Official Title:	**A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis.**
NCT Number:	NCT02738775
Document Date:	Protocol Version 8.0: 10 October 2017

Protocol version/Date: Version 8.0 / October 10, 2017

Local Protocol #: Protocol TG1101-RMS201

TITLE:

A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis.

Sponsor: TG Therapeutics, Inc.
2 Gansevoort St; 9th Floor
New York, NY 10014
Tel: (212) 554-4484

IND Numbers: 127265

Study Chair: [redacted], MD, PhD
[redacted]

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

Study Coordination: TG Therapeutics, Inc.
2 Gansevoort St; 9th Floor
New York, NY 10014
Tel: (212) 554-4484

Version: 1.0	**Date:** 17 September 2015
Version: 1.1	**Date:** 30 October 2015
Version: 2.0	**Date:** 22 January 2016 (date on approval from CIRBI)
Version: 2.1	**Date:** 14 March 2016
Version: 3.0	**Date:** 23 May 2016
Version: 4.0	**Date:** 17 June 2016
Version: 5.0	**Date:** 20 October 2016
Version: 6.0	**Date:** 13 December 2016
Version: 7.0	**Date:** 24 April 2017
Version: 8.0	Date: 10 October 2017

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this protocol and have approved Protocol TG1101-RMS201 for issuance.

Protocol Title:	A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis.
Protocol Number:	TG1101-RMS201
Trial Drug:	Ublituximab (TG-1101)
IND Numbers:	127265
Date FINAL:	10 October 2017

MEDICAL MONITOR, TG Therapeutics, Inc

[redacted] MD
Print Name

[redacted]
Signature

22 Nov 17
Date

STUDY CHAIR,

[redacted], MD, PhD
Print Name

[redacted]
Signature

21 Nov 2017
Date

SPONSOR CONTACTS, TG Therapeutics, Inc.

[redacted]
Print Name

DocuSigned by:
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11/22/2017
Date

[redacted], MS, MSF
Print Name

[redacted]
Signature

14 Nov 2017
Date

[redacted], PhD
Print Name

[redacted]
Signature

Nov. 14. 2017
Date

STATISTICIAN, Consultant to TG Therapeutics, Inc.

[redacted], Ph.D.
Print Name

[redacted]
Signature

22Nov2017
Date

PROTOCOL ACCEPTANCE FORM

Protocol Title:	A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis.
Protocol Number:	TG1101-RMS201
Trial Drug:	Ublituximab (TG-1101)
IND Numbers:	127265
Date FINAL:	10 October 2017

I have read the attached protocol and agree that it contains all the necessary details for performing TG1101-RMS201.

I will provide copies of the protocol and of the ublituximab Investigators' Brochure, which were furnished to me by TG Therapeutics (Sponsor), 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 and the conduct of the study.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining the prior approval of TG Therapeutics and of the IRB. I will submit the protocol modifications and/or any informed consent modifications to TG Therapeutics and the IRB, 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 up to and including the Washington Clarification (2002).

Print Name	Signature	Date

Version 1.1 (Dated 30 October 2015) of this Protocol is the first amendment to this clinical trial and contains the following modifications:

- 12 Lead ECG will be performed pre- and post-dose on any day of infusion
- Instead of 1.5T MRI, the study sites can use MRI machines ≥1.5 T

Version 2.0 (Dated 19 January 2016) of this Protocol is the second amendment to this clinical trial and contains the following modifications:

- Relabeled the superscript legend on page 35 to correct a mistake on the prior version for the ECG
- Further defined the unit of B cell count as a percentage of $CD19^{+}$
- In synopsis, directed the investigator to section 7.1.1 for complete listing of laboratory assessments
- Further defined PK and anti-drug- antibody (antibodies developed against ublituximab) collection instructions in trial synopsis and section 7.1.1, and added analysis time points at weeks 4, 16, and 48
- Quantitative immunoglobulin defined as IgA. IgM, IgG in section 7.1.1
- Treatment and subject enrollment scheme was amended with the addition of a placebo arm during the first 28 days. Following completion of Day 28, all placebo subjects will enter their respective "x" cohort and receive active treatment in Table 2 below. Cohort sizes were expanded to include 8 patients, of which 2 will be on placebo. Study title changed to include "Placebo-Controlled" in the title
- Added two additional PK analysis time points at weeks 4 and 25
- Added fibrinogen level testing
- Added a rescue clause in case subjects experience an MS relapse during the study
- Excluded subjects vaccinated with live virus within 2 months of randomization
- Added requirement for skilled personnel and adequate equipment at all sites to provide emergency treatment should subjects experience anaphylaxis, hypotension or respiratory distress
- Changed directions for infusion interruptions: If there is a second interruption of treatment due to IRR (infusion related reaction) symptoms, ublituximab infusion must be stopped. The treating physician may decide whether to attempt completion of the infusion on a second day
- The local radiologists will now review all MRI to 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 provide a report of the MRI to the treating physician. Further, physicians must obtain expert evaluations of brain MRI images of subjects with suspected opportunistic CNS infections including PML
- Formatting and spelling errors were corrected throughout
- Expansion of the rationale section
- Instead of 1.5T MRI, the study sites can use closed MRI machines ≥1.5 T
- Changed Per Protocol (PP) population to modified intent-to-treat population (mITT)
- Change in primary efficacy measure (% B cell depletion) to >95%
- Delete cohort 4
  Possible cohort expansion to include 25 – 900 mg ublituximab

Version 2.1 (Dated 14 March 2016) of this Protocol is the third amendment to this clinical trial and contains the following modifications:

- Change the premedication requirement to the following: Pre-medicate approximately 30 minutes prior to each dose of ublituximab with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to patient 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.

Version 3.0 (Dated 23 May 2016) of this protocol is the 4th amendment to this clinical trial and contains the following modifications:

- Modifications to EDSS assessment instructions to require the following: EDSS will be assessed based on a slightly modified neurological examination as fatigue will not contribute to the EDSS assessment
- Will exclude subjects previously treated with alemtuzumab
- Revised exclusion criteria for subjects previously treated with teriflunomide to the following:
- Patients treated with teriflunomide within 12 months prior to screening. Exceptions will be subjects who have undergone accelerated/rapid elimination with oral activated charcoal or oral cholestyramine ≥ 90 days of screening
- Deleted the section on prophylaxis for pulmonary events as this does not pertain to this study subject population or investigational drug

Version 4.0 (Dated 17 June 2016) of this protocol is the 5th amendment to this clinical trial and contains the following modifications:

- Section 8.1.1 was updated to include the most recent adverse event information related to sponsor study drugs

Version 5.0 (Dated 20 October 2016) of this protocol is the 6th amendment to this clinical