection of medical information of both the mother and baby throughout the pregnancy and until 6 months after the baby is born, as permitted by local regulations. Where required by local regulations, the consent of the male subject will also be obtained. If the mother is younger than legal age, her parent(s)/guardian(s) will also need to give consent, as required by local regulations.

Prior to discharge from the study, all subjects will be counseled by the treating team to have their teriflunomide plasma concentration re-measured prior to attempting to become pregnant or trying to impregnate their female partner.

Confirmed pregnancy must be reported to pharmacovigilance.

4 TREATMENT PLAN

4.1 DEFINITION OF STUDY STAFF

4.1.1 AT THE STUDY SITE

At each study center the staff will consist of a minimum of two neurologists. One neurologist will be the Treating Neurologist and one will be the Examining Neurologist for a given subject throughout the study. An MRI radiologist and technologist, and a clinical coordinator, and a pharmacist (or another authorized staff member) must also be members of the study staff at each center. A technician/staff nurse qualified to perform MSQoL54 (inclusive of SF36) and FIS must also be a member of the study staff at each center. When performing a relapse assessment or disability progression, the results from the Treating and Examining Neurologist will not be shared.

4.1.2 PRINCIPAL INVESTIGATOR

At each investigational center, a neurologist will be appointed to serve as a Principal Investigator and will have overall responsibility to lead the site study team (neurologists, radiologists, technicians, staff nurses, pharmacists and clinical coordinators) in all aspects of the study. The Principal Investigator will oversee the recruitment and accrual of appropriate subjects, the conduct of the study according to the study protocol, and the collection of required study data and regulatory requirements including timely reporting of all SAEs. The Principal Investigator may be the Treating Neurologist for a given subject but cannot be the Examining Neurologist (see Sections 4.1.3 and 4.1.4 for the roles and responsibilities of the Treating Neurologist and Examining Neurologist, respectively).

4.1.3 TREATING NEUROLOGIST

The Treating Neurologist will be responsible for subjects' care, eligibility evaluation, supervision of study medication administration, recording and treating of adverse events, serious adverse events and assessing and treating of MS relapses, performing neurological examinations and monitoring of safety assessments, including routine laboratory results and concomitant medications. The Treating Neurologist will provide no information to the Examining Neurologist. The MSFC and SDMT assessments may be performed by the Treating Neurologist, or may be delegated to another qualified team member, but must not be performed by the Examining Neurologist. The Treating Neurologist (who does not perform the EDSS assessment), other investigative site staff and subject should not have access to Examining Neurologist's EDSS scores. It is encouraged that the same physician maintain the role of Treating Neurologist for a given subject throughout the study.

4.1.4 EXAMINING NEUROLOGIST (EVALUATING NEUROLOGIST)

The Examining Neurologist (EDSS Rater) will be responsible for conducting and documenting all EDSS assessments. The Examining Neurologist will not share the findings of the EDSS assessment when evaluating relapses with the Treating Neurologist. The Examining Neurologist must possess current EDSS rater certification (Level C). Throughout the study, the Examining Neurologist is blinded to all subject information collected by the Treating Neurologist which includes adverse events, concomitant medications, laboratory results, and any clinical MS examination for enrolled subjects. Additionally, the Examining Neurologist should not have access to any prior EDSS scores from any time throughout the study or any clinical information when performing their examination.

The Examining Neurologist will also be responsible for entering the EDSS assessment data into the electronic Case Report Form (eCRF). The entry of EDSS assessment data into eCRF may be delegated to another staff member, provided that the staff member has been trained in the eCRF, maintains the same level of blinding as that of the Examining Neurologist and is not involved in any other study-related activities, other than EDSS assessments.

Every effort should be made to ensure that there is no change in the EDSS Rater throughout the course of the study for any individual subject. Whenever possible, the same person should perform the examination for the full study duration. All members of the study staff at the clinical site and the subject should not discuss safety issues with the Examining Neurologist. Subjects will be instructed not to discuss any clinical symptoms or experiences while on trial with the Examining Neurologist. The Examining Neurologist should remind the subject at the start of the examination to not discuss any clinical symptoms or experiences while on trial.

In exceptional cases, where a site clinical research nurse or a clinical coordinator has neurostatus EDSS rater certification level C and extensive experience with EDSS assessments in clinical trials, they may be delegated the responsibilities of the Examining Neurologist provided the required level of blinding is maintained. Additionally, TG Therapeutics' written approval will be required in advance of such a delegation.

The Treating Neurologist and the Examining Neurologist will NOT be allowed to switch roles.

4.1.5 MRI STAFF

The MRI staff will be responsible for performing the MRI according to the protocol and MRI manual. They will also prepare adequate electronic material according to the MRI manual for transfer of images to the central MRI reader. The MRI manual will provide instructions for storage of the primary data at the site.

Radiologist will review MRI scans locally for non-MS pathology and will provide reports to the Treating Neurologist. Local MRI reports after randomization must not contain details of the MS pathology, MRI scans will be read centrally for MS pathology by the central MRI reader.

4.1.6 CLINICAL COORDINATOR

The clinical coordinator will be responsible for coordinating and assisting all study site staff, including subject scheduling and completion and monitoring of all subjects' electronic Case Report Forms. He/she will instruct the subjects on proper study medication administration, subject diary adherence, obtain vital signs, collect, process, and send all blood and urine samples and requests to the central laboratory. Additionally, he/she will be responsible for administering the subject-reported questionnaires (MSQoL-54 and FIS) and coordinating subject's appointment with other departments, e.g.., imaging facility etc. Some or all of these study-related activities may instead be performed by the Treating Neurologist or a qualified technician/staff nurse.

4.2 STUDY COMMITTEES

4.2.1 DATA SAFETY MONITORING BOARD (DSMB)

The DSMB will be an independent group of individuals not involved in the study or study sites or have other conflicts of interest with the study and are charged with reviewing safety data and conduct of the trial. The independent DSMB will be comprised of five members with at least three MDs, a biostatistician, and the DSMB chair. The responsibilities of the DSMB will be described in a DSMB Charter. The committee will meet periodically, but at least annually to fulfill the duties and obligations outlined in the DSMB Charter. Minutes of these meetings will be prepared as specified in the DSMB Charter. There will be minutes from both an open session which will be transmitted to the Sponsor and CRO and minutes of the closed session maintained by an unblinded DSMB Coordinator from CRO until the study is complete, at which point they will be transmitted to the Sponsor and CRO. Statistical analyses required for the planned DSMB meetings will be prepared and disseminated to the DSMB members. The committee will receive unblinded safety data to allow review and assessment by treatment group. In addition, the committee will receive unblinded efficacy data to perform benefit/risk ratio assessment. On the basis of their reviews and analyses of safety and efficacy data, the committee shall have the right to advise the sponsor to stop the study after any meeting for efficacy or detrimental effects or futility. The process and options will be specified in the Charter.

4.2.2 STEERING COMMITTEE

An external Steering Committee will provide general guidance, assist with liaison to investigators and oversee some external communication of the results of the study.

4.2.3 INDEPENDENT RELAPSE ADJUDICATION PANEL (IRAP)

The IRAP will make all protocol-defined relapse determinations in this study. The IRAP will review all subject-reported, suspected, on-study relapses (i.e., new or worsening neurological symptoms) and all potential events are sent to the IRAP regardless of whether the Treating Neurologist considered the subject's symptoms to be the result of a relapse. Please see Appendix D, and Section 6.3.1 of this protocol, and the IRAP Charter for further details.

4.2.4 BLINDED ASSESSMENT RELAPSE TEAM (BART)

An independent committee, Blinded Assessment Relapse Team (BART), reporting to TG Therapeutics, and the DSMB will reassess the sample size for the study when 210 of the 220 participants in each arm have been randomized. Team will consist of a chair, 1 biostatistician and 1 other neurologist with MS experience.

4.3 DOSING SCHEMA

Table 3: Ublituximab/Oral Placebo and Teriflunomide (14 mg)/IV Placebo

<table>
<tr><th></th><th>Week 1
Day 1</th><th>Week 3
Day 15</th><th>Week 24</th><th>Week 48</th><th>Week 72</th><th>Week 96</th></tr>
<tr><td rowspan="2">Ublituximab plus oral placebo</td><td>UTX (150 mg/ 4h)</td><td>UTX (450 mg/ 1h)</td><td>UTX (450 mg/1h)</td><td>UTX (450 mg/ 1h)</td><td>UTX (450 mg/ 1h)</td><td></td></tr>
<tr><td colspan="6">Oral Placebo QD* from Week 1 Day 1 until the last day of Week 95</td></tr>
<tr><td rowspan="2">Teriflunomide plus placebo infusion</td><td colspan="6">Teriflunomide (14 mg) QD* from Week 1 Day 1 until the last day of Week 95</td></tr>
<tr><td>Infusion Placebo</td><td>Infusion Placebo</td><td>Infusion Placebo</td><td>Infusion Placebo</td><td>Infusion Placebo</td><td></td></tr>
</table>

*May be taken in the morning daily. Alternative dosing times are allowed if necessary.

4.3.1 STOPPING RULES

There are no pre-planned interim analyses planned with formal stopping rules for effectiveness. The DSMB may make recommendations to stop the trial and will provide their rationale justification along with such a recommendation as will be specified in the DSMB Charter.

4.4 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

The following treatments are prohibited while on clinical trial: other investigational drug treatments or interventional study participation, other DMTs used to treat MS, radiation therapy, hormonal therapy for cancer, cancer immunotherapy or other biologic therapy excluding study medication. The exceptions to this are:

- No glucocorticoids may be administered outside of protocol requirements for pre-medication or AE management, except low doses of steroids stabilized at ≤ 10 mg per day of prednisone or equivalent, and started at least 7 days prior to study entry (Screening).

Antiemetic for Ublituximab or IV placebo: Ublituximab or IV placebo is considered to be of low emetogenic potential that may be adequately prevented with prochlorperazine. Other antiemetic may be used at the discretion of the Treating Neurologist/PI if nausea and/or vomiting is not adequately controlled/prevented.

Pre-medication prior to infusion with ublituximab or IV placebo: Infusion Related Reactions have been reported with ublituximab or IV placebo with more profound reactions in subjects with hematologic malignancies. All subjects treated with ublituximab or IV placebo require pre-medication 30–60 minutes prior to each dose of ublituximab or IV placebo with an antihistamine (diphenhydramine 50 mg or equivalent; administered orally), and a corticosteroid (dexamethasone 10-20 mg or equivalent; administered orally).

Treatment of IRR: Symptomatic infusion reactions despite pre-medication, may be treated at the discretion of the treating physician, including but not limited to: oral acetaminophen 650 mg (only used for intervention), corticosteroids, antihistamines, oxygen and bronchodilators.

Note: In case the above referenced medications are not available, equivalents can be used at the investigator's discretion. If medications are given intravenously, the IV line used for ublituximab/IV placebo should not be used. If needed, please consult the Medical Monitor.

Antihypertensive Medications: Since infusion related hypotension may occur, the investigator should carefully consider withholding anti-hypertensive medication during the 24 hours prior to, and throughout the IV infusion of ublituximab or placebo.

4.4.1 MS RELAPSE DURING THE STUDY

MS Relapses During the Study

Subjects enrolled into the study will be closely monitored through the study course by the Site and Sponsor's personnel as well as by an external independent Data Safety Monitoring Board (DSMB) to ensure subjects' welfare.

Relapses that occur after study drugs are withdrawn will be assessed over the remainder of the study period and this data will be utilized as part of additional sensitivity analysis (described in the statistical plan) as long as the subject has not withdrawn their consent to be in the trial.

The confirmation of a protocol-defined relapse will be determined by the Independent Relapse Adjudication Committee (IRAP). The steps for confirming a relapse are as follows:

1. **Subject Reported Relapse**

Subjects who experience new or worsening neurologic symptoms are instructed to contact the Treating Neurologist within 48 hours of symptom onset. All new or worsening neurological events, reported at a visit or over the phone, consistent with MS representing a clinical relapse as assessed by the subject will be initially reported to the Treating Neurologist. In parallel, the Examining Neurologist will also be notified to perform additional assessments. Upon the notification to the Treating Neurologist, the time and date of suspected subject reported relapse will be documented in the dedicated page eCRF (subject reported) by the Treating Neurologist or designee.

The following should be recorded in the eCRF (subject reported) by the Treating Neurologist or designee:

- Date and time of symptom onset as reported by the subject
- Symptoms and events reported by the subject (both neurological and non-neurological)
- Date of initial contact by subject
- Time of initial contact by subject

Within 7 days of the subject reporting the suspected relapse to the Treating Neurologist, the subject will be scheduled and assessed by both the Treating and Examining Neurologist independently.

2. **Initial Assessment of Relapse by Treating Neurologist and Examining Neurologist**

The Treating Neurologist will perform a neurological and physical examination and safety assessment. The Treating Neurologist or designee will document in the eCRF the following:

- Time and date of neurological and physical examination
- Clinical findings of neurological and physical examination
- Review of previously documented concomitant medications and medical history
- Safety assessment, including vital signs, CBC, B-cell count, lymphocyte counts, fibrinogen, quantitative immunoglobulin

Subjects with suspected clinical relapses reported to the Treating Neurologist or designee will be referred to the blinded Examining Neurologist who will use Neurostatus to assess the EDSS independently of the Treating Neurologist.

The Examining Neurologist or designee will document in the eCRF the following:

- Date and time of assessment
- EDSS score
- FS Scores

In addition, subjects may not begin IV methylprednisolone (IVMP) treatment of a relapse until the Examining Neurologist has completed his/her examination.

Treatment of relapses may proceed at the discretion of the Treating Neurologist only after the Examining Neurologist has completed his/her exam. The Treating Neurologist will not know the results of the EDSS assessment. When making determination to treat a potential acute relapse the Treating Neurologist can use IVMP (1.0 g/day for at least 3 days and can be extended to 5 days) and will not affect the subject eligibility to continue in the study.

The subject must re-consent at the time of each IRAP-confirmed or Treating Neurologist medically confirmed relapse to continue.

The findings from either the Treating Neurologist and Examining Neurologist will not be shared. The Examining Neurologist must be blinded to the Treating Neurologist's assessment and vice versa.

Following the completion of assessments by the Treating and Examining Neurologists these results will be sent independently to the IRAP.

3. Confirmation of Relapse by IRAP

All assessments entered into the eCRF from both the Treating Neurologist and the blinded Examining Neurologist, will be sent to an Independent Relapse Adjudication Panel (IRAP). IRAP adjudicates each case based on all available data provided for that case and members are not permitted to contact the site or the sponsor for additional information. The IRAP will, in turn, make the final determination of whether the neurological events meet the criteria for a protocol-defined relapse.

Each episode of relapse must be confirmed by the IRAP, based on the neurological assessments performed by the Treating and/or Examining Neurologist independently by documenting either of the following:

- ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory or visual). Note, the change in FS scores should correspond to the patient's symptoms (e.g., patient reported change in visual acuity should correspond to a change in the vision FS score). Episodic spasm, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse;
- An increase of ≥0.5 points in the EDSS score (unless EDSS score = 0, then an increase of at least 1.0 points is required) from the previous clinically stable assessment.

MS relapses are defined as a new or worsening neurological symptoms lasting ≥24 hours with the absence of fever, injury, infection or adverse reactions to medications and accompanied by new neurological findings upon examination by the Examining Neurologist. The symptoms are attributed to MS and are preceded by 30 days of stability or improvement in neurological state. The change in EDSS score as assessed by the Examining Neurologist is ≥ 0.5 increase or ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory or visual). Note, the change in FS scale scores should correspond to the patient's symptoms (e.g., patient reported change in visual acuity should correspond to a change in the vision FS score). Episodic spasm, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Please note: sexual dysfunction and fatigue will not be scored. If the symptoms occur less than 30 days following the onset of a protocol defined relapse, it should be considered part of the same relapse and would not be treated with IVMP within the protocol. New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse and should not be treated with steroids.

The suspected relapse must be reviewed and confirmed by the IRAP; Appendix D. The IRAP will then notify the CRO and Treating Neurologist of the results of its review.

Treating Neurologist or designee will enter into the eCRF whether the neurological symptoms identified were a result of an IRAP-confirmed relapse.

IRAP-confirmed relapses are the sole confirmation of a protocol-defined relapse. However, for instances where IRAP-confirmed relapses may not be feasible, provisions are provided within Section 4.4.2 (Treating Neurologist medically confirmed relapse).

The subject must re-consent at the time of each IRAP-confirmed or Treating Neurologist medically confirmed relapse to continue.

Signing the informed consent form for re-consent (if the subject has a confirmed relapse), to proceed with the study at the next scheduled office visit should be within 6 weeks after first reporting of relapse.

4.4.2 TREATING NEUROLOGIST MEDICALLY CONFIRMED RELAPSE

In suspected relapse events for which IRAP confirmation is pending, may not be logistically possible, and/or complete case profiles for IRAP review are not available, the Treating Neurologist will medically evaluate the suspected relapse event. In these cases, all information from the Treating Neurologist's medical evaluation should still be entered into the eCRF and provided to the IRAP for adjudication. This is to ensure each suspected relapse is documented. Treating Neurologist medically confirmed relapses will not be included in the ARR calculation for the primary endpoint. For any relapse that is Treating Neurologist medically confirmed, subjects should re-consent to continue participation in the trial.

4.4.3 RE-CONSENT CRITERIA AFTER RELAPSING

If a relapse is confirmed by IRAP and/or deemed a Treating Neurologist medically confirmed relapse, the following actions will be taken:

- The subject will be reminded of the current approved MS medications/treatments and the opportunity to terminate the study and be treated with an approved MS medication.
- The subject will be requested to re-sign an informed consent form within 6 weeks after first reporting of the suspected relapse if he/she chooses to continue to participate in the study, in the same treatment assignment.

4.4.4 DISABILITY PROGRESSION

The method of disability progression calculation will be different than that of the relapsed confirmation. The EDSS score will be used to assess disability progression. EDSS assessment will be performed by the Examining Neurologist. The Examining Neurologist must not share the EDSS score with the Treating Neurologist. The scheduled EDSS assessment for disability progression will be performed at screening and on Week 1 Day 1 (prior to randomization) and Weeks 12, 24, 36, 48, 60, 72, 84 and 96. Disability progression is a post hoc analysis only and will not be calculated by the Evaluating Neurologist or other study staff.

Disability progression is defined as an increase of ≥1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥0.5 when the baseline score is above 5.5. Disability progression is considered confirmed when the increase in the EDSS score is confirmed at regularly scheduled visits at least 12 or 24 weeks after the initial documentation of neurological worsening..

4.5 DURATION OF THERAPY

For subjects randomized to ublituximab or treated with IV placebo, infusion will occur on Week 1 Day 1, Week 3 Day 15, and Weeks 24, 48 and 72.

For subjects randomized to teriflunomide or treated with oral placebo, administration may be taken in the morning until the last day of Week 95. Alternative dosing times are allowed if necessary.

If the subject discontinues the study, the reason for study removal and the date the subject was removed must be documented in the eCRF. Subjects who discontinue treatment due to an adverse event should be followed until resolution of the adverse event, unless the event is considered by the Treating Neurologist/PI to be due to the subject's underlying disease.

4.6 SUBJECT RETENTION STRATEGIES

Understanding adherence to pharmacotherapies is crucial in clinical practice and research studies to ensure optimal clinical outcomes and valid study results. Thus, subject adherence can apply to several different clinical trial facets that may include adherence to study procedures, study visit compliance, medications, and adverse event reporting.

For PIs and study site personnel associated with subject recruitment, selection of subjects who understand study burdens and are willing to commit to regimens is a critical up-front step in promoting research adherence. Effective screening is required by the study team to exclude subjects who might reasonably be identified as at risk for non-adherence based on histories of poor adherence with treatments, inconsistency with medical care (lateness or missed appointments), problematic communication or unsure about study participation. Additionally, the study must make sure that the subject will accept random allocation and communicate the importance of study adherence to the subject.

Table 4 (18) below shows different strategies that the study site can employ onto subjects should there be a risk of study adherence:

Table 4. Strategies to employ study adherence

Study adherence risk level	Subject indicators	Retention strategies
Low	No problems scheduling appointments or completing assessment information	Express appreciation of participants' involvement and efforts (routine) Ensure confidentiality of Information provided (routine)

		Obtain and update contact information (routine) Discuss potential or anticipated barriers to attending appointments (routine) Provide travel/meal reimbursement for study visits, in accordance with local regulation (routine)
Medium	Concerns about the study medication, behavioral treatment, or procedures Concern that current condition or circumstances could interfere with fulfilling study requirements Reluctant to schedule follow-up appointments due to aforementioned concerns about treatments, circumstances, or conditions	Normalize and accept concerns about the study (routine) Continue to provide education/communicate on the disease and treatments to the subject (routine) Remind subject about rationale for study involvement (routine) Provide a range of options to facilitate involvement (non-routine)
High	Cancels appointments frequently without rebooking, regular no-show, and is unresponsive to contacts for rescheduling appointments Reveals a desire to drop out of the trial	Conduct an adherence assessment; that is, learn the participant's explanation for nonattendance or wish to drop out (non-routine) Obtain consensus about risk factors associated with nonadherence (non-routine) Establish priorities for attending to risk factors (non-routine) Identify a range of options for addressing nonadherence (non-routine) Send out letters or emails to participants who are unresponsive to personal contact (non-routine) Delay decision making about dropping out (non-routine) Accept a "no" as temporary and obtain permission to re-contact at a later time (non-routine)

5 DOSING DELAYS

Subjects should be assessed clinically for toxicity at each visit using the NCI CTCAE v4.03 grading scale (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Dosing will occur only if a subject's clinical assessment is acceptable as determined by the Principal Investigator and/or Treating Neurologist. Subjects should be advised to seek immediate medical help and inform their Principal Investigator and/or Treating Neurologist if they experience signs or symptoms of an infection including a respiratory infection or meningoencephalitis.

A minimum of 16 weeks should be observed between subsequent infusions. If the postponement of an infusion visit occurs which subsequently results in less than 16 weeks before the next infusion visit, the case should be escalated to the Sponsor for consideration.

5.1 CRITERIA FOR ONGOING TREATMENT

Repeat treatment of ublituximab/oral placebo or teriflunomide/IV placebo should be administered per protocol provided that:

- Renal function is continually assessed
- Liver enzyme levels are monitored monthly for the first 6 months
- Recovered from Grade 3-4 non-hematologic toxicity to Grade 2 or less.
- Subject remains compliant to taking teriflunomide or oral placebo and all study scheduled study assessments.
- Treatment may be delayed to recover from toxicity, such as Infusion Related Reaction or per the discretion of the PI and/or Treating Neurologist.

5.2 GUIDANCE FOR SUSPECTED RELAPSE

If a subject experiences a suspected relapse at any study visit after the 1st dose of either study medication, the following actions are to be taken:

Suspected Relapse	Action to be Taken
At Scheduled Infusion Visit	Perform an unscheduled relapse visit and do not perform the infusion visit. The scheduled infusion visit is postponed until a) treatment of relapse has been completed, and b) subject is neurologically stable, per PI/Treating Neurologist discretion
At Non-Infusion Visit	Perform the unscheduled relapse visit and skip the scheduled non-infusion visit. Most of the assessments that should be performed at the scheduled non-infusion visits are also performed at the unscheduled relapse visit, so the scheduled non-infusion visit can be completely skipped and marked as Not Done in the CRF. However, the following assessments should still be done: -Subject diary and teriflunomide/oral placebo administration

Suspected Relapse	Action to be Taken
	- MRI will still be done (ideally prior to steroid treatment/ if not, then after 30 days
At Early Withdrawal From Treatment Visit	Perform the unscheduled relapse visit and skip the scheduled non-infusion visit. The patient should then return for the Early Withdrawal from Treatment Visit once a)treatment of relapse has been completed, and b)subject is neurologically stable, per PT/Treating Neurologist discretion.
Teriflunomide/Oral Placebo	Administration of teriflunomide/oral placebo can continue during a relapse at discretion of the PI/Treating Neurologist

5.3 GUIDANCE FOR LABORATORY ABNORMALITIES

For RMS subjects, the hematologic dose modifications are graded by the CTCAE v4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

If a subject experiences neutropenia, thrombocytopenia, anemia, and elevated liver enzymes at any study visit after the 1st dose of either study medication, the following actions are to be taken:

Worst CTCAE Grade Toxicity	Action to be Taken
Neutropenia	
Grade	**Management**
≤ Grade 1	No action required.
Grade 2	No action required.
Grade 3 or 4 1st and Subsequent Occurrences	**Withhold** study medications (both ublituximab/oral placebo and teriflunomide/IV placebo). If during an infusion visit, postpone entire infusion visit. If during a non-infusion visit, entire visit can be conducted. MRI can proceed as scheduled. **Repeat** hematology testing within 2 weeks. For confirmed neutropenia Grade 3 or 4, repeat hematology testing at the discretion of the PI and/or Treating Neurologist until <Grade 3. **Resume** teriflunomide/oral placebo at discretion of PI and/or Treating Neurologist if < Grade 3. **Perform** the next ublituximab/IV placebo infusion at discretion of PI and/or Treating Neurologist if < Grade 3.
Management of neutropenia are per institution guidelines and if in the opinion of PI and/or Treating Neurologist, are appropriate for subject care.	

Worst CTCAE Grade Toxicity	Action to be Taken
Thrombocytopenia or Anemia	
Grade	**Management**
≤ Grade 1	No action required.
Grade 2	No action required.

Worst CTCAE Grade Toxicity	Action to be Taken
Thrombocytopenia or Anemia	
Grade	**Management**
Grade 3 or 4 1st and Subsequent Occurrences	**Withhold** study medications (both ublituximab/oral placebo and teriflunomide/IV placebo). If during an infusion visit, postpone entire infusion visit. If during a non-infusion visit, entire visit can be conducted. MRI can proceed as scheduled. **Repeat** hematology testing within 2 weeks. For confirmed thrombocytopenia or anemia Grade 3 or 4, repeat hematology testing at the discretion of the PI and/or Treating Neurologist until <Grade 3. **Resume** teriflunomide/oral placebo at discretion of PI and/or Treating Neurologist if < Grade 3. **Perform** the next ublituximab/IV placebo infusion at discretion of PI and/or Treating Neurologist if < Grade 3.
Management of thrombocytopenia and anemia are per institution guidelines and if in the opinion of PI and/or Treating Neurologist, are appropriate for subject care.	

Worst CTCAE Grade Toxicity	Action to be Taken
Elevated Liver Enzymes (ALT and AST)	
Grade	**Management**
≤ Grade 1	No action required.
Grade 2, 3 or 4 1st and subsequent occurrences	**Withhold** study medications (both ublituximab/oral placebo and teriflunomide/IV placebo). If during an infusion visit, postpone entire infusion visit. If during a non-infusion visit, entire visit can be conducted. MRI can proceed as scheduled. **Repeat** chemistry testing within 2 weeks. For confirmed liver enzyme(s) Grade 2 or higher, repeat chemistry weekly until <Grade 2. **Resume** teriflunomide/oral placebo at discretion of PI and/or Treating Neurologist if < Grade 2. **Perform** the next ublituximab/IV placebo infusion at discretion of PI and/or Treating Neurologist if < Grade 2.
Management of elevated liver enzymes are at the discretion of the PI and/or Treating Neurologist and should be discussed with CRO.	

6 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Individual trial procedures are detailed in Tables 5-7. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Treating and Examining Neurologists.

Additional evaluations/testing may be deemed necessary by the Treating Neurologist and/or the Sponsor for reasons related to subject safety.

Table 5: Schedule of Assessments and Procedures: Screening through Week 20

	Screening	Baseline	Treatment Period								Unscheduled Relapse Visit[14]
Week		W1	W1	W2	W3	W4	W8[4]	W12[4]	W16[4]	W20[4]	
Day[4]	D (-28 to 0)	D1	D2	D8	D15	D28	D56[4]	D84[4]	D112[4]	D140[4]	
Subject consent	X										X[10]
Medical history	X										
Serum pregnancy test[1]	X[11]										X
Urine pregnancy test[1,5]					X	X	X	X	X	X	
EDSS, MSFC, and neurological examination[4,13]	X	X[22]						X			X[18]
Physical examination[8] & vital signs (heart rate, blood pressure, temperature and body weight)[4, 13]	X	X	X	X	X	X	X	X	X	X	X
MSQoL54 (inclusive of SF36), SDMT, and FIS assessment[13]		X									
MRI[4,13]	X							X			
Subject diary and teriflunomide or oral placebo dispensation		X						X			
12 lead ECG[9]	X	X			X						
Blood collection for CBC, pancreatic enzymes and serum chemistry[3,4, 20]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[13]	X	X	X	X	X	X	X	X	X	X	X
Blood collection for B lymphocyte cell counts (% CD19+ B cells) [3,4]	X	X	X	X	X	X	X	X	X	X	X
Fibrinogen[3,4]		X			X						X
[redacted]											
Teriflunomide drug concentration test		X[3,17]									
Subject diary review and teriflunomide/oral placebo accountability		X	X	X	X	X	X	X	X	X	X
Serology: HIV, HCV, HBV, varicella[2]	X										
Anti-Drug Abs (ADA)[3,7]		X			X						
PT/INR[5]		X									
Quantitative immunoglobulin[3,4,13]		X			X						X
Adverse events (CTCAE v4.03)		X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Ublituximab/placebo infusion[24]		X			X						
Initiate teriflunomide/oral placebo administration[16]		X									

Table 6: Schedule of Assessments and Procedures: Weeks 24 through 84

	Treatment Period						Unscheduled Relapse Visit[14]
Week	**W24[4]**	**W36[4]**	**W48[4]**	**W60[4]**	**W72[4]**	**W84[4]**	
Day[4]	**D168[4]**	**D252[4]**	**D336[4]**	**D420[4]**	**D504[4]**	**D588[4]**	
Subject consent							X[10]
Urine pregnancy test[1,5,21]	X	X	X	X	X	X	
Serum pregnancy test[1]							X
EDSS, MSFC and neurological examination[4,13]	X	X	X	X	X	X	X[18]
Physical examination[8] & vital signs (heart rate, blood pressure, temperature and body weight)[4,13]	X	X	X	X	X	X	X
MSQoL54(inclusive of SF36), **SDMT and FIS assessment[5,13]**	X		X				
MRI[4,13]	X		X				
Subject diary and teriflunomide or oral placebo dispensation	X	X	X	X	X	X	
12 Lead ECG[9]	X		X		X		
Blood collection for CBC, pancreatic enzymes and serum chemistry[3,4,12]	X	X	X	X	X	X	X
Urinalysis[13]	X	X	X	X	X	X	X
Blood collection for B lymphocyte cell counts (% CD19+ B cells) [3,4]	X	X	X	X	X	X	X
Fibrinogen[3,4]	X		X		X		X
[redacted]							
Teriflunomide drug concentration test			X[3]				
Study diary review and teriflunomide/oral placebo accountability	X	X	X	X	X	X	X
Anti-Drug Abs (ADA)[3,7]	X		X		X		
Quantitative immunoglobulin[3,4]	X		X		X		X
Adverse events (CTCAE v4.03)	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X
Ublituximab/placebo infusion[24]	X		X		X		

Table 7: Schedule of Assessments and Procedures: End of Study, Follow-up, and Early Withdrawal from Treatment Visits

	End of Study	Follow-up Period					Early Withdrawal from Treatment	Unscheduled Relapse Visit[14]
Week	**W96[4]**	**W100[4]**	**W104[4]**	**W108[4]**	**W112[4]**	**W116[4]**		
Day[4]	**D672[4]**	**D700[4]**	**D728[4]**	**D756[4]**	**D784[4]**	**D812[4]**		
Subject consent							X	X[10]
Serum pregnancy test[1]							X	X
Urine pregnancy test[1,5]	X	X	X	X	X	X		
EDSS, MSFC and neurological examinations[4]	X						X	X[18]
Physical examination[8] & vital signs (heart rate, blood pressure, temperature and body weight)[4]	X	X	X			X	X	X
Subject Phone Consult				X	X			
MSQoL54 (inclusive of SF36), SDMT and FIS assessment[5]	X						X	
MRI	X[4]						X[4]	
12 lead ECG							X	
Blood collection for CBC, pancreatic enzymes and serum chemistry[4]	X	X	X				X	X
Urinalysis	X	X	X				X	X
Blood collection for B lymphocyte cell counts (% CD19+ B cells)[4]	X	X	X				X	X
Fibrinogen							X	X
[redacted]								
Anti-Drug Abs (ADA)[3,7]	X							
Quantitative immunoglobulin[4]	X						X	X
Adverse events (CTCAE v4.03)	X	X	X	X	X	X	X	X
Dispensation of activated charcoal or cholestyramine for accelerated procedure and dispensation of rapid elimination diary		X					X[23]	
Completion of accelerated teriflunomide elimination procedure; elimination procedure diary review and elimination drug accountability[19]			X					
Teriflunomide drug concentration test	X[12]					X	X[12]	

Concomitant medication	X	X	X	X	X	X	X	X
Study diary review and teriflunomide/oral placebo accountability[14]	X						X	X

[1] For women of child bearing potential

[2] To confirm negative HIV 1 and 2, Hepatitis B Virus, Hepatitis C Virus and varicella

[3] Labs drawn pre-infusion on any infusion days

[4] Weeks 8 and beyond, collections/assessments may occur ±5 days from specified time points, except for MRI scans, which can occur ±7days on Weeks 12 and 96 and must be performed pre-infusion on infusion days (- 7 days) on Weeks 24 and 48. MRI scan at Early Withdrawal from Treatment Visit should be performed within 4 weeks after withdrawing from the study.

[5] Prior to each infusion except PT/INR which is completed at baseline. Urine Pregnancy Test on non-infusion days subjects will test upon arrival at the site

[6] Prior to infusion and 30 minutes +/- 15 minutes post-infusion on infusion days. For non-infusion days, one PK sample should be obtained

[7] Anti-Drug Antibodies are antibodies developed against ublituximab

[8] Physical examination will occur on all visits except Week 1 Day 2 and Week 2 Day 8

[9] Within 2 hours pre-infusion and 60 minutes +/- 15 minutes post-infusion on any infusion day

[10] Re-consent following a suspected relapse is required if the relapse is confirmed by IRAP or by the Treating Neurologist (Treating Neurologist medically confirmed relapse), whichever comes first. Re-consent must occur within 6 weeks after first reporting of relapse. Re-consent may occur at the next schedule office visit but may require an unscheduled visit if the relapse occurs between Weeks 24 and 96 (where the frequency of scheduled visits is every 12 weeks).

[11] Serum pregnancy test must be completed within 5 days prior to Week 1 Day 1

[12] Obtain blood sample for teriflunomide drug concentration test prior to first dose of accelerated teriflunomide elimination procedure

[13] Prior to each infusion

[14] The Unscheduled Relapse Visit will be conducted if a possible relapse is reported by the subject. The visit is to be planned as soon as possible, within 7 days from subject notification of the relapse to the site. Infusion visit is delayed until relapse is back to baseline, or Treating Neurologist/PI does not expect any improvements.

[redacted]

[16] Teriflunomide/oral placebo administration shall be taken in the morning until the last day of Week 95. Alternative dosing times are allowed if necessary.

[17] Sample for teriflunomide concentration to be collected before the first oral dose of teriflunomide/oral placebo

[18] For Unscheduled Relapse Visit, EDSS assessment (by Examining Neurologist) and neurological examination (by Treating Neurologist) will be performed independently

[19] Acknowledge completion of 11-day accelerated teriflunomide elimination procedure started at week 100

[20] If the subject experiences neutropenia, thrombocytopenia, anemia, or elevated liver enzymes, follow guidelines and procedures on laboratory retests and study treatment per Section 5.2.

[21] Post Week 24 (including during the Follow-Up Period), urine pregnancy test will be administered every 4 weeks (+/- 5 days). On days when there is not a study visit, the subject will need to perform the test at home and contact the study site to provide the outcome

[22] Week 1/Day 1 EDSS must be assessed within 1 day prior to randomization (i.e., on the day before randomization or on the day of randomization but before randomization occurs)

[23] Start 11-day accelerated teriflunomide elimination procedure the day after the early withdraw from treatment visit is completed

[24] Pre-medicate 30-60 minutes prior to each infusion of ublituximab/IV placebo with an anti-histamine (diphenhydramine 50 mg or equivalent) and corticosteroid (dexamethasone 10-20 mg or equivalent)

6.1 OVERVIEW

All subjects should visit the study center on the days specified within this protocol. The complete schedule of assessments is shown in Section 6 (Tables 5, 6, and 7) and Appendix F. The screening physical examination with vital signs, medical history, evaluation of concomitant medications, EDSS (fatigue will not contribute to the EDSS score), complete blood count/full blood count (3 part differential accepted), serum chemistry, and a baseline ECG should be done within 28 days prior to initiation of treatment. For women of child bearing potential, a serum pregnancy test should be completed within 5 days prior to Week 1 Day 1. MRI scans should be performed ≤28 days prior to initiation of treatment.

Week 1/Day 1 EDSS must be assessed within 1 day prior to randomization (i.e., on the day before randomization or on the day of randomization but before randomization occurs) and must be documented.

6.2 LABORATORY EVALUATION

1. Hematologic profile: CBC/FBC with differential and platelet count should be obtained at:

    a. For all subjects:
        i. Blood collection for CBC at screening, and Week 1 Day 1 (pre-dose), Day 2, Day 8, Week 3 Day 15 (pre-dose), and Weeks 4, 8, 12, 16, 20, 24 (pre-dose), 36, 48 (pre-dose) 60, 72 (pre-dose), 84, 96, 100 and 104
    b. For subjects who have an Unscheduled Relapse Visit, blood collection for CBC and serum chemistry will be assessed
    c. For subjects who withdraw from treatment early, blood collection for CBC and serum chemistry will be assessed
    d. Hematology and differential panel will include the following: hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets

2. Serum chemistry should be obtained at screening, and Week 1 Day 1 (pre-dose), Day 2, Day 8, Week 3 Day 15 (pre-dose), and Weeks 4, 8, 12, 16, 20, 24 (pre-dose), 36, 48 (pre-dose) 60, 72 (pre-dose), 84, 96, 100 and 104. The serum chemistry parameters to be analyzed are shown in the table below.

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphate	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

3. Serum pregnancy test should be obtained within 5 days prior to the initiation of therapy and at Week 104 for women of childbearing potential. Additionally, serum pregnancy test will be

obtained if a female subject of childbearing potential withdraws from treatment early or has an Unscheduled Relapse Visit. Serum pregnancy test may be performed at any time during the study in case of a missed or late menstrual cycle.

4. Urine pregnancy test will be performed on a monthly basis, inclusive of the 20 week Follow-up Period. During study visits urine pregnancy tests will be performed at the site and on days of ublituximab or IV placebo infusion urine pregnancy tests will be performed prior to infusion. Post Week 24, urine pregnancy test will be administered every 4 weeks (+/- 5 days), unless serum testing is conducted instead. On days when there is not a study visit, the subject will need to perform at home and provide the outcome to the study staff at the study site. If a urine pregnancy test is positive, the subject should be informed of the potential teratogenic effects, therefore consideration to withhold further teriflunomide/oral placebo dosing should be made and a follow-up appointment should be scheduled as soon as possible where a serum pregnant test will be performed for confirmation.
5. PT/INR should be drawn on Week 1 Day 1 prior to study medications administration. This is the only time PT/INR will be drawn.
6. Quantitative immunoglobulin (IgG, IgM, IgA) test should be analyzed on Week 1 Day 1 (pre-dose) and Week 3 Day 15 (pre-dose), Weeks 24 (pre-dose), 48 (pre-dose), 72 (pre-dose) and 96. Additionally, quantitative immunoglobulin (IgG, IgM, IgA) test will be analyzed for subjects who withdraw from treatment early or have an Unscheduled Relapse Visit.
7. Fibrinogen tests
    a. All subjects will have 5 serum samples taken prior to the infusions on Week 1 Day 1, Week 3 Day 15 and Weeks 24, 48, and 72. Additionally, fibrinogen will be analyzed for subjects who withdraw from treatment early or have an Unscheduled Relapse Visit.
8. Anti-Drug Antibody (antibodies developed against ublituximab; Central Lab)
    a. All subjects will have 6 serum samples taken to assess for the presence of ADA prior to the infusions on Week 1 Day 1, Week 3 Day 15 and Weeks 24, 48, and 72. In addition, a serum sample will be taken at Week 96.

[redacted]

    a. Serum samples will be drawn from all subjects pre-infusion any time on infusion days of ublituximab or IV placebo and at 30 minutes +/- 15 minutes post infusion on infusion days (Week 1 Day 1, Week 3 Day 15, Weeks 24, 48, and 72). One additional serum sample will be taken on Week 96. [redacted]

[redacted]

[redacted]

[redacted]

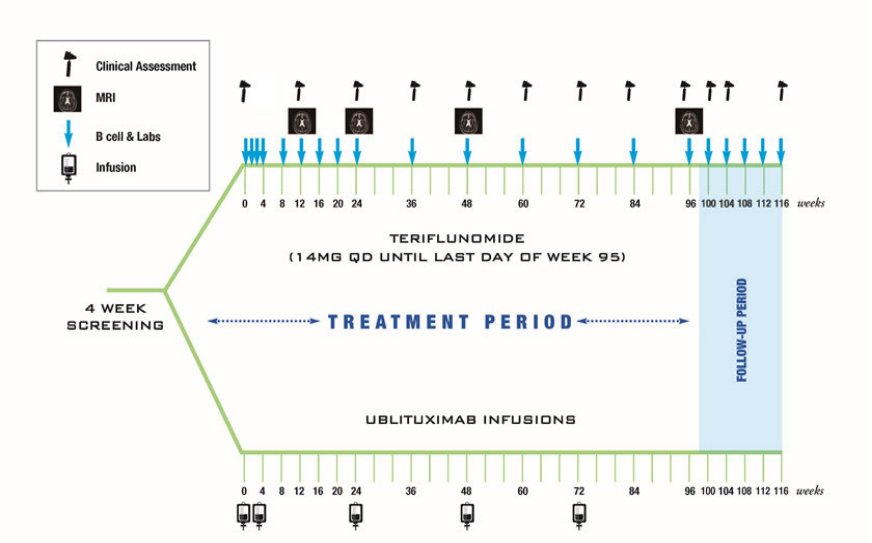
10. Plasma concentration for teriflunomide

    a. In order to assess teriflunomide compliance, four plasma samples will be taken from all subjects. The first sample will be taken prior to oral administration of teriflunomide or oral placebo on Week 1 Day 1. The second sample will be taken prior to infusion of ublituximab or IV placebo on Week 48. The third sample will be taken at Week 96, prior to first dose of accelerated teriflunomide elimination procedure which begins at Week 100. The last plasma sample for teriflunomide will be taken at Week 116 following the accelerated teriflunomide elimination procedure with either active charcoal or cholestyramine. For subjects who withdraw from treatment early, a blood sample will be collected at the Early Withdrawal from Treatment Visit prior to first dose of accelerated teriflunomide elimination procedure.

    b. Only plasma samples from subjects treated with teriflunomide will be analyzed for plasma teriflunomide concentrations. See the Laboratory Manual for PK collection and processing instructions.

11. Liver function panel: SGOT/AST, SGPT/ALT, serum gamma-glutamyl transferase (SGGT), total bilirubin, direct/indirect bilirubin. Samples will be taken for analysis as directed in the schedule of assessment (Tables 5, 6, and 7) and as shown in bullet number 2 (Serum Chemistry)
12. Pancreatic enzyme panel: serum amylase and lipase. Samples will be taken for analysis as directed in the schedule of assessment (Tables 5, 6, and 7) and as shown in bullet number 2 (Serum Chemistry)
13. Urinalysis panel for routine safety will be sampled as follows at screening, and Week 1 Day 1 (pre-dose), Day 2, Day 8, Week 3 Day 15 (pre-dose), and Weeks 4, 8, 12, 16, 20, 24 (pre-dose), 36, 48 (pre-dose) 60, 72 (pre-dose), 84, 96, 100 and 104. The urine is to be analyzed for the following pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity and leucocyte esterase. Additionally, a sample should be obtained for subjects who withdraw from treatment early or have an Unscheduled Relapse Visit.
14. B lymphocyte cell counts (% $CD19^+$ B cells). Samples will be taken for analysis at screening, and Week 1 Day 1 (pre-dose), Day 2, Day 8, Week 3 Day 15 (pre-dose), and Weeks 4, 8, 12, 16, 20, 24 (pre-dose), 36, 48 (pre-dose) 60, 72 (pre-dose), 84, 96, 100 and 104. Additionally, B lymphocyte cell counts will be analyzed for subjects who withdraw from treatment early or have an Unscheduled Relapse Visit.
15. At screening the following assessments will be performed: HIV, HCV, HBV, Varicella

Note, the study site staff will remain blinded to the results of the PK, ADA and teriflunomide concentration analysis for all subjects. The study site staff will also remain blinded to the results of the B lymphocyte cell counts (% CD19+ B cells) from Week 1 Day 1 onwards.



6.3 CLINICAL ASSESSMENT AND PROCEDURES

In addition to being a double-blind, double-dummy study, this study is also an assessor blinded study. Each site will have 2 neurologists: Treating Neurologist (can be the PI) and an Examining Neurologist. Please refer to Section 4.1 for definition and responsibility for each neurologist. The Examining Neurologist will be blinded to subject randomization.

6.3.1 ASSESSMENT OF RELAPSE

MS Relapses During the Study
Subjects enrolled into the study will be closely monitored through the study course by the Site and Sponsor's personnel as well as by an external independent Data Safety Monitoring Board (DSMB) to ensure subjects' welfare.

Relapses that occur after study drugs are withdrawn will be assessed over the remainder of the study period and this data will be utilized as part of additional sensitivity analysis (described in the statistical plan) as long as the subject has not withdrawn their consent to be in the trial.

The confirmation of a protocol-defined relapse will be determined by the Independent Relapse Adjudication Committee (IRAP). The steps for confirming a relapse are as follows:

1. **<u>Subject Reported Relapse</u>**

Subjects who experience new or worsening neurologic symptoms are instructed to contact the Treating Neurologist within 48 hours of symptom onset. All new or worsening neurological events,

reported at a visit or over the phone, consistent with MS representing a clinical relapse as assessed by the subject will be initially reported to the Treating Neurologist. In parallel, the Examining Neurologist will also be notified to perform additional assessments. Upon the notification to the Treating Neurologist; the time and date of suspected subject reported relapse will be documented in the dedicated page eCRF (subject reported) by the Treating Neurologist or designee.

The following should be recorded in the eCRF (subject reported) by the Treating Neurologist or designee:

- Date and time of symptom onset as reported by the subject
- Symptoms and events reported by the subject (both neurological and non-neurological)
- Date of initial contact by subject
- Time of initial contact by subject.

Within 7 days of the subject reporting the suspected relapse to the Treating Neurologist, the subject will be scheduled and assessed by both the Treating and Examining Neurologist independently.

2. <u>Initial Assessment of Relapse by Treating Neurologist and Examining Neurologist</u>

The Treating Neurologist will perform a neurological and physical examination and safety assessment. The Treating Neurologist or designee will document in the eCRF the following:

- Time and date of neurological and physical examination
- Clinical findings of neurological and physical examination
- Review of previously documented concomitant medications and medical history
- Safety assessment, including vital signs, CBC, B-cell count, lymphocyte counts, fibrinogen, quantitative immunoglobulin.

Subjects with suspected clinical relapses reported to the Treating Neurologist or designee will be referred to the blinded Examining Neurologist who will use Neurostatus to assess the EDSS independently of the Treating Neurologist.

The Examining Neurologist or designee will document in the eCRF the following:

- Date and time of assessment
- EDSS score
- FS Scores.

In addition, subjects may not begin IV methylprednisolone (IVMP) treatment of a relapse until the Examining Neurologist has completed his/her examination.

Treatment of relapses may proceed at the discretion of the Treating Neurologist only after the Examining Neurologist has completed his/her exam. The Treating Neurologist will not know the results of the EDSS assessment. When making determination to treat a potential acute relapse the Treating Neurologist can use IVMP (1.0 g/day for at least 3 days and can be extended to 5 days) and will not affect the subject eligibility to continue in the study.

The subject must re-consent at the time of each IRAP-confirmed or Treating Neurologist medically confirmed relapse to continue.

The findings from either the Treating Neurologist and Examining Neurologist will not be shared. The Examining Neurologist must be blinded to the Treating Neurologist's assessment and vice versa.

Following the completion of assessments by the Treating and Examining Neurologists these results will be sent independently to the IRAP.

3. Confirmation of Relapse by IRAP

All assessments entered into the eCRF from both the Treating Neurologist and the blinded Examining Neurologist, will be sent to an Independent Relapse Adjudication Panel (IRAP). IRAP adjudicates each case based on all available data provided for that case and members are not permitted to contact the site or the sponsor for additional information. The IRAP will, in turn, make the final determination of whether the neurological events meet the criteria for a protocol-defined relapse.

Each episode of relapse must be confirmed by the IRAP, based on the neurological assessments performed by the Treating and/or Examining Neurologist independently by documenting either of the following:

- ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory or visual). Note, the change in FS scores should correspond to the patient's symptoms (e.g., patient reported change in visual acuity should correspond to a change in the vision FS score). Episodic spasm, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse;
- An increase of ≥0.5 points in the EDSS score (unless EDSS score = 0, then an increase of at least 1.0 points is required) from the previous clinically stable assessment.

MS relapses are defined as a new or worsening neurological symptoms lasting ≥24 hours with the absence of fever, injury, infection or adverse reactions to medications and accompanied by new neurological findings upon examination by the Examining Neurologist. The symptoms are attributed to MS and are preceded by 30 days of stability or improvement in neurological state. The change in EDSS score as assessed by the Examining Neurologist is ≥ 0.5 increase or ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory or visual). Note, the change in FS scores should correspond to the patient's symptoms (e.g., patient reported change in visual acuity should correspond to a change in the vision FS score). Episodic spasm, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Please note: sexual dysfunction and fatigue will not be scored. If the symptoms occur less than 30 days following the onset of a protocol defined relapse, it should be considered part of the same relapse and would not be treated with IVMP within the protocol. New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse and should not be treated with steroids.

The suspected relapse must be reviewed and confirmed by the IRAP; Appendix D. The IRAP will then notify the CRO and Treating Neurologist of the results of its review.

Treating Neurologist/designee will enter into the eCRF whether the neurological symptoms identified were a result of an IRAP-confirmed relapse.

IRAP-confirmed relapses are the sole confirmation of a protocol-defined relapse. However, for instances where IRAP-confirmed relapses may not be feasible, provisions are provided within Section 4.4.2 (Treating Neurologist medically confirmed relapse).

The subject must re-consent at the time of each IRAP-confirmed or Treating Neurologist medically confirmed relapse to continue.

Signing the informed consent form for re-consent (if the subject has a confirmed relapse), to proceed with the study at the next scheduled office visit should be within 6 weeks after first reporting of relapse.

Treating Neurologist Medically Reported Relapse
In suspected relapse events for which IRAP confirmation is pending, may not be logistically possible and/or complete case profiles for IRAP review are not available, the Treating Neurologist will medically evaluate the relapse event. In these cases, all information from the Treating Neurologist's medical evaluation should still be entered into the eCRF and provided to the IRAP for adjudication. This is to ensure each suspected relapse is documented. Treating Neurologist medically confirmed relapses will not be included in the ARR calculation for the primary endpoint.

For any relapse that is Treating Neurologist medically confirmed, subjects should re-consent to continue participation in the trial.

Re-consent criteria
In case of an IRAP-confirmed relapse (as defined in the protocol, Appendix C) or Treating Neurologist medically confirmed relapse during the study, the following actions will be taken:

- The subject will be reminded of the current approved MS medications/treatments and the opportunity to terminate the study and be treated with an approved MS medication.
- The subject will be requested to re-sign an informed consent form within 6 weeks of first reporting of the suspected relapse if he/she chooses to continue to participate in the study, in the same treatment assignment.

Re-consenting may occur at the next scheduled office visit, but may require an unscheduled visit if the relapse occurs between Weeks 24 and 96 (where the frequency of scheduled visits is every 12 weeks).

6.3.2 DISABILITY EVALUATION

Disability Progression
The method of disability progression calculation will be different than that of the relapsed confirmation. The EDSS score will be used to assess disability progression. EDSS assessment will be performed by the Examining Neurologist. The Examining Neurologist must not share the EDSS score with the Treating Neurologist. The EDSS assessment for disability progression will be performed at screening and on Week 1 Day 1 (prior to randomization) and Weeks 12, 24, 36, 48, 60, 72, 84 and 96. Disability progression is a post hoc analysis only and will not be calculated by the Evaluating Neurologist or other study staff.

The EDSS is based on a standard neurological examination, incorporating the following function systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral) and ambulation rated and scores as function system scores (FS). Each FS score is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and used of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death).

The randomization process must ensure that the baseline EDSS is assessed for the subject by the Examining Neurologist and is documented before treatment is assigned.

Disability progression can only be assessed from the EDSS scores performed at baseline and on Week 1 Day 1 and Weeks 12, 24, 36, 48, 60, 72, 84 and 96.

Disability progression is defined as an increase of ≥1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥0.5 when the baseline score is above 5.5.

Disability progression is considered confirmed when the increase in the EDSS score is confirmed at regularly scheduled visits at least 12 or 24 weeks after the initial documentation of neurological worsening.

6.3.3 RADIOLOGICAL EVALUATION

Magnetic Resonance Imaging (MRI) is a useful tool for monitoring CNS lesions in MS. Different MRI derived parameters have been related to clinical activity and T1 weighted gadolinium-enhancing lesions or new and/or enlarging hyperintense T2 lesions have been related to relapses. It is hypothesized that changes in brain volume may reflect brain atrophy as a result of MS-related tissue loss and may thereby correlate with long-term clinical outcomes in RMS subjects.

Brain MRI scans will be obtained in all subjects as detailed in the Schedule of Assessments in Section 6. In addition, brain MRI scans will be obtained in subjects who had withdrawn from the trial. Scans will be performed by trained and certified MRI technicians.

Assessment of effect on Gd enhancing lesion and new, enlarging T2 lesions, brain volume, T1 hypointense will be evaluated as outlined in the schedule of events by a central reader. The following time windows apply:

- "Baseline" MRI should be performed after informed consent is obtained, but preferably 10 days prior to the Week 1 Day 1 visit.
- MRI are scheduled as follows: Weeks 12 (+/- 7 days), 24 (pre-dose; - 7 days), 48 (pre-dose; - 7 days) and 96 (+/- 7 days)
- MRI scans may be performed on the day of withdrawal or within 4 weeks after withdrawing from the study.
    - The MRI may not be needed if an MRI was obtained within 30 days prior to withdrawal from the trial.

If subjects receive corticosteroids for a relapse, every effort should be made to obtain the scan prior to the first steroid dose if the pre-steroid scan is within 1 week of the scheduled visit. In subjects receiving corticosteroids, there should be an interval of at least 30 days between the last dose of corticosteroids and the scan.

At each time point, the MRI will include acquisition of scans with and without intravenously administered gadolinium contrast enhancement.

MRI scans will be read by a centralized reading center located in Montreal, Canada for efficacy endpoints. The centralized reading center is blinded to the treatment assignment and the reading is performed in the absence of clinical information. Additional details on scanning acquisition sequences, methods, handling and transmission of the scans, certification of site MRI radiologists/technicians, and the procedure for the blinded analysis of the scans at the central reading center will be described in a separate MRI Manual.

All MRI scans will also be reviewed locally by a radiologist for safety (identify any new clinical relevant abnormal MRI findings that are not consistent with the diagnosis of MS, with particular attention to the possibility of progressive multifocal leukoencephalopathy) and the MRI report will be provided to the Treating Neurologist/PI. After randomization, the MRI reports provided to the Treating Neurologist/PI will contain **only non-MS pathology**. At the investigational site, only the local radiologist/technician assigned to this study may have access to the MRI scan post-randomization; **the Treating Neurologist should not review the MRI scans unless a safety concern arises**.

6.3.4 NEUROLOGICAL EVALUATION

Assessment of effect on relapse rate will be evaluated as outlined in the schedule of events (see Study Evaluation Tables 5, 6, and 7 and Appendix F). EDSS score will be calculated via Neurostatus as stated in Sections 6.3.1. and 6.3.2.

Multiple Sclerosis Functional Composite (MSFC) score will be assessed as outlined in the schedule of events (see Study Evaluation Tables 5, 6, and 7 and Appendix F). The MSFC consists of three subscales, including the 9-hole-peg test, Paced Auditory Serial Addition Test (PASAT) and Timed 25-Foot Walk (T25FW), which provide a global quantitative estimate of MS progression. The MSFC assessments may be performed by the Treating Neurologist, or may be delegated to another qualified team member, but must not be performed by the Examining Neurologist.

EDSS will be assessed by the Examining Neurologist. The results of the EDSS assessment by the Examining Neurologist will not be shared with the Treating Neurologist and the PI.

6.3.5 COGNITION ASSESSMENT

The Symbol Digit Modality Test (SDMT) has demonstrated sensitivity in detecting not only the presence of cognitive impairment, but also changes in cognitive functioning over time and in response to treatment. The SDMT is brief, easy to administer verbally and involves a simple substitution task that normal children and adults can perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses will be done verbally. The administration time is approximately 5 minutes.

The SDMT will be administered verbally by the Treating Neurologist at the time points indicated in the Study Evaluation Tables 5, 6, and 7 and Appendix F. The SDMT assessments may be delegated to another qualified team member, but must not be performed by the Examining Neurologist.

6.3.6 SUBJECT REPORTED OUTCOMES

Assessment of effect on MSQoL54 (inclusive of SF36) and FIS will be evaluated as outlined in the Study Evaluation Tables 5, 6, and 7 and Appendix F by a qualified coordinator or member of the study site. This will be done prior to each infusion.

MSQoL54 (inclusive of SF36) is a multidimensional health-related quality of life measurement that combined generic and MS specific items into a single assessment. The 54-item instrument generates 12 subscales along with 2 summary scores and 2 additional single-item measures. The subscales are physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life and sexual function. The summary score as are the physical health composite and mental health composite. The single item measure is satisfaction with sexual function and change in health. The MSQoL54 will be performed at Week 1 Day 1 (prior to dosing of study medications), Weeks 24 (pre-dose), 48 (pre-dose) and 96 or Early Withdrawal from Treatment Visit.

The Fatigue Impact Scale (FIS) is a detailed tool, which takes ~ 3 minutes to complete. The subject completes the tool personally, rather than having an interview. The score reflects functional limitation due to fatigue experienced within the previous assessment rather than a measure of the level of fatigue. There are 40 items, each of which is scored 0 (no problem) to 4 (extreme problem), providing a continuous scale of 0 – 160. It is composed of three subscales that describe how fatigue impacts cognition, physicality and psychosocial functions. The cognitive function includes concentration, memory, thinking and organization of thoughts. Physical function reflects motivation, effort, stamina and coordination. Psychosocial function includes the impact of fatigue on isolation, emotions, workload and coping. The FIS assessment will be performed at Week 1 Day 1 (prior to dosing of study medications), Weeks 24 (pre-dose), 48 (pre-dose) and 96 or Early Withdrawal from Treatment Visit.

6.3.7 SAFETY DATA

Subject safety will be evaluated throughout the study during the following assessments:

- Adverse events
- Physical examination: cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, and musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, extremities, genitourinary, weight
- Hematology and differential panel: hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets
- Fibrinogen
- Pregnancy testing (serum or urine levels of β-human chorionic gonadotrophin (HCG)) in women of childbearing potential). In addition, pregnancy test should be conducted in case of an unexpected delay of menorrhea
- ECG (within 2 hours pre-infusion and 60 minutes +/- 15 minutes post-infusion on days of infusion; for non-infusion days one ECG assessment should be performed)
- Blood chemistry panel: Albumin, Alkaline Phosphatase, BUN, Calcium, Chloride, Creatinine, Glucose, LDH, Magnesium, Phosphate, Potassium, SGOT (AST), SGOT (ALT), Sodium, Total Bilirubin, Total Protein, Uric Acid, and direct/ indirect bilirubin
- Liver function panel: SGOT/AST, SGPT/ALT, serum gamma-glutamyl transferase (SGGT), total bilirubin, direct/indirect bilirubin.
- Pancreatic enzyme panel: serum amylase and lipase

- Urinalysis panel for routine safety: pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity and leucocyte esterase.
- Vital signs: (within 2 hours pre-infusion and 60 minutes +/- 15 minutes post-infusion on days of infusion) systolic and diastolic blood pressure, heart rate, body temperature, and weight

6.4 REPLACEMENT POLICY

Subjects who discontinue and/or withdraw from the study for any reason will not be replaced.

6.5 DEFINITIONS

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment on Week 1 Day 1.

Evaluable for radiological and neurological response. Only those subjects who have had a pre-treatment baseline efficacy evaluation and at least one post-treatment efficacy evaluation will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

6.6 DISEASE PARAMETERS

Measurable disease: Diagnosis of RMS will be based on the 2010 McDonald's criteria (Appendix C).

6.7 DURATION OF RESPONSE

Duration of stable disease:

Stable disease is measured from the start of the treatment (Week 1 Day 1) until the criteria for relapse or progression of disease are met or there is evidence of new radiological activity as assessed by MRI, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.8 RESPONSE REVIEW

Subjects will be assessed for relapse by the Treating Neurologist at screening, baseline (pre-dose), and all scheduled visits and, if necessary, at unscheduled visits. If a relapse is suspected, the Treating Neurologist and Examining Neurologist will follow the procedures as outlined in Section 6.3.1.

MS relapses are defined as new or worsening neurological symptoms lasting ≥24 hours with the absence of fever, injury, infection or adverse reactions to medications. The symptoms are attributed to MS and are preceded by 30 days of stability. The change in EDSS score as assessed by the Examining Neurologist is ≥ 0.5 increase from prior visit or ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS.

6.9 RE-SCREENING PROCEDURES

Subjects may be re-screened under the following conditions:

- After a relapse recovery (see Section 4.4.1) and upon re-consent
- Varicella titer does not indicate immunity at initial screening and subject is re-immunized (see Section 3.2)
- He/she, at initial screening, is not eligible to participate in the study based on inclusion/exclusion criteria (Sections 3.1 and 3.2) and wishes to re-assess eligibility after a waiting period deemed sufficient by the site investigator.
- The subject was determined eligible, but 28 days or more has elapsed between the initial screen and the first infusion (Week 1 Day 1).

Re-screening procedures are identical to initial screening procedures (Appendix F), but with the following modifications:

- Medical history does not need to be taken again.
- Screening MRI may not need to be repeated if there was one obtained within 30 days prior to this screening

6.10 END OF STUDY FOLLOW-UP

After early termination of trial or at the end of study visit at Week 96, subjects will enter a 20-week Follow-up Period inclusive of the accelerated elimination of teriflunomide. The 11-day elimination procedure will commence at Week 100 for all subjects who completed all study visits including Week 96. For those subjects who had terminated early (discontinued or withdrawn from the study), the 11-day elimination procedure will commence the day after the Early Withdrawal from Treatment Visit. The follow up period will include visits at Weeks 100, 104, and 116. Weeks 108 and 112 will be performed via a phone call.

For subjects who withdraw their consent to participate in the study, the site should inform these subjects of the 20-week Follow-up Period inclusive of the accelerated teriflunomide elimination procedure and document this in the eCRF. Participation in the 20-week Follow-up Period inclusive of the accelerated teriflunomide elimination procedure for subjects who withdraw early is left to the discretion of the subject. If he/she elects not to participate in the 20-week Follow-up inclusive of the accelerated teriflunomide elimination procedure, after withdrawing consent and after discussion with the site, it should be documented in the eCRF.

For subjects who will participate in the 20-week Follow-up Period inclusive of the accelerated teriflunomide elimination procedure after withdrawing consent for this study, a new consent form to participate in the 20-week Follow-up Period inclusive of the accelerated teriflunomide elimination procedure will need to be signed. If he/she re-consents, the sites will complete the eCRF for Weeks 100, 104, 108, 112, and 116, accordingly.

The purpose of this follow-up is to monitor safety and relapses after the discontinuation of study medications and to eliminate residual teriflunomide from the study subjects. Because blinding is maintained until the data from the treatment period (through Week 96) is locked, all subjects will undergo the accelerated teriflunomide elimination procedure regardless of whether they were randomized to ublituximab/oral placebo or teriflunomide/IV placebo. Study subjects that enter the Follow-up Period of TG1101-RMS302 (post-Week 96 to Week 116) are not allowed to receive DMTs. Please refer to the exclusion criteria of the protocol for a list of MS therapies (Section 3.2). It should be noted that use of systemic corticosteroids for the treatment of a relapse is allowed. When deciding

to treat a potential acute relapse the Treating Neurologist can use IVMP (1.0 g/day for at least 3 days and can be extended to 5 days).

The procedures of each visit are below:

Week 100 Visit:

- Physical examination and vital signs
- Urine pregnancy test
- Report concomitant medications and Adverse Events
- Initiate rapid teriflunomide elimination program (Section 6.10.1 below)
- Hematology and serum chemistry, urinalysis, and B cell assays (as per Section 6)

Week 104 Visit:

- Physical examination and vital signs
- Urine pregnancy test
- Report concomitant medications and Adverse Events
- Hematology and serum chemistry, urinalysis, and B cell assays (as per Section 6)
- Acknowledgment of the completion of teriflunomide rapid elimination program by the site on eCRF

Week 108 and 112 (Phone Call):

- Follow-up phone call to subject to collect information on concomitant medications, Adverse Events and urine pregnancy test outcomes

Week 116 Visit (Final Visit):

- Physical examination and vital signs
- Urine pregnancy test
- Report concomitant medications and Adverse Events
- Teriflunomide drug concentration test: Draw blood to test teriflunomide plasma concentration

TG1101-RMS303 is a 172-week open label extension (OLE) trial. Subjects completing 96-weeks of treatment in TG1101-RMS301 or TG1101-RMS302 trials in United States, Croatia, Ukraine, Russia, Republic of Belarus, Serbia, Poland, and Georgia may be eligible to participate. Regardless of which treatment group the subject was assigned to in the core study, all subjects enrolled in the OLE will receive ublituximab on the following schedule: Week 1 Day 1, Week 3 Day 15, and Weeks 24, 48, 72, 96, 120, 144, and 168 or until physician or subject decision to withdraw prior to this time. Subjects will have final assessments done at Week 172. TG1101-RMS302 is considered a core study protocol for OLE. The TG1101-RMS303 subjects, sponsor and investigators will not know TG1101-RMS301 and TG1101-RMS302 treatment assignments until these studies are unblinded.

6.10.1 ACCELERATED TERIFLUNOMIDE ELIMINATION PROCEDURE

All subjects should undergo the 11-day accelerated teriflunomide elimination procedure during the Follow-up Period: Oral cholestyramine 8 g is administered three times per day for 11 days. If subjects do not tolerate this regimen, then the dosage may be reduced to 4 g three times per day.

If tolerability issues persist, cholestyramine administration does not need to occur on consecutive days unless there is an acute need to lower teriflunomide levels.

As an alternative to cholestyramine, oral activated charcoal administered as 50 g twice a day for 11 days may be used.

It needs to be documented in the eCRF which elimination treatment was used.

Plasma will be drawn at Week 116 to determine the concentration of teriflunomide. However, results will not be shared with the site or subject to maintain blinding. Prior to discharge from the study, all subjects will be counseled by the treating team to have their teriflunomide plasma concentration re-measured prior to attempting to become pregnant or trying to impregnate a female partner.

7 PHARMACEUTICAL INFORMATION

7.1 TERIFLUNOMIDE

Chemical Name: Teriflunomide

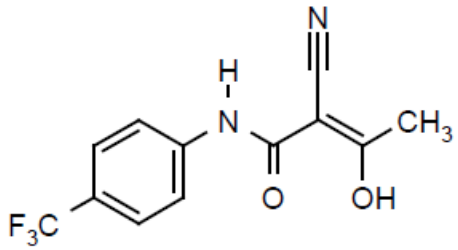
Other Names: None

Classification: Oral de novo pyrimidine synthesis inhibitor of the DHO-DH enzyme

Formulation: Teriflunomide is formulated as film-coated tablets for oral administration. Teriflunomide tablets contain 14 mg of teriflunomide and the following inactive ingredients: lactose monohydrate, corn starch, hydroxypropylcellulose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating for the 14 mg tablet is made of hypromellose, titanium dioxide, talc, polyethylene glycol and indigo carmine aluminum lake.

Mode of Action: De novo pyrimidine synthesis inhibitor of the DHO-DH enzyme

Description: Teriflunomide is an oral de novo pyrimidine synthesis inhibitor of the DHO-DH enzyme, with the chemical name (Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4trifluoromethylphenyl)-amide. Its molecular weight is 270.21, and the empirical formula is $C_{12}H_9F_3N_2O_2$ with the following chemical structure:



How Supplied: The 14 mg tablet is white to off white, round film-coated tablet with the dose strength “14” engraved on one side and engraved with a “B” on the other side

Each tablet contains 14 mg of teriflunomide.

Storage: United States: Store at 68°F to 77°F (20°C to 25°C) with excursions permitted between 59°F and 86°F (15°C and 30°C).

Europe: Store below 25°C. Do not refrigerate or freeze.

Route of Administration:	Oral
Packaging:	Box of 28 tablets containing 1 wallet composed of 2 folded blister cards of 14 tablets per blister card with one wallet package in a box. Four (4) box will be supplied to the subject at a time.
Availability:	Bioequivalent teriflunomide product (currently non-marketed) is used in the study, and is available from TG Therapeutics.

7.1.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS) FOR TERIFLUNOMIDE

The following adverse events were observed in subjects treated with teriflunomide [15, 16, 17] and were considered at least possibly related to study medication. Please see the latest teriflunomide Investigator Brochure for a complete list of all adverse events reported regardless of causality.

7.1.1.1 VERY COMMON (≥10%)

- **Gastrointestinal Disorders:** Diarrhea, Nausea
- **Hepatic Disorders:** Elevated Alanine Aminotransferase Level
- **Nervous System Disorders:** Headache
- **Skin and Subcutaneous Tissue Disorders:** Hair Loss

7.1.1.2 COMMON (≥<10-%)

- **Blood And Lymphatic System Disorders:** Neutropenia
- **Musculoskeletal and Connective Tissue Disorders:** Joint Pain
- **Nervous System Disorders:** Numbness
- **Vascular Disorders:** Hypertension

7.2 UBLITUXIMAB

Chemical Name:	Ublituximab
Other Names:	TG-1101
Classification:	Recombinant chimeric anti-CD20 monoclonal antibody
Formulation:	See Investigator Brochure
Mode of Action:	Targets CD20 antigen on B-cells
Description:	Ublituximab is a genetically engineered chimeric murine/human mAb directed against the CD20 antigen found on the surface of B lymphocytes. Ublituximab displays the typical structure of immunoglobulins, consisting of two gamma (γ) heavy chains and two kappa (κ) light chains linked by disulfide bridges. It is composed of a murine variable region (37.2% of total amino acids) fused onto human constant regions.

How Supplied:	Concentration of 10 mg/mL in 15 mL (150 mg) single-use glass vials. **OR** Concentration of 25 mg/mL in 6 mL (150 mg) single-use glass vials.
Storage:	Ublituximab must be stored in a secured limited-access area at a temperature ranging +2°C / + 8°C (36°F to 46°F). Ublituximab must not be frozen.
Stability:	Once a vial of ublituximab has been opened and/or diluted it is highly recommended that it be used immediately. After dilution, ublituximab is stable in static conditions for 24 hours at 25°C, and in dynamic conditions it is stable for 8 hours at 25°C. Ublituximab has a shelf-life of 36 months if stored between +2°C / + 8°C, based on stability data
Route of Administration:	Intravenous
Packaging:	Ublituximab is packed in unit boxes. Each of the unit boxes contains: • One 15 mL vial containing 10 mg/mL solution of ublituximab **OR** • One 6 mL vial containing 25 mg/mL solution of ublituximab The container closure system for the vials containing 15 mL is a type I glass vial closed by a siliconized chlorobutyl rubber stopper sealed with a white plastic and aluminum cap. The container closure system for the vials containing 6 mL is a Type I plus borosilicate vial closed by a siliconized bromobutyl rubber stopper sealed with an aqua plastic and aluminum cap.
Availability:	Ublituximab is available from TG Therapeutics, Inc.

7.2.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS) FOR UBLITUXIMAB

The following adverse events were observed in subjects treated with single agent ublituximab and were considered at least possibly related to study medication. Please see the ublituximab Investigator Brochure for a complete list of all adverse events reported regardless of causality.

7.2.1.1 VERY COMMON (≥10%)

- **Blood and Lymphatic System Disorders:** Neutropenia, Thrombocytopenia
- **General Disorders and Administration Site Conditions:** Pyrexia
- **Injury, Poisoning and Procedural Complications:** Infusion Related Reaction

- **Nervous System Disorders:** Headache

7.2.1.2 COMMON (≥2-<10%)

- **Blood and Lymphatic System Disorders:** Anemia, Pancytopenia
- **Musculoskeletal and Connective Tissue Disorders:** Muscular Weakness
- **Nervous System Disorders:** Dysgeusia
- **Vascular Disorders:** Hypertension
- **Gastrointestinal Disorders:** Diarrhea, Nausea, Abdominal Pain, Oral Pruritus
- **General Disorders and Administration Site Conditions:** Fatigue, Asthenia, Chills, Edema Peripheral, Pain
- **Hepatobiliary Disorders:** Cytolytic Hepatitis
- **Infection and Infestations:** Herpes Zoster
- **Investigations:** Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Gamma-glutamyltransferase Increased
- **Respiratory, Thoracic and Mediastinal Disorders:** Throat Irritation, Throat Tightness
- **Skin and Subcutaneous Tissue Disorders:** Pruritus, Hyperhidrosis

7.3 ORDERING STUDY MEDICATIONS

Once the clinical trial site receives both IRB/EC and Regulatory Authorities approval, the Sponsor's or its designee will perform the Site Initiation Visit and inspection of pharmacy. Following completion of these tasks the site can then be officially open and an automatic shipment of pre-determined quantity of all study medication (ublituximab, teriflunomide, IV placebo and oral placebo) and treatment supplies (i.e., normal saline, infusion kit, cholestyramine, activated charcoal) will be shipped to the clinical trial site, accordingly. A separate Drug Distribution Plan will detail country variances and specifics.

Upon receipt of study medication and treatment supplies, the Pharmacist or the appropriate person of the site should update the accountability forms.

If any abnormality on the shipment invoice compared to what was actually shipped is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact the CRO.

7.4 BLINDING, PACKAGING AND LABELING

7.4.1 TERIFLUNOMIDE OR ORAL PLACEBO

Each tablet of teriflunomide (14 mg) or oral placebo is a white to off white, round-film-coated tablet with the dose strength "14" engraved on one side and engraved with a "B" on the other side.

Teriflunomide or oral placebo will be supplied to the subject in a box containing 28 tablets (composed of 2 folded blister cards of 14 tablets per blister card as a wallet). Four (4) boxes will be supplied to

the subject every 12 weeks. The packaging of the teriflunomide or oral placebo in the blister pack will be child resistant.

Therefore, to assist in drug accountability for the site, the subjects over 12 weeks should have received 112 tablets and when returning back to the sites in approximately 12 weeks; approximately 84 tablets should have been taken and approximately 28 tablets should be returned to the site. Approximately every 12 weeks, the site must collect all unused teriflunomide or oral placebo tablets.

New boxes of teriflunomide or oral placebo will be provided to the subject. The study side will not re-dispense previously unused tablets back to the subject. These tablets should be quarantined until the study monitor can inventory them and instruct the site on destruction of them.

The box of teriflunomide or oral placebo dispensed to the subject will be labeled in compliance with the applicable regulatory regulations in that country.

7.4.2 UBLITUXIMAB OR IV PLACEBO

Ublituximab or IV placebo is provided to the study site in unit boxes. Each unit box contains one 15 mL vial (10 mg/mL) or one 6 mL vial (25 mg/mL) solution of ublituximab or IV placebo. The container closure system for the vials containing 15 mL is a Type I plus borosilicate vial closed by a siliconized bromobutyl rubber stopper sealed with an aqua plastic and aluminum cap and the container closure system for the vials containing 6 mL is a type I glass vial closed by a siliconized chlorobutyl rubber stopper sealed with a white plastic and aluminum cap.

The empty vials should be maintained until the study monitor performs reconciliation.

The box of ublituximab or IV placebo provided to the study site will be labeled in compliance with the applicable regulatory regulations in that country.

7.5 DISPENSING AND ADMINISTRATION

The exact dose and the date and time of administration of ublituximab/oral placebo or teriflunomide/IV placebo must be recorded within the eCRF, subject's medical records, and in the drug accountability records.

The Pharmacist or his/her representative should record the date dispensed and subject's number and initials on the labels. He/she should complete the accountability forms with information concerning the dispensation of ublituximab/oral placebo and teriflunomide/IV placebo.

7.5.1 DISPENSING AND ADMINISTRATION OF TERIFLUNOMIDE OR ORAL PLACEBO

Teriflunomide or oral placebo will be dispensed every 12 weeks to the subject (see Section 7.3 for further details).

7.5.1.1 GUIDELINES FOR ORAL TREATMENT OF TERIFLUNOMIDE OR ORAL PLACEBO

- *Necessity of MS Center/Neurology Department:* Center must have personnel and equipment necessary to provide adequate emergency treatment.

- Subjects who withdraw from treatment should be followed up for 20 weeks inclusive of the 11-day accelerated teriflunomide elimination procedure, during which they receive cholestyramine or activated charcoal.
- If a pregnancy is confirmed, the trial drug(s) must be immediately and permanently stopped, the subject must be discontinued from the trial, and the Treating Neurologist must report this to pharmacoviligance as soon as possible. Further, the subject needs to undergo immediate accelerated washout with either oral cholestyramine or oral activated charcoal and be followed for AEs for 20 weeks after their last dose of the trial drug (please see Section 6.10.1).
- Teriflunomide or oral placebo shall be taken each in the morning daily until the last day of Week 95. Alternative dosing times are allowed if necessary.
    - On Week 1 Day 1, teriflunomide or oral placebo dosing should occur upon completion of infusion. If vomiting occurs during the infusion of ublituximab or IV placebo, refrain from administering teriflunomide or oral placebo on Week 1 Day 1. The first dose of teriflunomide or oral placebo will be administered on Week 1 Day 2.
- Compliance to administration of teriflunomide or oral placebo
    - Plasma samples to determine the concentration of teriflunomide will be obtained from all subjects at the following time-points: Week 1 Day 1 and Week 48 (pre-infusion of ublituximab or IV placebo), and Week 96 or Early Withdrawal from Treatment Visit and Week 116.
    - The study sites will instruct the subjects enrolled into the study to return with their used and unused teriflunomide or oral placebo blister packs to the investigation site during every visit as shown in the Schedule of Assessments in Section 6 as part of the teriflunomide or oral placebo drug accountability assessment program. Compliance with teriflunomide or oral placebo administration will be reviewed with all subjects during those times by the study site and documented on the eCRF by the study site. A comment will be entered into the subject's subject diary and on the accountability log for any variation from the prescribed dosing schedule, such as additional or missed doses.
    - Compliance will also be assessed by inspection of the blister packs and counting of the used and unused tablets at each visit by the study site. Details of teriflunomide or oral placebo (date and time of first dose, last dose prior to visit, number of tablets dispensed and number of returned tablets) will be recorded in the eCRF.

7.5.2 DISPENSING AND ADMINISTRATION OF UBLITUXIMAB OR IV PLACEBO

Subjects in the United States (US) during 2017 will initially receive ublituximab at a concentration of 10 mg/mL and will be switched to the higher concentration (25 mg/mL) in January 2018. All US based subjects enrolled in the study after December 2017, will begin the study using 25 mg/mL. All subjects in Europe will begin and complete the study with the higher concentration (25 mg/mL).

Ublituximab or IV placebo will be administered in the MS center/neurology department/ infusion center associated with MS center or neurology department. The MS centers/neurology department

must have skilled personnel and adequate equipment to provide emergency treatment should the subject experience IRR, anaphylaxis, hypotension and/or respiratory distress.

If randomized to ublituximab, each subject will receive ublituximab, a single dose of 150 mg of ublituximab on Week 1 Day 1 with an infusion rate of 4 hours for a total volume of 250 mL to be infused. Subjects will receive 450 mg of ublituximab on Week 3 Day 15, Weeks 24, 48, and 72 with an infusion rate of 1 hour for a total volume of 250 mL. Subjects receiving IV placebo will receive the same infusion volume and infusion rate as those subjects receiving ublituximab. Please see Sections 7.5.2.2 (dilution of ublituximab or IV placebo) and 7.5.2.3 (administration) for further details.

If the liver enzymes (ALT and/or AST) are Grade 2 or higher, or if the neutrophil count or platelets counts are Grade 3 or 4, the dosing of ublituximab or IV placebo will be withheld. A re-test will occur within 14 days after the initial test. Ublituximab or IV placebo infusion can occur once the liver enzymes are less than Grade 2, and if the neutrophil count or platelets counts are less than Grade 3. Please see Section 5.2 (Guidance for Laboratory Abnormalities) for further details.

7.5.2.1 GUIDELINES FOR INFUSION TREATMENT OF UBLITUXIMAB OR IV PLACEBO

- *Necessity of MS Center/Neurology Department:* Center must have personnel and equipment necessary to provide adequate emergency treatment for anaphylaxis, hypotension and respiratory distress.
- *Method of Administration:* Ublituximab or IV placebo must be administered as an intravenous infusion through a dedicated intravenous line and will be done under the supervision of the study investigator or a designee
- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Pre-medications:* Pre-medicate 30-60 minutes prior to each dose of ublituximab or IV placebo with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20 mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to subject who experience fever or pyrexia after Week 1 dose, or as clinically warranted and additional medication (which needs to be documented) may be used at discretion of the physician if adverse reactions occur.

  Note: In case the above referenced medications are not available, equivalents can be used at the Investigator's discretion. If medications are given intravenously, the IV line used for ublituximab/IV placebo should not be used. If needed, please consult the Medical Monitor.
- *Subject Care Implications*:
  - Ublituximab or IV placebo should not be administered as an IV push or bolus.
  - Ublituximab or IV placebo should only be diluted in 0.9% NaCl.
  - Diluted ublituximab or IV placebo should be checked before administration for cloudiness, color, or deposits. Ublituximab or IV placebo should not be administered if it does not conform to the manufacturer's specifications. The Monitor/Sponsor must be informed immediately of any quality concerns or questions about the product.
  - It is recommended that ublituximab or IV placebo be administered immediately after dilution within 24 hours.

- Monitoring of subjects after ublituximab or IV placebo infusion should be followed based on institution's guideline

Ublituximab or IV placebo will be prepared as described below in Section 7.5.2.2 for IV dilution.

7.5.2.2 DILUTIONS OF UBLITUXIMAB OR IV PLACEBO

Ublituximab or IV placebo must not be mixed with other medicinal products.

Ublituximab or IV placebo should only be diluted in 0.9% NaCl before use. [redacted]

[redacted]

[redacted]

[redacted]

Time of Dosing	Dose of ublituximab or IV placebo for infusion	[redacted]
Week 1 Day 1	150 mg	
Week 3 Day 15, Weeks 24, 48 and 72	450 mg	

[redacted]

Time of Dosing	Dose of ublituximab or IV placebo for infusion	[redacted]
Week 1 Day 1	150 mg	
Week 3 Day 15, Weeks 24, 48 and 72	450 mg	

7.5.2.3 ADMINISTRATION FOR UBLITUXIMAB OR IV PLACEBO INFUSION

- IV administration only. Ublituximab or IV placebo should not be administered as an IV push or bolus.
- Ublituximab or IV placebo in the perfusion bag must be checked before being administered for cloudiness, color, soapy aspect, or deposits.
- Ublituximab or IV placebo must not be administered if does not conform to the specifications. The Principal Investigator and/or Treating Neurologist must immediately inform the Monitor and Sponsor.
- In accordance with Section 7.5.2.1 and in the text below (pre-medication prior to infusion of ublituximab or IV infusion) is a list of pre-medications that should be administered 30-60 minutes prior infusion of ublituximab or IV placebo.

- Since infusion-related hypotension may occur, the investigator should carefully consider withholding antihypertensive medications during the 24 hours prior to and throughout the IV infusion of ublituximab or placebo.
- No other treatment may be co-administered with ublituximab or IV placebo (other than for immediate intervention for adverse event). Teriflunomide or oral placebo will be administered after the completion of the infusion of ublituximab or IV placebo.
- It is recommended that ublituximab or IV placebo be administered immediately after dilution, within 24 hours.
- Upon completion of infusion on Week 1 Day 1 and Week 3 Day 15, the subject should be monitored for at least one (1) hour post infusion. Subsequent infusions (Weeks 24, 48 and 72) do not require one hour monitor unless IRR and/or hypersensitivity has been observed.

Pre-medication Prior to Infusion of ublituximab or IV placebo:

30 to 60 minutes prior to the infusion of ublituximab or IV placebo the following pre-medication will be administered: antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20 mg or equivalent).

Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to subject who experience fever or pyrexia after Week 1 Day 1 dose, or as clinically warranted and additional medication (which needs to be documented) may be used at discretion of the physician if adverse reactions occur.

Emergency Management for Hypersensitivity Reactions to ublituximab or IV placebo:

Available at the bedside prior to ublituximab or IV placebo administration will be medications and resuscitation equipment for the emergency management of IRR, anaphylaxis, hypotension and/or respiratory distress per institution guidelines.

Ublituximab or IV placebo should be administered intravenously through a dedicated line. No other treatment may be co-administered with ublituximab or IV placebo (other than for immediate intervention for adverse event).

Ublituximab or IV placebo should be administered only by slow infusion via intravenous route as a single administration as described below:

1st infusion Week 1 Day 1 (infused for approximately 4 hours)

Treatment Group	Ublituximab Dose	Total volume to be infused	Infusion rate			
			T0 to T30'	T30' to T1H	T1H to T2H	T2H to T4H
Ublituximab	150 mg	250 mL	10 mL/H	20 mL/H	35 mL/H	100 mL/H
Placebo	0 mg	250 mL	10 mL/H	20 mL/H	35 mL/H	100 mL/H

Week 3 Day 15, Weeks 24, 48, and 72 (infused for approximately 1 hour)

Treatment Group	Ublituximab Dose	Total volume to be infused	Infusion rate	
			T0 to T30min	T30min to T60min
Ublituximab	450 mg	250 mL	100 mL/H	400 mL/H
Placebo	0 mg	250 mL	100 mL/H	400 mL/H

7.5.2.4 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE

Infusion Related Reactions (IRR) are potential AEs associated with the infusion of ublituximab.

IRR, including severe reactions, have been reported with ublituximab administration in subjects with CLL, NHL, and RMS. Guidelines are provided below for subjects who experience such reactions. Symptomatic infusion reactions, despite pre-medication, may be treated at the discretion of the Treating Neurologist and/or PI using the following: oral acetaminophen 650 mg (only use for intervention), corticosteroids, antihistamines, oxygen, and bronchodilators or other appropriate treatments, as deemed necessary.

IRRs, defined as infusion related AEs reported during or within 24 hours of the end of an infusion, will be assessed for safety over the 96-week trial. An AE that is an IRR will be identified on the eCRF as "Infusion Relation Reaction (IRR)".

If an IRR occurs during the infusion the dose of ublituximab or IV placebo may be reduced or delayed. The following are recommended infusion rate reduction/delay guidelines for subjects who experience severe Infusion Related Reactions (IRRs) that require treatment interruption. The final decision for the infusion rate reduction/delay or discontinuation of the infusion resides with the Principal Investigator and/or Treating Neurologist at the study site.

Infusion rates described in the table (Section 7.5.2.3) are considered targets infusion rates to reduce the potential for IRR. If the PI and/or Treating Neurologist decides to interrupt the infusion or slow the infusion rate, then the reduction/delay and the reason for it must be noted on the eCRF and infusion log.

Infusion Rate Reductions Due to IRR

The following are recommended infusion rate reduction/delay guidelines for subjects who experience severe IRRs in which treatment must be interrupted. The final decision for the infusion rate reduction/delay or discontinuation resides with the Treating Neurologist and/or Principal Investigator at the study site.

Dose Interruption for any infusion at any time-point:

- The subject must be closely monitored until complete disappearance of the IRR symptoms and should be documented as an AE in the eCRF.
- Following the judgment of the Treating Neurologist and/or PI, once vital signs have returned to normal resume ublituximab /IV placebo with the following modifications:
    - **Initial Dose (Week 1 Day 1):**
        - The new initial rate of infusion should be approximately 50% less than the rate in which the infusion was stopped
        - The rate of infusion can be increased by 50% for every 30 minutes to a maximum rate of 100 mL/hr as long as the subject can tolerate the infusion of ublituximab or IV placebo

- **Subsequent Doses of 450mg ublituximab/IV placebo (Week 3 Day 15, Weeks 24, 48, and 72):**
  - The suggested initial rate of infusion should be 100 mL/hr. If 100 mL/hr is tolerated for 30 minutes, then the remainder of the infusion can be completed based on Treating Neurologist/PI discretion (rates of 100 mL/hr up to a maximum of 400 mL/hr).
  - At Treating Neurologist/PI discretion, subjects may receive ublituximab/IV placebo at even slower rates, as long as the known stability profile of diluted ublituximab is not violated (see ublituximab IB). An example of such an infusion scheme is 25 mL/hr for 30 minutes, increasing to 50 mL/hr after 30 minutes, then 75 mL/hr after 30 minutes, concluding at 100 mL/hr for 1 hour and 45 minutes.
  - If there are any questions about a particular infusion scheme, please contact the CRO or Sponsor.

If there is a second interruption of the infusion on the same infusion day due to IRR symptoms, the infusion of ublituximab or IV placebo must be stopped and the subject should be scheduled for the next day. IRR is not a reason to discontinue a subject from the study or future infusions.

Infusion Delays due to Relapse
For subjects reporting a suspected relapse the Treating Neurologist should perform an Unscheduled Relapse Visit. The next scheduled infusion visit is postponed until the subject is back to baseline or PI/Treating Neurologist does not expect any improvement.

7.5.3 CO-ADMINISTRATION FOR UBLITUXIMAB/ORAL PLACEBO AND TERIFLUNOMIDE/IV PLACEBO ON UBLITUXIMAB/PLACEBO ON INFUSION DAYS

Ublituximab or IV placebo infusion days are defined as Week 1 Day 1, Week 3 Day 15 and Weeks 24, 48, and 72. On those infusion days teriflunomide or oral placebo should be administered after completion of the IV infusion.

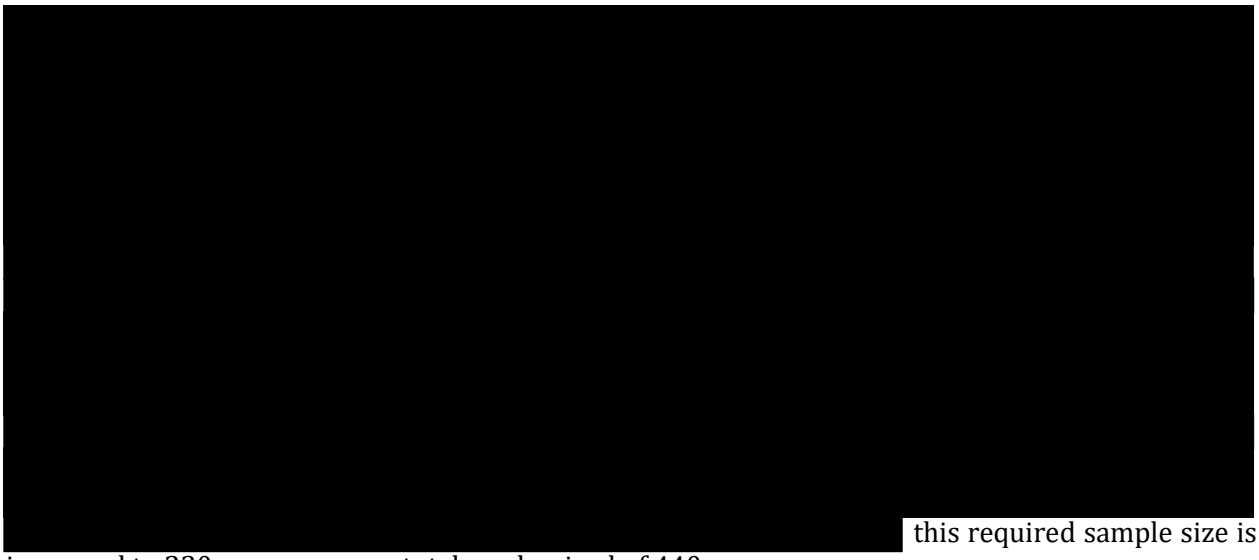
On Week 1 Day 1, if vomiting occurs during the ublituximab or IV placebo infusion, do not administer teriflunomide or oral placebo on Week 1 Day 1. The first dose of teriflunomide or oral placebo will occur on Week 1 Day2. On other ublituximab or IV placebo infusion days, if vomiting occurs during infusion, do not administer teriflunomide or oral placebo on that day. Resume administration of teriflunomide or oral placebo the next day.

8 STATISTICAL CONSIDERATIONS

This section describes the statistical methods to be used to analyze the efficacy and safety endpoints. Safety related analyses are described in Section 9. Full details will be provided in a formal statistical analysis plan (SAP). The final Clinical Study Report will describe deviations from the SAP, if any.

The statistical analyses will be done once all subjects have completed Week 96 (Week 96 visit or earlier if withdrawn).

8.1 SAMPLE SIZE AND POWER


this required sample size is increased to 220 per group or a total randomized of 440.

8.2 GENERAL ANALYSIS CONVENTION

Unless otherwise stated, all analyses will be performed using SAS Version 9.4 or higher and the primary hypothesis test on relapses will be conducted at the two-sided type I error set to 0.05. All tertiary hypotheses will be conducted at a two-sided significance level of 0.05. P-values will be presented with 4 decimals and p-values that are less than 0.0001 will be presented as <0.0001.

Continuous (non-survival related) data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts.

8.3 STATISTICAL ANALYSES WILL BE DESCRIBED IN DETAIL IN THE STATISTICAL ANALYSIS PLAN COMPLETED PRIOR TO FINAL DATA LOCK.ANALYSIS POPULATIONS

8.3.1 SAFETY POPULATION

The Safety Population will include all subjects who receive at least one dose of study drug (ublituximab or teriflunomide, with corresponding placebos). All safety assessments including toxicity will be performed on the Safety Population by treatment actually received.

8.3.2 INTENTION-TO-TREAT (ITT)

The Intention-to-Treat (ITT) population will consist of all randomized subjects. Subjects will be analyzed by randomized treatment group. Analyses of key efficacy endpoints based on ITT population will serve as sensitivity analyses.

8.3.3 MODIFIED INTENTION-TO-TREAT (MITT)

The modified Intention-to-Treat (mITT) population will consist of all subjects in the ITT population who received at least one dose of study medication and have at least one baseline and post baseline efficacy assessment. The primary efficacy analyses will be performed based on the mITT population.

The MRI analyses will be based on the subset of subjects in the mITT population who have one baseline and post-baseline MRI efficacy assessment.

Subjects will be analyzed by randomized treatment group.

8.3.4 PER-PROTOCOL GROUP (PP)

The Per-Protocol (PP) population will consist of all subjects in the mITT group who were treated for at least 1.75 years and do not have a major protocol deviation that might impact efficacy analysis. The Per-Protocol population will only be used for sensitivity analysis of the primary efficacy and key secondary variables. Subjects will be analyzed by randomized treatment group.

8.4 SUBJECT DISPOSITION

8.4.1 SCREENING AND ENROLLMENT

Enrollment will be summarized by treatment group. A table will present the number and percentages of subjects by treatment group. Details include number of subjects screened, number of screening failures with reason and number of subjects enrolled.

8.4.2 DISPOSITION

The disposition of subjects (number randomized, treated, study medications exposure, duration of follow-up, subjects' allocation by country & region) will be tabulated by treatment group. Discontinuation of study medications prior to the end of study will be summarized by treatment group and reason for discontinuation will be displayed. Drug discontinuation and termination from study prior to the end of the study will be summarized by treatment group and reason for discontinuation and/or withdrawal (termination) will be displayed. Listings will present time to and

reason for discontinuation or termination by treatment group and subject. In addition, a table of major protocol deviations will be presented by group.

8.5 SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline demographic and clinical characteristics will be summarized as percentages for categorical variables and as mean, standard deviation, median, minimum and maximum for continuous measures. The analyses of baseline characteristics will be presented for the Safety, ITT, mITT, and PP Populations by treatment group.

8.6 MEDICAL HISTORY

Medical history will be captured at the Screening visit. Medical history will be coded using MedDRA and will be listed and summarized by MedDRA system organ class and preferred term for the Safety population.

All prior and concomitant medications and procedures will be classified by preferred terms according to the World Health Organization (WHO) Drug Dictionary and will be summarized by the number and percentage of subjects by preferred term. Prior medications and procedures are those which have a stop date prior to the randomization date, and concomitant medications and procedures are those which have a stop date after treatment start date or are ongoing. Concomitant medications will be assessed at both scheduled and unscheduled visits.

8.7 EXTENT OF EXPOSURE

The dose (mg) of study drugs administered, the total number of doses of study drugs, and the duration of treatment will be summarized with descriptive statistics.

For ublituximab or IV placebo infusions, treatment exposure is summarized as the total number of infusions (greater than 50% complete) received over the 5 expected infusions. Furthermore, the overall number of infusions, number and percentage (based on all infusions) of infusions completed with/without interruption and infusions not completed will be calculated per arm. The number and percentage of patients (based on all patients with at least one infusion) with and without any infusion complication (interruption or stop) per arm will be presented as well. The percentage of planned total infusion received will also be calculated.

For teriflunomide or oral placebo, the proportion of at least 80 percent of taken oral medication will be calculated. These proportions will be summarized by treatment group.

8.8 INTERIM SAMPLE SIZE REASSESSMENT

An independent committee, Blinded Assessment Relapse Team (BART), reporting to TG Therapeutics, and the DSMB will reassess the sample size for the study when 210 of the 220 participants have been randomized. Assuming a uniform rate of recruitment, we need an estimate as to how many person years of exposure will occur before an interim adjustment occurs. If

recruitment is going to be accomplished in 8 to 10 months, the average exposure time when 210 subjects per group are recruited would experience half of the recruitment period or 9/2=4.5 months. We can use all of the data available at that time and thus will have approximately 4.5 x 210 = 945 person months or approximately 43 person years of observation (the denominator to compute the ARR).

The Table below provides the sample sizes (total adjusted sample sizes) needed per group per study based on the findings at the interim (Columns of the Table) for reductions in the ARR of teriflunomide by 40%. As an example, if the estimated ARR in the pooled population is 0.20 and we are assuming an hypothesized 40% reduction in the ARR rate by ublituximab, then the ARR in the individual groups (red numbers in the table below) can be derived by solving a simple equation; $(N_U*0.6\ P_T + N_T*P_T)/(N_U + N_T)=0.20$ where P_T is the ARR in the teriflunomide group and N_T and N_U are the sample sizes, assumed to be equal. Thus, if the combined ARR=0.20, then this equation under the hypothesized reduction of 40% yields an estimated ARR of 0.25 in teriflunomide and 0.15 in ublituximab. Calculating the required sample size using a negative binomial comparison with 1.75 years of observation overall, results in an updated sample size of 219 per group. Thus, the original sample size of N=200 would be adjusted upward by adding 19 participants per treatment group, plus the 10% for dropouts yielding a total of 241 subjects per group or 21 additional participants.

In the Table below, which can guide the interim sample size reassessment, we see two color blocks in the table. The green area shows results that have two (2) characteristics - one, they require smaller sample sizes and two, they are unlikely to occur because the ARR rate in the teriflunomide group would have to exceed 0.31 (arbitrarily chosen, but some level is reasonable as an upper limit on what the rate is likely to be). Either way, if the blinded ARR falls in the green area or above, the sample size will not be reduced since we do not plan to reduce the sample size and 210 participants per group will have already been enrolled. The yellow area is the range for the combined total rates. If the overall ARR =0.19 then the estimated teriflunomide rate would be estimated at 0.2375 and ublituximab would be estimated at 0.1425 and the sample size required would be 233 per group. Thus, a rate <= 0.19, the sample size will be increased by 30 per treatment group in each study, but no more. Such observed relapse rates are quite low and unexpected, so that further adjustments are probably not warranted.

Recruitment will continue while the interim analysis is ongoing and if the participants recruited beyond the 220 per group will be used in the final analyses if the sample size is not increased and will count toward the additional sample size if warranted.

% Reduction in ARR		Findings at Interim findings at interim								
	Treatment	0.160	0.180	0.200	0.220	0.240	0.260	0.280	0.290	0.300
40%	Ublituximab /oral placebo	0.120	0.135	0.150	0.165	0.180	0.195	0.210	0.218	0.225
	Teriflunomide/IV placebo	0.200	0.225	0.250	0.275	0.300	0.325	0.350	0.363	0.375
Avg Follow-Up = 1.75 years	N	268	243	224	208	195	183	174	169	165

8.9 EFFICACY ANALYSES

The primary efficacy endpoint will be tested at a two-sided Type I error of 5%. If the null hypothesis on the primary efficacy endpoint is rejected, the null hypotheses on the secondary efficacy endpoints will be tested. The key secondary outcomes will be tested using a hierarchical approach with the order specified as in the objectives using a step-down procedure where each test is a Type1 error 0.05 (see Section 8.9.2).

For subjects who have withdrawn consent from the study, all data compiled up to the point of withdrawal will be used for analysis. For subjects who withdraw from their active treatment will not have the blind broken and all data up to the time of withdrawal from treatment will be used in the primary analysis. Sensitivity analyses will use all their data over the entire study period. Subjects who are withdrawn prematurely from study treatment will be included in all analyses regardless of the duration of treatment. Subjects who withdraw before they receive study medication they will be replaced, with new subjects who will be assigned new randomization numbers. If subjects withdraw prematurely from treatment, the subject will not be replaced. There will be no imputation for missing data except where sensitivity analyses are conducted.

8.9.1 PRIMARY EFFICACY VARIABLE

The primary efficacy variable will be Annualized Relapse Rate, defined as the number of relapses (protocol defined and confirmed by Independent Relapse Adjudication Panel) per subject-year (a year is equal to 365.25 days).

The primary efficacy analysis will be performed using the mITT with a Negative Binomial regression model to accommodate the potential over-dispersed data appropriately. The model will include the total number of confirmed relapses with onset between randomization date and the day of last study treatment as response variable, treatment group, EDSS strata (baseline EDSS score ≤3.5 versus >3.5) and clinic region as covariates.

Relapses that occur after study drugs are withdrawn will be assessed over the remainder of the study period and this data will be utilized as part of additional sensitivity analysis (described in the statistical plan) as long as the subject has not withdrawn their consent to be in the trial.

The treatment group will have 2 levels (teriflunomide/ IV placebo or ublituximab/oral placebo). In order to account for different treatment durations among subjects, the log-transformed standardized treatment duration (randomization to date last treatment before early withdrawal or completion of Week 96 assessment) will be included in the model as an "offset" variable for appropriate computation of the Annualized Relapse Rate. [redacted] will be used to assess the overall model with subjects in a repeated statement using a Generalized Estimating Equation (GEE) approach.

Two-sided 95% confidence intervals of the rate ratio will be provided for the comparisons of Ublituximab/oral placebo versus teriflunomide/IV placebo. The estimated relapse rate and its 2-sided 95% confidence intervals will be provided for each treatment group.

8.9.2 SECONDARY EFFICACY VARIABLES

The key secondary outcomes will be tested using a hierarchical approach with the order specified below using a step-down procedure where each test is at a Type I error 0.05. If any endpoints fail to reach significance, then formal testing of significance of the subsequent secondary outcomes will not be performed.

1. Total number of gadolinium enhancing (Gd-enhancing) T1-lesions per MRI scan by Week 96.
2. Total number of new and enlarging T2 hyperintense lesions (NELs) per MRI scan by Week 96.
3. Time to Confirmed Disability Progression (CDP) for at least 12 weeks occurring during the 96-week, double-blind treatment period. *
4. Proportion of subjects with No Evidence of Disease Activity (NEDA) from Week 24 to Week 96.
5. Proportion of subjects reaching impaired SDMT (Symbol Digit Modalities Test) from baseline to Week 96.
6. Percentage change in Brain Volume from baseline to Week 96.

* Confirmed Disability Progression for at least 12 weeks during the 96-week treatment period will be analyzed using pooled data from the two identical studies TG1101-RMS301 and TG1101-RMS302.

The total number of gadolinium enhancing (Gd-enhancing) T1-lesions will be calculated as the sum of the individual number of lesions at weeks 12, 24, 48, and 96, divided by the total number of MRI scans of the brain. The total number of new and enlarging T2 hyperintense lesions will be calculated as the sum of the individual number of lesions at weeks 24, 48, and 96, divided by the total number of MRI scans of the brain. The MRI count variables will be assessed for differences between the treatment groups using negative binomial regression with an offset based on time on study and covariates, region, baseline EDSS strata, and baseline MRI counts. Percent brain volume change will be assessed between the two groups using linear mixed effects models [redacted] with covariates region, baseline EDSS strata, and baseline brain volume.

Disability progression is defined as an increase of ≥1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥0.5 when the baseline score is above 5.5. Disability progression is considered confirmed when the increase in the EDSS score is confirmed at regularly scheduled visits at least 12 or 24 weeks after the initial documentation of neurological worsening.

Please note that Confirmed Disability Progression for at least 12 weeks during the 96-week treatment period will be analyzed using pooled data from the two identical studies TG1101-RMS301 and TG1101-RMS302. With the exception of this endpoint (CDP), which will be analyzed at the pooled level, all other secondary efficacy endpoints will be tested if and only if the individual study secondary endpoint listed ahead of it has reached the significance level at 0.05.

All pre-specified pooled analyses are listed below. However, only CDP for at least 12 weeks is part of the secondary analysis and the remainder are included in the tertiary analysis.

1. Time to Confirmed Disability Progression for at least 12 weeks (secondary analysis)
2. Time to Confirmed Disability Progression for at least 24 weeks (tertiary analysis)
3. Time to Confirmed Disability Improvement for at least 12 weeks (tertiary analysis)
4. Time to Confirmed Disability Improvement for at least 24 weeks (tertiary analysis)

Summary tables of progression to CDP will present the proportion who achieved CDP at Week 96 and associated 95% CIs for each treatment group. The median time-to-event with 2-sided 95% CIs as well as the proportion of subjects remaining event-free at times of interest will be estimated using Kaplan-Meier methods implemented with [redacted]. All time to CDP (and CDI) endpoints will be analyzed similarly.

The proportion of subjects with No Evidence of Disease Activity (NEDA) will be calculated at Week 96. A subject with NEDA is defined as a subject without relapses confirmed by the IRAP, without MRI activities (no T1 Gd+ lesions and no new/enlarging T2 lesions), and no 12-week Confirmed Disability Progression. Any evidence of disease activity from Week 24 to Week 96 will be counted as not reaching NEDA. Any evidence of disease activity before Week 24 will not count. NEDA rates will be compared using logistic regression [redacted] with baseline adjustments the same as used in the primary analysis plus baseline MRI counts and without an offset to take into account time on study.

Change in cognition (SDMT) will be assessed using the total score at each SDMT visit which is defined as the total number of correct answers reported in the CRF. Impaired SDMT is defined as a decrease from baseline of at least 4 points at any post-baseline assessment up to the Week 96 visit. The proportion of impaired SDMT will be analyzed in all subjects in the mITT population. SDMT rates will be compared using logistic regression [redacted] with baseline adjustments the same as used in the primary endpoint analysis, without treatment duration offset, but including log-transformed baseline MRI counts (T1 unenhancing, T2, Gad enhancing). To avoid zero values for the log transformation of MRI counts, 1 will be added to each observation before transforming.

8.9.3 SENSITIVITY ANALYSES

Sensitivity Analysis

1. The primary analysis will be repeated based on all reported MS relapses (rather than just confirmed ones).

2. A time to relapses analysis using Cox proportional hazards model with first IRAP-confirmed relapse as the primary event will be conducted to compare with the primary analysis in a negative binomial model. The Cox proportional hazards model will be specified with treatment, region, number of relapses in previous year, baseline EDSS score, baseline number of T1 Gd-enhancing lesions sex and the subject's age at baseline as covariates.

3. To assess the effects of treatment withdrawals, the primary analysis will be repeated using the information on relapses which occur during the period following drug withdrawal to the end of the study period regardless of whether additional treatment were utilized. Relapses which occurred after permanent discontinuation of study medication will be included and natural log (time on study in years) rather than the natural log (time on study drug in years) will be used as the offset variable in the negative binomial model, which is the primary analysis.

4. We will examine the dropouts from the trial using all participants who provided withdrawal of consent excluding deaths. Multiple imputation will be used to impute the expected number of relapses a participant would have had if they had continued to participate in the trial. To perform the imputation, 10 replicates will be used since a relapse on treatment is relatively low frequency event. The covariates used to model and predict the imputations will include: treatment, region, number of relapses in previous year, baseline EDSS score, baseline number of T1 Gd-enhancing lesions sex and the subject's age at baseline as covariates.

5. For secondary outcomes T1 Gd enhancing, T2 NELs, and 12 week CDP, the effects of dropouts and study discontinuations will be similarly evaluated as number 4 above.

6. Additional sensitivity analyses may be defined in the analysis plan prior to database lock.

8.9.4 TERTIARY EFFICACY AND OTHER VARIABLES

All tertiary analyses will be assessed at a Type I error of 0.05 with no adjustment for multiplicity.

1. Change in MSFC score from baseline to Week 96
2. Time to Confirmed Disability Progression (CDP) for at least 24 weeks
3. Time to Confirmed Disability Improvement (CDI) for at least 12 weeks
4. Time to Confirmed Disability Improvement (CDI) for at least 24 weeks
5. Health outcomes (MSQoL-54 (inclusive of SF36); FIS, hospitalization, steroid use, time out of work)
6. Total volume of Gd enhancing T1 lesions per MRI scan over the treatment period
7. Volume of T2 lesions
8. Volume of hypointense T1 lesion component (black holes)
9. Proportion of subjects free of disability progression at Weeks 24, 48 and 96.
10. Proportion of subjects with a relapse
11. Time to first confirmed relapse

Change in MSFC and Health Outomes (MSQoL-54 (inclusive of SF36), FIS), will be analyzed using linear Mixed Models. including results with baseline as a covariate along with region and other covariates if used in the primary analyses.

The analysis of CDI at 12 and 24 weeks will utilize the same approach as that used for CDP. 12 Week Confirmed Disability Improvement (12 Week CDI) is defined as a reduction from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained and confirmed at the next scheduled visit at least 12 weeks after the initial documentation of neurological improvement. Similarly, 24-week Confirmed Disability Improvement (24 Week CDI) requires an initial reduction from baseline EDSS score and a subsequent confirmation of the reduction at all regular scheduled visits for at least 24 Weeks after the initial documentation of neurological worsening

Hospitalization, Steroid Use, and Time Out of Work will be summarized by descriptive statistics as well as frequency and percentage. For Time Out of Work, percentages of missed work hours will be compared between arms using Wilcoxon rank sum tests. For Steroid Use, the number of IRAP confirmed relapses treated with steroid will be analyzed the same way as the primary endpoint.

For analysis of lesion volume related variables (Total volume of Gd enhancing T1 lesions per MRI scan over the treatment period, Volume of T2 lesions, Volume of hypointense T1 lesion component (black holes)) Mixed Model Repeated Measures (MMRM) analyses will be implemented via [redacted]

Time to first confirmed relapse is defined as (date of relapse onset – date of randomization + 1) and will be regarded as censored at the end of treatment. The analysis will be similar to the one of time to confirmed disability progression. The proportions of subjects with a relapse and subjects free of disability progression at different time points will be estimated using the Kaplan-Meier method.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.9.6 ANTI-DRUG ANTIBODY (ADA) ANALYSIS

Immunogenicity results will be reported based on all subjects in the safety population. The percentage of subjects developing ADA will be summarized. .

9 SAFETY REPORTING AND ANALYSIS

9.1 SAFETY ANALYSES

To evaluate the safety of ublituximab/placebo and teriflunomide/oral placebo, as determined by adverse events (AEs) and serious adverse events (SAEs), including MS worsening.

Safety will be tabulated as described below in the safety section. Tables will summarize the proportion of subjects ever experiencing a particular AE, and in select tables will also include the number of times a particular AE occurs.

Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the subject's physical examination, vital signs, and clinical laboratory results. Safety analyses will be performed using the safety population. Safety variables will be tabulated and presented by treatment actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated. Must obtain expert evaluations of brain MRI images of subjects with suspected opportunistic CNS infections including PML.

For select laboratory values, box plots of the values over time will be used for displays of these parameters. In the event of higher than expected incidence rates of abnormalities, further exploration of combinations of events, such as Hy's law, will be examined.

9.2 ADVERSE EVENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial.

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

9.3 ADVERSE EVENT CHARACTERISTICS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the following web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03 is to be used for the grading of severity of symptoms and abnormal findings. For adverse events not covered by the NCI-CTCAE Version 4.03 grading system, the following definitions will be used:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or non-invasive intervention indicated.
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

9.4 ADVERSE EVENT EXPECTEDNESS

AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. Expected AEs are those listed in the Investigator Brochures for either ublituximab or teriflunomide.

9.5 TREATMENT EMERGENT ADVERSE EVENTS (TEAE'S)

The frequency and percentages of subjects with treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and preferred term (PT), where treatment-emergent is defined as any AE with an onset on or after the first dose of study medication and through 30 days after the last dose of study medication or with an onset prior to the first dose of study medication that increases in severity on, or after the first dose of study medication and through 30 days after the last dose of study medication.

In addition, TEAEs that are considered at least possibly related to study treatment will be tabulated as well as deaths, SAEs, and events resulting in treatment discontinuation or termination. Additionally, the subset of events which occurred after the last study drug administration will be summarized.

9.6 ADVERSE EVENTS / SERIOUS ADVERSE EVENT CAUSALITY ASSESSMENT

The Investigator must also assess the relationship of any adverse event to the use of study drug, (whether none, one, or all) based on available information, using the following guidelines:

1. **Not Related**: Clear-cut temporal and/or mechanistic relation to a cause other than the study drug.
2. **Doubtful**: There is no reasonable possibility that the event is related to the study medications but a definite cause cannot be ascertained.
3. **Possible**: There is still a reasonable possibility that the cause of the event was the study medications but there exists a more likely cause of the event such as complications of progressive disease.
4. **Probable**: The most likely cause of the event is the study medications but other causes cannot be completely excluded.
5. **Definite:** Clear cut temporal and/or mechanistic relation to the study medications. All other causes have been eliminated. Events classified as definite will often be confirmed

by documenting resolution on discontinuation of the study medications and recurrence upon resumption.

In the summary of drug related AEs, "Not Related" and "Doubtful" will be considered as "Not Drug Related" and "Possible", "Probable", and "Definite" will be considered as "Drug Related." In the event that causality is missing for an AE, it will be considered as "Drug Related."

9.6.1 RECORDING OF ADVERSE EVENTS

All adverse events of any subject during the course of the trial will be reported on the electronic CaseRreport Form, and the investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration –ublituximab/IV placebo or teriflunomide/oral placebo). If the adverse event is serious, it should be reported as soon as possible and no greater than 24 hours to the sponsor or designee. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs (i.e., AEs that occur prior to assignment of trial treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs regardless of seriousness or relationship to ublituximab/IV placebo and/or teriflunomide/oral placebo treatment, as well as all pregnancies, spanning from the signing of the informed consent and until 20 weeks after discontinuation or completion of either protocol-specific treatment as defined by the protocol for that subject, are to be recorded on the eCRF/Pregnancy Report Form.

9.6.2 ABNORMAL LABORATORY VALUES AND VITAL SIGNS

The reporting of abnormalities of vital signs as adverse events should be avoided. Abnormalities of vital signs should not be reported unless any criterion for an SAE is fulfilled, the vital signs abnormalities cause the subject to discontinue trial treatment, or the investigator insists that the abnormality should be reported as an AE. Abnormal laboratory results should be noted in the eCRF as an adverse event if they are associated with an overdose, require prolong in-patient hospitalization, or are otherwise considered clinically significant by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected in the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

Clinical Laboratory Results will be summarized. Summary statistics for actual values and for changes from baseline will be tabulated for laboratory results by scheduled visit. Subjects with laboratory values outside of the normal reference range at any post-baseline assessment will be summarized, and graded per NCI CTCAE Version 4.03 when applicable. Subject incidence of laboratory toxicity will be summarized by treatment group and maximum grade for each laboratory test.

9.6.3 HANDLING OF ADVERSE EVENTS

All adverse events resulting in discontinuation from the trial should be followed until resolution or stabilization. Subjects must be followed for AEs for 20 weeks after discontinuation or completion of protocol-specific treatment. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease or the subject is lost to follow up. In this case, the investigators must record his or her reasoning for this decision in the subject's medical record and as a comment on the eCRF. After 20 weeks, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

9.7 SERIOUS ADVERSE EVENTS

9.7.1 DEFINITIONS OF SERIOUS ADVERSE EVENTS

The definitions of serious adverse events (SAEs) are given below. The Principal Investigator is responsible for ensuring that all staff involved in the trial are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that:

- Results in death, is immediately life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, and/or
- Causes a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

A SUSAR is defined as a suspected unexpected SAE, and SUSAR reporting is encompassed within SAE reporting guidelines as defined in this section.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Out-patient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization due to MS relapse does not need to be reported to the Sponsor as an SAE if the Treating Neurologist medically confirms the relapse. The subsequent IRAP adjudication will not impact the reporting status of the SAE.

Events related to underlying MS disease (i.e., MS progression) also do not require reporting as an SAE.

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial), does not require reporting as a serious adverse event to the Sponsor.

9.7.2 SERIOUS ADVERSE EVENT REPORTING BY INVESTIGATORS

It is important to distinguish between "serious" and "severe" adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to the Sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from the signing of the informed consent form through the 20-week Follow-up Period after the last trial treatment. Sponsor or designee must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, see the appropriate SAE eCRF page.

All SAEs and medically confirmed deaths (regardless of causality assessment) spanning from the signing of the informed consent and until 20 weeks of last trial treatment must be expeditiously reported to the sponsor as SAEs within the eCRF and followed until resolution (with autopsy report if applicable).

The investigator must review and sign off on the SAE data on the SAE report. The SAE will be reported to the Sponsor (or Sponsor designee) as outlined in the Safety Monitoring Plan.

If an SAE is reported to the sponsor or designee via fax, the same information must be entered on the eCRF within 24 hours (1 business day). The SAE transmission should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the sponsor or designee as soon as it is available; these reports should be submitted using the appropriate eCRF. The detailed SAE reporting process will be provided to the sites in the Investigator Study Guide.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRBs/EC)/Independent Ethics Committee according to the policies of the responsible IRB or Ethics Committee.

9.8 SPONSOR SAE REPORTING REQUIREMENTS

Sponsor is responsible for reporting relevant SAEs to the Competent Authority, other applicable Regulatory Authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

Sponsor is responsible for reporting related, unexpected fatal or life-threatening events associated with the use of the trial drugs to the regulatory agencies and competent authorities via telephone or fax within 7 calendar days after being notified of the event. The Sponsor will report all related, unexpected SAEs including non-death/non-life-threatening SAEs associated with the use of the trial medications to the applicable Regulatory Authorities, investigators, and central IRBs or EC by a written safety report within 15 calendar days of notification. Investigators using local IRBs or EC are responsible for sending written safety reports for these events to their IRBs or EC within 15 calendar days or accordingly to the timelines outlined in the policies of the responsible IRB or EC.

9.9 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE eCRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE eCRF; AEs that meet the definition of an SAE should additionally be reported.

9.10 DIAGNOSIS VS. SIGNS AND SYMPTOMS

All AEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the PI and/or Treating Neurologist, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF). If a diagnosis is subsequently established, it should be reported, as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

9.10.1 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF. If a persistent AE becomes more severe (changes from a Grade 1 or 2 AE to a Grade 3 or 4 AE) or lessens in severity (changes from a Grade 3 or 4 AE to a Grade 1 or 2 AE), it should be recorded on a separate SAE Report Form and/or AE eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF for each recurrence.

9.10.2 ABNORMAL LABORATORY VALUES

Abnormal laboratory results should be noted in the eCRF as an adverse event if they are associated with an overdose, require or prolong in-patient hospitalization, or are otherwise considered clinically significant by the investigator. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected in the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

9.10.3 DEATHS

All medically confirmed deaths, regardless of attribution, spanning from the signing of the informed consent and until 20 weeks after discontinuation or completion of either protocol-specific treatment will be recorded within the eCRF and expeditiously reported to the Sponsor.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event page of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event page.

9.10.4 HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

Any AE that results in in-patient hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE (refer to Sections 9.7.1 and 9.7.2).

9.10.5 PRE-EXISTING MEDICAL CONDITIONS

A pre-existing relevant medical condition is one that is present at the start of the trial. Such conditions should be recorded on the study's appropriate medical history eCRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on the appropriate SAE Report Form and/or AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

9.10.6 PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

Reference the ublituximab Investigator Brochure for Adverse Events of Special Interest (AESI). AEs that are considered AESIs are to be reported in the appropriate eCRF. SAEs that are considered AESIs should be reported following the timeline and reporting process outlined in Section 9.7.2.

Pregnancy:

Since pregnancy as such is not considered to be an adverse event, it does not need to be reported as an AESI. However, if pregnancy is associated with adverse events, it is these adverse events that need to be reported in eCRF. Pregnancy reporting requirements outlined in Appendix A must be followed.

Overdose:

All instances of overdose, whether symptomatic or asymptomatic, of either ublituximab/IV placebo or Teriflunomide/oral placebo must be reported in eCRF on the Overdose form. Anything over the prescribed daily dose is considered an overdose.

If an overdose is associated with adverse events, it is these adverse events that need to be reported in eCRF. If an adverse event associated with an overdose meets a seriousness criterion, it must be expeditiously reported as an SAE.

Suicidal ideation and behavior will be identified by the AE preferred terms included in MedDRA SMQ "Suicide/self-injury".

10 STOPPING RULES

The DSMB (Study Chairs, Medical Monitor and Sponsor Representative) will be in charge of reviewing safety data. These events will be reviewed by the DSMB and potentially other study investigators during the course of the study. All other serious and non-serious adverse events will be documented, managed for each subject including review of the safety data by the DSMB and possible study participation termination at the investigator and DSMB discretion. The independent DSMB will be comprised of a total of 5 members with at least 3 MDs, a biostatistician and the DSMB chair.

The DSMB may stop the study due to safety reasons after reviewing the safety data.

11 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

11.1 IRB/EC APPROVAL

The trial protocol, ICF, IBs, available safety information, subject documents (e.g., trial diary), subject recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the subjects and documentation evidencing the PI's qualifications must be submitted to the IRB/EC for ethical review and approval prior to the trial start.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure initial and ongoing, IRB/EC trial review. The PI/Sponsor and/or designee (as appropriate) must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB/EC.

If applicable, the PI will notify the IRB/EC **within 90 days** of the end of the trial, or if the trial terminates early, the PI must notify the IRB/EC **within 15 days** of the termination. A reason for the early termination must be provided (as defined in Directive 2001/20/EC). The Sponsor will either prepare or review all submission documents prior to submission to the IRB/EC.

11.2 REGULATORY APPROVAL

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant Regulatory Authorities.

Safety updates for ublituximab/IV placebo and teriflunomide/oral placebo will be prepared by the Sponsor (or its representative), as required, for submission to the relevant Regulatory Authority.

11.3 INSURANCE AND INDEMNITY

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

11.4 INFORMED CONSENT

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

The ICF will be submitted for approval to the IRB/EC that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the responsible Regulatory Authority, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the subject's medical record. A copy of the informed consent form, including the subject's signature, will be provided by the investigator to the subject.

If an amendment to the protocol substantially alters the trial design or the potential risks to the subjects, the subject's consent to continue participation in the trial must be obtained. Additionally, upon either IRAP-confirmed or Treating Neurologist medically confirmed relapse, subjects should re-consent to continue participation in the trial.

11.5 CONFIDENTIALITY

Subject Confidentiality

Confidentiality of subject's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA; for USA only), and national data protection laws. HIPAA regulations require that, in order to participate in the trial, a subject must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from subjects in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization.

In the event that a subject revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the Regulatory Authorities and the IRB/EC direct access to review the subject's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and year of birth will identify subjects on the eCRF or other documents submitted to the Sponsor. This information will be used in the database for subject identification. Subject names, addresses or birthdate/month will not be entered in the eCRF or database. No material bearing a subject's name will be kept on file by the Sponsor. Subjects will be informed of their rights within the ICF.

11.6 INVESTIGATOR AND STAFF INFORMATION

Personal data of the investigators and sub-investigators may be included in the Sponsor database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

11.7 FINANCIAL INFORMATION

The finances for this trial will be subject to a separate written agreement between the Sponsor and/or designee and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

12 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

12.1 AMENDMENTS TO THE PROTOCOL

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of the Sponsor. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB/EC at the investigator's facility for the board's approval.

Amendments specifically involving change to trial design, risk to subject, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB/EC at the Investigator's facility.

The amendment will be submitted to Regulatory Authorities by the Sponsor or designee as applicable, and specifically when an increase to dosing or subject exposure and/or subject number has been proposed.

Items requiring a protocol amendment with IRB/EC and Regulatory Authority approval include, but are not limited to, the following:

- Change to trial design
- Risk to subject
- Increase to dose or subject exposure to drug
- Subject number increase of more than 20%
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the trial design or the potential risks to the subjects, their consent to continue participation in the trial should be obtained.

12.2 DOCUMENTATION REQUIRED TO INITIATE TRIAL

Before the trial may begin, documentation required by FDA regulations must be provided by the Investigator. The required documentation should be submitted to the Sponsor or designee.

Documents at a minimum required to begin the trial include, but are not limited to, the following:

- A signature-authorized protocol and contract;
- A copy of the official IRB/EC approval of the trial and the IRB/EC members list;
- Current Curricula Vitae for the Principal Investigator and any associate investigator(s) who will be involved in the trial;

- Indication of appropriate accreditation for any laboratories to be used in the trial and a copy of the normal ranges for tests to be performed by that laboratory;
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed;
- A copy of the IRB/EC-approved consent form containing permission for audit by representatives of the Sponsor, the IRB/EC, the FDA, and other applicable regulatory agencies;
- Financial disclosure forms for all investigators listed on Form FDA 1572;
- GCP Certificate for trial training;
- Site qualification reports, where applicable;
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

The Sponsor/Sponsor designee will ensure that all documentation that is required to be in place before the trial may start, in accordance with ICH E6 and Sponsor SOPs, will be available before any trial sites are initiated.

12.3 TRIAL DOCUMENTATION AND STORAGE

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the subject's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the subject's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, EKG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and trial staff are responsible for maintaining a comprehensive and centralized filing system (Site Trial File/SSF or ISF) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable Regulatory Authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 13 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB/EC approval documents, Financial Disclosure forms, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment.

In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB/EC shall maintain adequate documentation / records of IRB/EC activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories and any other trial-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from Regulatory Authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating subjects (sufficient information to link records e.g., medical records), all original, signed informed consent forms, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor or its representative will notify the investigator(s)/institutions(s) when the trial-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the trial, the sponsor and/or its representative should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to sponsor. The investigator must obtain the sponsor written permission before disposing of any records, even if retention requirements have been met. All trial files will be maintained by the Sponsor or its representative throughout the trial, and will be transferred to the Sponsor at the conclusion of the trial.

12.4 DATA COLLECTION

The trial eCRF is the primary data collection instrument for the trial. An electronic Case Report Form (eCRF) will be utilized for the collection of all data and all data will be entered using the English language and should be kept current to enable the monitor to review the subjects' status throughout the course of the trial.

In order to maintain confidentiality, only subject number and year of birth will identify the subject in the eCRF. If the subject's name or full date of birth appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the investigator site and replaced instead with the subject number and subject's year of birth. The investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to

enable records to be identified and verified as authentic. Subject data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

12.5 TRIAL MONITORING, AUDITING, AND INSPECTING

The investigator will permit trial-related monitoring, quality audits, and inspections by the government Regulatory Authorities, the Sponsor or its representative(s) of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, electronic Case Report Forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government Regulatory Authorities, the sponsor or its representative(s).

At the Sponsor's discretion Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

12.6 QUALITY ASSURANCE AND QUALITY CONTROL

In addition to the Clinical Monitoring component of this protocol, the Sponsor's Quality Assurance (QA) department shall establish an Auditing Plan document separate from the protocol to establish the criteria by which independent auditing shall be conducted during the conduct of the trial to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

Each trial site shall be required to have processes and/or procedures in place that will ensure the study is conducted according to the protocol, GCP and any applicable local, national or international regulations.

12.7 DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial.

A Clinical Study Report will be prepared upon completion of the study. The Sponsor will disclose the trial results, in the form of a clinical study report synopsis, to the IEC and the applicable Regulatory Authorities within one year of the end of the trial. The format of this synopsis and that of the Clinical Study Report and its addendum will comply with ICH E3 guidelines for structure and content of a Clinical Study Report.

The financial disclosure information will be provided to the Sponsor or designee prior to trial participation from all PIs and Sub-Investigators who are involved in the trial and named on the FDA 1572 form.

By conducting this study, the Investigator affirms to the Sponsor that he or she will maintain, in strict confidence, information furnished by the Sponsor including data generated from this study and preliminary laboratory results, except as exempted for regulatory purposes.

All data generated during the conduct of this study is owned by the Sponsor and may not be used by the Investigator or affiliates without the expressed written consent of the Sponsor.

All manuscripts, abstracts, or other presentation materials generated by site investigators must be reviewed and approved by the Sponsor prior to submission.

13 REFERENCES

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17 Confavreux C *et al. Lancet Neurol*. 2014; **13**:247-256.

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19. https://www.aubagio.com/media/pdf/Guide_to_Accelerated_Elimination_Procedure_for_AUBAGIO(R)(teriflunomide).pdf

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14 APPENDIX A; PREGNANCY

Women Not of Childbearing Potential are Defined as Follows:

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea (based on the subject's medical history) with serum FSH levels > 40 mIU/mL [for US only: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. In addition, female patients with hysterectomy but with available ovaries are not considered WOCBP because of their belonging to surgically sterile category of patients.

Contraceptive Guidelines for Women of Child-Bearing Potential:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use effective contraception during the study and for 20 weeks after the last study drug was administered. The effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.
4. Oral contraception, injected or implanted hormonal methods.
5. Use of a combination of any two of the following (a+b):
    a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Women of child-bearing potential must have a negative serum pregnancy test within 5 days prior to initiating treatment.

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, and for an additional 20 weeks after the last study drug was administered, and should not father a child in this period. Male subjects must also not donate sperm during active treatment and for 20 weeks following the last study drug administered.

Female partners of fertile male participants must also use effective measures of contraceptives as described above for females.

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to TG Therapeutics Inc. within 24 hours of learning of its occurrence. The pregnant subject/male subject's partner will be asked to provide informed consent to allow the pregnancy to be followed up for the full duration (or until termination) to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Additionally, medical information will be collected on the newborn for 6 months after birth, as permitted by local regulations.

Pregnancy should be recorded on a Pregnancy Report Form and reported by the investigator to TG Therapeutics Inc. Pregnancy follow-up should be recorded on the same form and reported by the investigator to TG Therapeutics Inc. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

15 APPENDIX B; NYHA CLASSIFICATIONS

New York Heart Association (NYHA) Classifications

Class	Functional Capacity	Objective Assessment
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

16 APPENDIX C; 2010 MCDONALD DIAGNOSTIC CRITERIA FOR MS

2010 Revised McDonald Diagnostic Criteria for MS [12]

Clinical (Attacks)	Lesions	Additional Criteria to Make Diagnosis
≥ 2	Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
≥ 2	Objective clinical evidence of 1 lesion	Dissemination in time, demonstrated by: • ≥1 T2 lesion in ≥ 2 MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR • Await further clinical attack implicating a different CNS site
1	Objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: • Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR • A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; OR • Await a second clinical attack
1	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1T2 lesion in at least 2 MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR • Await further clinical attack implicating a different CNS site AND Dissemination in time, demonstrated by • Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR

		• A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; OR • Aware a second clinical attack
0 (Progression from onset)		One year of disease progression (retrospective or prospective) AND ≥ 2 out of 3 criteria: • Dissemination in space in the brain based on ≥1 T2 lesion in periventricular, juxtacortical or infratentorial regions; • Dissemination in space in the spinal cord based on ≥2 T2 lesions; OR • Positive CSF

What is an attack?

- Neurological disturbance of kind seen in MS
- Subjective report or objective observation
- ≥ 24 Hours duration in the absence of fever or infection
- Excludes pseudo-attacks, single paroxysmal symptoms (multiple episodes of paroxysmal symptoms occurring over 24 hours or more are acceptable as evidence)
- Some historical events with symptoms and pattern typical for MS can provide reasonable evidence of previous demyelinating event(s), even in the absence of objective findings

Determining Time Between Attacks: 30 days between onset of event 1 and onset of event 2

Provides Evidence for Dissemination in Space (DIS)?

- ≥1 T2 lesion in at least 2 out of four areas of the CNS: periventricular, juxtacortical, infratentorial or spinal cord
- Gd enhancement of lesions is not required for DIS
- If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count

What provides MRI Evidence of Dissemination in Time (DIT)?

- A new T2 and/or Gd-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI OR
- Simultaneous presence of asymptomatic Gd-enhancing and non-enhancing lesions at any time

What is Positive CSF: Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index

17 APPENDIX D; INDEPENDENT RELAPSE ADJUDICATION PANEL (IRAP)

Independent Relapse Adjudication Panel (IRAP)

The Phase III study includes an objective definition of relapse and a standardized procedure for assessment of all suspected relapses as described in Section 4.4.1. As outlined in this section, the Treating Neurologist will, within these guidelines, exercise his or her best clinical judgement in treating the suspected relapse. However, neither the Treating Neurologist nor the blinded rater/Examining Neurologist will make the final determination of whether a suspected event is counted as a relapse for the purpose of calculating the primary study outcome of Annualized Relapse Rate (ARR). Instead, an independent, blinded IRAP will make all relapse determinations in the Phase III study. The purpose of the IRAP is to ensure that relapses are scored in a manner that is consistent and objective as possible, and to minimize the variability between sites.

The IRAP will review all subject records pertaining to suspected on-study relapses (i.e., new or worsening neurological symptoms of acute onset) that occur outside the scheduled study visits and are reported by the subject within 48 hours. Upon receiving the report by the subject, of a suspected relapse/acute neurological event, the Treating Neurologist and Examining Neurologists will in an independent manner, and blinded to the results of their separate examinations follow the procedures and timelines as described below and outlined in Appendix E. All suspected relapses initially reported by the subject are evaluated by the IRAP regardless of whether the Treating Neurologist considered the subject's symptoms to be the result of a relapse.

The IRAP comprises of 6 independent neurologists with expertise in MS clinical research who are not investigators in any other TG Therapeutics-sponsored studies with ublituximab. The IRAP members are trained on study procedures by the Sponsor and an independent Contract Research Organization (CRO) who manages all IRAP activities throughout the study. IRAP members are required to review trial data and perform adjudications in accordance with the protocol- specified definition (Section 4.4.1).

The CRO transfers blinded data that are relevant to assessment of relapses (entered into the eCRF by both the Treating Neurologist and the Examining Neurologist) and prepares blinded case dossiers to be reviewed by the IRAP via a secure electronic portal. The dossiers include a standardized listing for each suspected relapse that specified onset date, type and severity of reported symptoms, whether the event had disqualifying characteristics (e.g., lasted less than 24 hours, or symptoms not MS-related), and whether event has been treated with methylprednisolone. The dossiers also include vital signs, AEs related to the potential relapse, physical examinations, and EDSS scores with all supporting data from the standardized Neurostatus exam; values from baseline and the most recent prior quarterly assessment are provided as context for values from the relapse evaluation visit. Medical/surgical history and clinical episode history are also provided. In order to minimize the potential for inclusion of data which can potentially unblind an individual case under review (e.g., inclusion of adverse event with details that could suggest a treatment assignment), the CRO will perform additional programmatic checks on text fields pertaining to Adverse Events and physical examination findings for data points that are part of the relapse case listing.

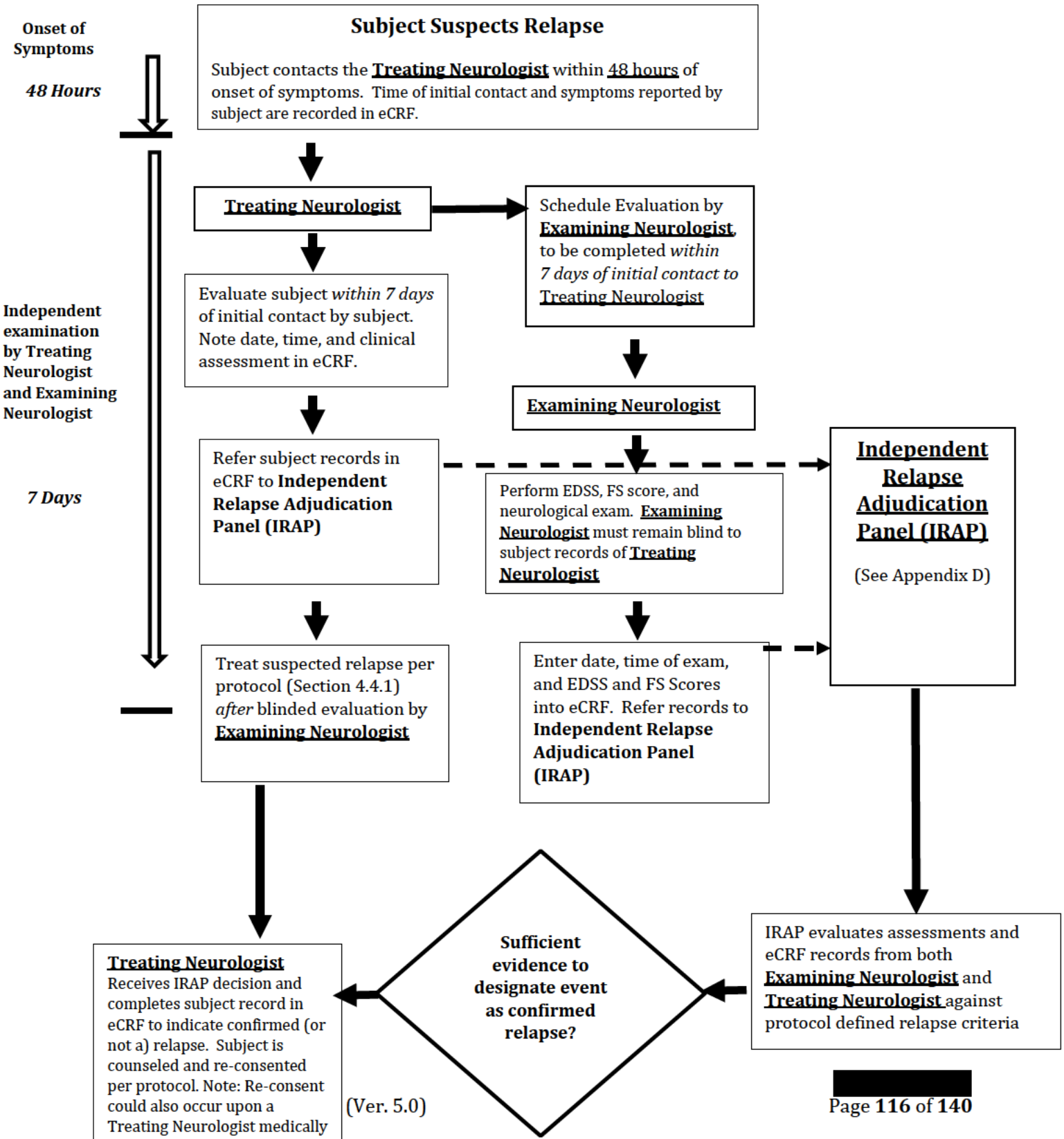
Each potential relapse is reviewed by 2 IRAP members who have worked and entered their evaluations independently, on cases randomly assigned to them by the CRO. The IRAP adjudicates

each case based on all available data provided for that case and members are not permitted to contact the site or the sponsor for additional information. If 2 IRAP reviewers reached the same decision as to whether an episode constitutes a relapse, the decision is recorded by the CRO. If the 2 reviewers provide a conflicting assessment, a third IRAP member will review the case so that a majority vote can be obtained. The majority vote of up to 3 IRAP members serves as the final determination as to whether an event meets criteria for an on-study protocol defined relapse.

Relapse determinations by the IRAP are communicated to the Treating Neurologist, who will in turn, notify the subject and update the eCRF accordingly. The IRAP has no involvement in subsequent subject management decisions. In order to maintain independence and blinding, the Examining Neurologist will not receive this report. Furthermore, neither the Treating Neurologist nor the subject may disclose the IRAP decision to the Examining Neurologist. The Treating Neurologist, upon receiving the IRAP decision, will counsel the subject per Section 4.4.1. The subject will need to give her/his consent to continue study participation.

For the Phase III study, the results of IRAP adjudications are transferred to the Sponsor only after the last subject completes the study. The Sponsor has no knowledge of IRAP adjudications while the study is ongoing.

18 APPENDIX E: EVALUATION PROCEDURE FOR SUBJECT REPORTED RELAPSES



19 APPENDIX F: PER VISIT PROCEDURE

<table>
<tr><td>Visit:</td><td>Screening (Within 28 Days of First Infusion)</td></tr>
<tr><td>Time Required:</td><td>Full day plus MRI appointment; Serum Pregnancy test must be performed within 5 days of first infusion and may therefore require a separate visit</td></tr>
<tr><td>Treatment:</td><td>None</td></tr>
<tr><td>Tests:</td><td>☐ 12 Lead ECG
☐ MRI; Scans performed within 28 days of first infusion. See MRI Manual for full details and instructions
☐ Serum Pregnancy; Must be performed within 5 days of the first infusion of ublituximab/IV placebo</td></tr>
<tr><td>Clinical Assessments:</td><td>☐ Medical History
☐ Concomitant medications
☐ Physical examination/vital signs
☐ EDSS, MSFC and neurological examination</td></tr>
<tr><td>Labs:
(see Laboratory Manual for full details, instructions, and shipping information)</td><td>☐ Hematologic profile; CBC/FBC with differential and platelet count
☐ Serum chemistry panel;
<table>
<tr><th colspan="3">Serum Chemistry</th></tr>
<tr><td>Albumin</td><td>Glucose</td><td>SGPT [ALT]</td></tr>
<tr><td>Alkaline phosphatase</td><td>LDH</td><td>Sodium</td></tr>
<tr><td>Bicarbonate</td><td>Magnesium</td><td>Total bilirubin</td></tr>
<tr><td>BUN</td><td>Phosphorus</td><td>Total Protein</td></tr>
<tr><td>Calcium</td><td>Potassium</td><td>Uric acid</td></tr>
<tr><td>Chloride</td><td>SGGT</td><td>Indirect/direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>SGOT [AST]</td><td></td></tr>
</table>
☐ Pancreatic Enzyme
☐ Absolute B cell lymphocyte count and % B cell
☐ Serum Pregnancy Test; within 5 days of first infusion
☐ Serology; HIV, HCV, HBV, Varicella
☐ Urinalysis</td></tr>
<tr><td>Documents / Forms:</td><td>☐ Informed Consent Form
☐ Signed Eligibility Screening Worksheet
☐ MRI data transfer to Central MRI Reading Center</td></tr>
<tr><td>Drug Preparation / Dispensation:</td><td>None</td></tr>
<tr><td>Timing and Sequence Considerations:</td><td>Once signed consent is obtained, procedures can be scheduled for the day at investigator and subject convenience. We recommend that labs be performed prior to MRI with Gadolinium contrast agent.</td></tr>
</table>

<table>
<tr><td>Visit:</td><td>Week 1 Day 1</td></tr>
<tr><td>Time Required:</td><td>Full day; Allow 8 hours</td></tr>
<tr><td>Treatment:</td><td>☐ Ublituximab 150 mg or placebo infusion in 250 mL volume; 4 hour infusion time
Pre-medicate 30-60 minutes prior to each dose of ublituximab or IV placebo with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20 mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to subject who experience fever or pyrexia after Week 1 dose, or as clinically warranted and additional medication (which needs to be documented) may be used at discretion of the physician if adverse reactions occur.
☐ Teriflunomide (14 mg) or oral placebo until last day of Week 95</td></tr>
<tr><td>Tests:</td><td>☐ 12 Lead ECG; pre- and post-infusion</td></tr>
<tr><td>Clinical Assessments:</td><td>☐ Adverse Event
☐ Concomitant medications
☐ Physical examination/vital signs
☐ EDSS, MSFC, MSQOL54, SDMT, FIS and neurological examination</td></tr>
<tr><td>Labs:
(see Laboratory Manual for full details, instructions, and shipping information)</td><td>☐ Hematologic profile; CBC/FBC with differential and platelet count
☐ Serum chemistry panel;<table><tr><th colspan="3">Serum Chemistry</th></tr><tr><td>Albumin</td><td>Glucose</td><td>SGPT [ALT]</td></tr><tr><td>Alkaline phosphatase</td><td>LDH</td><td>Sodium</td></tr><tr><td>Bicarbonate</td><td>Magnesium</td><td>Total bilirubin</td></tr><tr><td>BUN</td><td>Phosphorus</td><td>Total Protein</td></tr><tr><td>Calcium</td><td>Potassium</td><td>Uric acid</td></tr><tr><td>Chloride</td><td>SGGT</td><td>Indirect/direct bilirubin</td></tr><tr><td>Creatinine</td><td>SGOT [AST]</td><td></td></tr></table>☐ Pancreatic Enzyme
☐ Absolute B cell lymphocyte count and % B cell
☐ Urinalysis
☐ Fibrinogen
☐ Quantitative Immunoglobulin; Total Ig, IgG, IgM, IgA
☐ PT/INR
☐ Pharmacokinetics (for all subjects); Prior to first infusion and at 30 minutes +/- 15 minutes after end of infusion on infusion day
☐ Anti-Drug Antibodies; Drawn prior to infusion
☐ Teriflunomide Drug Concentration Test; Collected before first oral dose of teriflunomide or oral placebo</td></tr>
<tr><td>Documents / Forms:</td><td>☐ Subject Randomization
☐ eCRF documentation
☐ Infusion Log</td></tr>
</table>

	☐ AE and SAE Reporting (If applicable) ☐ Sample shipping ☐ Teriflunomide or oral placebo dispensation ☐ Dispensing of Subject Diary
Drug Preparation / Dispensation:	For ublituximab or IV placebo (**See Pharmacy Manual**) 150 mg ublituximab diluted in 0.9% Normal Saline for total volume of 250 mg For teriflunomide or oral placebo give subject 4 boxes of teriflunomide or oral placebo
Timing and Sequence Considerations:	Prior to infusion • All labs, and ADA, drawn prior to start of pre-treatment and infusion • PK • Physical examination, EDSS and clinical assessments pre-infusion • 12 lead ECG • Vital signs During infusion • Infusion log Post Infusion • At 30 minutes +/-15 minutes after end of infusion • 12 lead ECG

Visit:	**Week 1 Day 2**
Time Required:	Approximately 1 hour
Treatment:	Continue with Teriflunomide treatment until the last day of Week 95
Tests:	None
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ Vital Signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum Chemistry Panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

☐ Pancreatic Enzyme

	□ Absolute B cell lymphocyte count and % B cell □ Urinalysis
Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Subject diary review and teriflunomide/oral placebo accountability
Drug Preparation / Dispensation:	None

Visit:	**Week 2 Day 8**
Time Required:	Approximately 1 hour
Treatment:	Continue with Teriflunomide treatment until the last day of Week 95
Tests:	None
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Vital Signs

Labs: (see Laboratory Manual for full details, instructions, and shipping information)

□ Hematologic profile; *CBC/FBC with differential and platelet count*
□ Serum Chemistry Panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

□ Pancreatic Enzyme
□ Absolute B cell lymphocyte count and % B cell
□ Urinalysis

Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □Subject diary review and teriflunomide/oral placebo accountability

Drug Preparation / Dispensation:	None

Visit:	**Week 3 Day 15**
Time Required:	Full day; *Approximately 3 – 5 hours*
Treatment:	☐ Ublituximab 450 mg or placebo infusion in 250 mL volume; 1 *hour infusion time* • Pre-medicate 30-60 minutes prior to each dose of ublituximab or IV placebo with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20 mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to subject who experience fever or pyrexia after Week 1 dose, or as clinically warranted and additional medication (which needs to be documented) may be used at discretion of the physician if adverse reactions occur. ☐ Teriflunomide (14 mg) or oral placebo until last day of Week 95 **Can use Week 2 laboratory analysis to assess whether to move forward with the infusion**
Tests:	☐ 12 Lead ECG; *pre- and post-infusion* ☐ Urine Pregnancy Test; *Must have confirmed negative result prior to start of infusion*
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

☐ Pancreatic Enzyme
☐ Absolute B cell lymphocyte count and % B cell
☐ Urinalysis
☐ Fibrinogen
☐ Quantitative Immunoglobulin; *Total Ig, IgG, IgM, IgA*
☐ Pharmacokinetics (for all subjects); *Prior to infusion and at 30 minutes +/- 15 minutes after end of infusion on infusion day*
☐ Anti-Drug Antibodies; *Drawn prior to infusion*

	☐ eCRF documentation

Documents / Forms:	□ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Subject diary review and teriflunomide/oral placebo accountability
Drug Preparation / Dispensation:	For ublituximab or IV placebo (**See Pharmacy Manual**) 450 mg ublituximab diluted in 0.9% Normal Saline for total volume of 250 mg
Timing and Sequence Considerations:	Prior to infusion • Perform urine pregnancy test; *Must have confirmed negative prior to start of infusion* • All labs, and ADA, drawn prior to start of pre-treatment and infusion • PK • Physical examination, EDSS and clinical assessments pre-infusion • 12 lead ECG • Vital signs During infusion • Infusion log Post Infusion • Additional PK at 30 minutes +/- 15 minutes after end of infusion • 12 lead ECG

Visit:	**Week 4 Day 28**
Time Required:	Approximately 1 hour
Treatment:	□ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	□ Urine Pregnancy Test; *Must have confirmed negative*
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	□ Hematologic profile; *CBC/FBC with differential and platelet count* □ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin

	Creatinine	SGOT [AST]	

□ Pancreatic Enzyme
□ Absolute B cell lymphocyte count and % B cell
□ Urinalysis
□ Pharmacokinetics **(for subjects in United States, United Kingdom, Spain and Ukraine only)**

Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Subject diary review and teriflunomide/oral placebo accountability
Drug Preparation / Dispensation:	None

Visit:	**Week 8 Day 56**
Time Required:	Approximately 1 hour
Treatment:	□ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	□ Urine Pregnancy Test; *Must have confirmed negative*
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Physical examination/vital signs

Labs: (see Laboratory Manual for full details, instructions, and shipping information)

□ Hematologic profile; *CBC/FBC with differential and platelet count*
□ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

□ Pancreatic Enzyme
□ Absolute B cell lymphocyte count and % B cell
□ Urinalysis
□ Pharmacokinetics **(for subjects in United States, United Kingdom, Spain and Ukraine only)**

Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Subject diary review and teriflunomide/oral placebo accountability
Drug Preparation / Dispensation:	None

Visit:	**Week 12 Day 84**
Time Required:	Approximately 1 hour
Treatment:	□ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	□ Urine Pregnancy Test; *Must have confirmed negative* □ MRI; *See MRI Manual for full details and instructions*
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Physical examination/vital signs □ EDSS, MSFC, and neurological examination
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	□ Hematologic profile; *CBC/FBC with differential and platelet count* □ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

	□ Pancreatic Enzyme □ Absolute B cell lymphocyte count and % B cell □ Urinalysis
Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Subject diary review and teriflunomide/oral placebo accountability □ Teriflunomide or oral placebo dispensation □ Dispensing Subject Diary

Drug Preparation / Dispensation:	Dispense the next 12-week blister pack of teriflunomide or oral placebo

Visit:	**Week 16 Day 112**
Time Required:	Approximately 1 hour
Treatment:	□ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	□ Urine Pregnancy Test; *Must have confirmed negative result*
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	□ Hematologic profile; *CBC/FBC with differential and platelet count* □ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

	□ Pancreatic Enzyme □ Absolute B cell lymphocyte count and % B cell □ Urinalysis
Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Subject diary review and teriflunomide/oral placebo accountability
Drug Preparation / Dispensation:	None
Visit:	**Week 20 Day 140**

Time Required:	Approximately 1 hour
Treatment:	☐ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	☐ Urine Pregnancy Test; *Must have confirmed negative result*
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

☐ Pancreatic Enzyme
☐ Absolute B cell lymphocyte count and % B cell
☐ Urinalysis

Documents / Forms:	☐ eCRF documentation ☐ Infusion Log ☐ AE and SAE Reporting (If applicable) ☐ Sample shipping ☐ Subject diary review and teriflunomide/oral placebo accountability
Drug Preparation / Dispensation:	None

Visit:	**Week 24 Day 168**
Time Required:	Full day; *Approximately 3 – 5 hours plus time for MRI*
Treatment:	☐ Ublituximab 450 mg or IV placebo infusion in 250 mL volume; 1 *hour infusion time* • Pre-medicate 30-60 minutes prior to each dose of ublituximab or IV placebo with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20 mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to subject who experience fever or pyrexia after Week 1 dose, or as clinically warranted and additional medication (which needs to be documented) may be used at discretion of the physician if adverse reactions occur.

	☐ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	☐ 12 Lead ECG; *pre- and post-infusion* ☐ MRI; *See MRI Manual for full details and instructions (must be done before infusion)* ☐ Urine Pregnancy Test; *Must have confirmed negative result prior to start of infusion*
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ EDSS, MSFC, MSQOL54, SDMT, FIS and neurological examination ☐ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

☐ Pancreatic Enzyme
☐ Absolute B cell lymphocyte count and % B cell
☐ Urinalysis
☐ Fibrinogen
☐ Quantitative Immunoglobulin; *Total Ig, IgG, IgM, IgA*
☐ Pharmacokinetics (for all subjects); *Prior to first infusion and at 30 minutes +/- 15 minutes after end of infusion on infusion days*
☐ Anti-Drug Antibodies; *Drawn prior to infusion*

Documents / Forms:	☐ eCRF documentation ☐ Infusion Log ☐ AE and SAE Reporting (If applicable) ☐ Sample shipping ☐ Teriflunomide or oral placebo dispensation ☐ Subject diary review and teriflunomide/oral placebo accountability ☐ Dispensing Subject Diary
Drug Preparation / Dispensation:	For ublituximab or IV placebo (**See Pharmacy Manual**) 450 mg ublituximab diluted in 0.9% Normal Saline for total volume of 250 mg Dispense the next 12-week blister pack of teriflunomide or oral placebo
Timing and Sequence Considerations:	Prior to infusion • Perform urine pregnancy test; *Must have confirmed negative prior to start of infusion* • All labs, and ADA, drawn prior to start of pre-treatment and infusion • PK • Physical examination, EDSS and clinical assessments pre-infusion

- MRI
- 12 lead ECG
- Vital signs

During infusion
- Infusion log

Post Infusion
- Additional PK 30 minutes +/- 15 minutes after end of infusion
- 12 lead ECG

Visit:	**Week 36 Day 252**
Time Required:	Approximately 1 hour
Treatment:	□ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	□ Urine Pregnancy Test; *Must have confirmed negative result*
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Physical examination/vital signs □ EDSS, MSFC and neurological examination
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	□ Hematologic profile; *CBC/FBC with differential and platelet count* □ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

	□ Pancreatic Enzyme □ Absolute B cell lymphocyte count and % B cell □ Urinalysis
Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Teriflunomide or oral placebo dispensation □ Subject diary review and teriflunomide/oral placebo accountability □ Dispensing Subject Diary

Drug Preparation / Dispensation:	Dispense the next 12 week blister pack of teriflunomide or oral placebo

Visit:	**Week 48 Day 336**
Time Required:	Full day; *Approximately 3 – 5 hours plus time for MRI*
Treatment:	☐ Ublituximab 450 mg or placebo infusion in 250 mL volume; 1 *hour infusion time* • Pre-medicate 30-60 minutes prior to each dose of ublituximab or IV placebo with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20 mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to subject who experience fever or pyrexia after Week 1 dose, or as clinically warranted and additional medication (which needs to be documented) may be used at discretion of the physician if adverse reactions occur. ☐ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	☐ 12 Lead ECG; *pre- and post-infusion* ☐ MRI; *See MRI Manual for full details and instructions (must be done before infusion)* ☐ Urine Pregnancy Test; *Must have confirmed negative result prior to start of infusion*
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ EDSS, MSFC, MSQOL54, SDMT, FIS and neurological examination ☐ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

☐ Pancreatic Enzyme
☐ Absolute B cell lymphocyte count and % B cell
☐ Urinalysis
☐ Fibrinogen
☐ Quantitative Immunoglobulin; *Total Ig, IgG, IgM, IgA*
☐ Pharmacokinetics (for all subjects); P*rior to first infusion and at 30 minutes +/- 15 minutes after end of infusion on infusion day*
☐ Anti-Drug Antibodies; *Drawn prior to infusion*
☐ Teriflunomide Drug Concentration Test

Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Teriflunomide or oral placebo dispensation □ Subject diary review and teriflunomide/oral placebo accountability □ Dispensing Subject Diary
Drug Preparation / Dispensation:	For ublituximab or IV placebo (**See Pharmacy Manual**) 450 mg ublituximab diluted in 0.9% Normal Saline for total volume of 250 mg Dispense the next 12-week blister pack of teriflunomide or oral placebo
Timing and Sequence Considerations:	Prior to infusion • Perform urine pregnancy test; *Must have confirmed negative prior to start of infusion* • All labs and ADA, drawn prior to start of pre-treatment and infusion • PK • Physical examination, EDSS and clinical assessments pre-infusion • MRI • 12 lead ECG • Vital signs During infusion • Infusion log Post Infusion • Additional PK at 30 minutes +/- 15 minutes after end of infusion • 12 lead ECG

Visit:	**Week 60 Day 420**
Time Required:	Approximately 1 hour
Treatment:	□ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	□ Urine Pregnancy Test; *Must have confirmed negative result*
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Physical examination/vital signs □ EDSS, MSFC and neurological examination
Labs: (see Laboratory	□ Hematologic profile; *CBC/FBC with differential and platelet count* □ Serum chemistry panel; **Serum Chemistry**

Manual for full details, instructions, and shipping information)	Albumin	Glucose	SGPT [ALT]
	Alkaline phosphatase	LDH	Sodium
	Bicarbonate	Magnesium	Total bilirubin
	BUN	Phosphorus	Total Protein
	Calcium	Potassium	Uric acid
	Chloride	SGGT	Indirect/direct bilirubin
	Creatinine	SGOT [AST]	
	☐ Pancreatic Enzyme		
	☐ Absolute B cell lymphocyte count and % B cell		
	☐ Urinalysis		
Documents / Forms:	☐ eCRF documentation ☐ Infusion Log ☐ AE and SAE Reporting (If applicable) ☐ Sample shipping ☐ Teriflunomide or oral placebo dispensation ☐ Subject diary review and teriflunomide/oral placebo accountability ☐ Dispensing Subject Diary		
Drug Preparation / Dispensation:	Dispense the next 12-week blister pack of teriflunomide or oral placebo		

Visit:	**Week 72 Day 504**
Time Required:	Full day; *Approximately 3 – 5 hours*
Treatment:	☐ Ublituximab 450 mg or placebo infusion in 250 mL volume; 1 *hour infusion time* • Pre-medicate 30-60 minutes prior to each dose of ublituximab or IV placebo with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20 mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to subject who experience fever or pyrexia after Week 1 dose, or as clinically warranted and additional medication (which needs to be documented) may be used at discretion of the physician if adverse reactions occur. ☐ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	☐ 12 Lead ECG; *pre- and post-infusion* ☐ Urine Pregnancy Test; *Must have confirmed negative result prior to start of infusion*
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ EDSS, MSFC and neurological examination ☐ Physical examination/vital signs
Labs:	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum chemistry panel;

(see Laboratory Manual for full details, instructions, and shipping information)	**Serum Chemistry** Albumin, Glucose, SGPT [ALT] Alkaline phosphatase, LDH, Sodium Bicarbonate, Magnesium, Total bilirubin BUN, Phosphorus, Total Protein Calcium, Potassium, Uric acid Chloride, SGGT, Indirect/direct bilirubin Creatinine, SGOT [AST] ☐ Pancreatic Enzyme ☐ Absolute B cell lymphocyte count and % B cell ☐ Urinalysis ☐ Fibrinogen ☐ Quantitative Immunoglobulin; *Total Ig, IgG, IgM, IgA* ☐ Pharmacokinetics (for all subjects); *Prior to first infusion and at 30 minutes +/- 15 minutes after end of infusion* ☐ Anti-Drug Antibodies; *Drawn prior to infusion*
Documents / Forms:	☐ eCRF documentation ☐ Infusion Log ☐ AE and SAE Reporting (If applicable) ☐ Sample shipping ☐ Teriflunomide or oral placebo dispensation ☐ Subject diary review and teriflunomide/oral placebo accountability ☐ Dispensing Subject Diary
Drug Preparation / Dispensation:	For ublituximab or IV placebo (**See Pharmacy Manual**) 450 mg ublituximab diluted in 0.9% Normal Saline for total volume of 250 mg Dispense the next 12-week blister pack of teriflunomide or oral placebo
Timing and Sequence Considerations:	Prior to infusion • Perform urine pregnancy test; *Must have confirmed negative prior to start of infusion* • All labs and ADA, drawn prior to start of pre-treatment and infusion • PK • Physical examination, EDSS and clinical assessments pre-infusion • 12 lead ECG • Vital signs During infusion • Infusion log Post Infusion • Additional PK at 30 minutes +/- 15 minutes after end of infusion • 12 lead ECG

Visit: | **Week 84 Day 588**

Time Required:	Approximately 1 hour
Treatment:	□ Teriflunomide (14 mg) or oral placebo until last day of Week 95
Tests:	□ Urine Pregnancy Test; *Must have confirmed negative result*
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Physical examination/vital signs □ EDSS, MSFC and neurological examination
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	□ Hematologic profile; *CBC/FBC with differential and platelet count* □ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

	□ Pancreatic Enzyme □ Absolute B cell lymphocyte count and % B cell □ Urinalysis
Documents / Forms:	□ eCRF documentation □ Infusion Log □ AE and SAE Reporting (If applicable) □ Sample shipping □ Teriflunomide or oral placebo dispensation □ Subject diary review and teriflunomide/oral placebo accountability □ Dispensing Subject Diary
Drug Preparation / Dispensation:	Dispense the next 12-week blister pack of teriflunomide or oral placebo

Visit:	**Week 96 Day 672**
Time Required:	Full day; *Approximately 3 – 5 hours plus time for MRI*
Treatment:	None
Tests:	□ MRI; *See MRI Manual for full details and instructions*

	☐ Urine Pregnancy Test; *Must have confirmed negative result*
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ EDSS, MSFC, MSQOL54, SDMT, FIS and neurological examination ☐ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum Chemistry Panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

	☐ Pancreatic Enzyme ☐ Absolute B cell lymphocyte count and % B cell ☐ Urinalysis ☐ Quantitative Immunoglobulin; *Total Ig, IgG, IgM, IgA* ☐ Pharmacokinetics (for all subjects); P*rior to first infusion and at 30 minutes +/- 15 minutes after end of infusion* ☐ Anti-Drug Antibodies; *Drawn prior to infusion* ☐ Teriflunomide Drug Concentration Test
Documents / Forms:	☐ eCRF documentation ☐ Infusion Log ☐ AE and SAE Reporting (If applicable) ☐ Sample shipping ☐ Teriflunomide or oral placebo accountability
Visit:	**Week 100 Day 700**
Time Required:	Approximately 1 hour
Treatment:	☐ Initiate the teriflunomide rapid elimination process (11 days) via activated charcoal or cholestyramine
Tests:	☐ Urine Pregnancy Test
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ Physical examination/vital signs

Labs: (see Laboratory Manual for full details, instructions, and shipping information)	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

	☐ Pancreatic Enzyme ☐ Absolute B cell lymphocyte count and % B cell ☐ Urinalysis
Documents / Forms:	☐ eCRF documentation ☐ AE and SAE Reporting (If applicable) ☐ Sample shipping ☐ Dispensing Subject Diary for elimination drug accountability
Visit:	**Week 104 Day 728**
Time Required:	Approximately 1 hour
Treatment:	None
Tests:	☐ Urine pregnancy test; *must be negative*
Clinical Assessments:	☐ Adverse Event ☐ Concomitant medications ☐ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	☐ Hematologic profile; *CBC/FBC with differential and platelet count* ☐ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

	☐ Pancreatic Enzyme ☐ Absolute B cell lymphocyte count and % B cell ☐ Urinalysis

Documents / Forms:	□ eCRF documentation □ AE and SAE Reporting (If applicable) □ Sample shipping □ Acknowledgement of completion of teriflunomide elimination program
Drug Preparation / Dispensation:	None

Visit:	**Week 108 Day 756**
Time Required:	Approximately < 1 hour; *this will be done over the phone*
Treatment:	None
Tests:	□ Urine Pregnancy Test
Clinical Assessments:	□ Adverse Event □ Concomitant medications
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	None
Documents / Forms:	□ eCRF documentation; *completed by staff at study site* □ AE and SAE Reporting (If applicable) □ Study staff to remind all subjects of the importance of using contraception throughout the study
Drug Preparation / Dispensation:	None

Visit:	**Week 112 Day 784**
Time Required:	Approximately < 1 hour; *this will be done over the phone*

Treatment:	None
Tests:	□ Urine Pregnancy Test
Clinical Assessments:	□ Adverse Event □ Concomitant medications
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	None
Documents / Forms:	□ eCRF documentation; *completed by staff at study site* □ AE and SAE Reporting (If applicable) □ Study staff to remind all subjects of the importance of using contraception throughout the study
Drug Preparation / Dispensation:	None

Visit:	**Week 116 Day 812**
Time Required:	Approximately < 1 hour
Treatment:	None
Tests:	□ Urine Pregnancy Test
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	□ Teriflunomide Drug Concentration Test. Prior to discharge from the study, all subjects will be counseled by the treating team to have their teriflunomide plasma concentration re-measured prior to attempting to become pregnant or trying to impregnate a female partner.

Documents / Forms:	□ eCRF documentation □ AE and SAE Reporting (If applicable)
Drug Preparation / Dispensation:	None

Visit:	**Unscheduled Relapse Visit**
Time Required:	Full day; *Approximately 3 – 5 hours*
Treatment:	None
Tests:	□ Serum Pregnancy Test; *must be negative results*
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ EDSS Assessment □ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	□ Hematologic profile; *CBC/FBC with differential and platelet count* □ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

□ Pancreatic Enzyme
□ Absolute B cell lymphocyte count and % B cell
□ Urinalysis
□ Fibrinogen
□ Quantitative Immunoglobulin; *Total Ig, IgG, IgM, IgA*

Documents / Forms:	□ Informed Consent Form □ eCRF documentation □ AE and SAE Reporting (If applicable) □ Sample shipping □ Teriflunomide or oral placebo accountability
Drug Preparation / Dispensation:	None

Timing and Sequence Considerations:	Once signed consent is obtained, procedures can be scheduled for the day at Investigator and subject convenience.

Visit:	**Early Withdrawal from Treatment**
Time Required:	Full day; *Approximately 3 – 5 hours plus time for MRI*
Treatment:	□ Initiate the teriflunomide rapid elimination process (11 days) via activated charcoal or cholestyramine
Tests:	□ Serum Pregnancy Test; *must be negative results* □ MRI □ 12 lead ECG
Clinical Assessments:	□ Adverse Event □ Concomitant medications □ EDSS, MSFC, MSQOL54, SDMT, FIS and neurological examination □ Physical examination/vital signs
Labs: (see Laboratory Manual for full details, instructions, and shipping information)	□ Hematologic profile; *CBC/FBC with differential and platelet count* □ Serum chemistry panel;

Serum Chemistry		
Albumin	Glucose	SGPT [ALT]
Alkaline phosphatase	LDH	Sodium
Bicarbonate	Magnesium	Total bilirubin
BUN	Phosphorus	Total Protein
Calcium	Potassium	Uric acid
Chloride	SGGT	Indirect/direct bilirubin
Creatinine	SGOT [AST]	

	□ Pancreatic Enzyme □ Absolute B cell lymphocyte count and % B cell □ Urinalysis □ Fibrinogen □ Teriflunomide Drug Concentration Test □ Quantitative Immunoglobulin
Documents / Forms:	□ Informed Consent Form □ eCRF documentation □ AE and SAE Reporting (If applicable) □ Sample shipping □ Subject diary review and teriflunomide or oral placebo accountability
Drug Preparation / Dispensation:	None

Timing and Sequence Considerations:	Once signed consent is obtained, procedures can be scheduled for the day at Investigator and subject convenience.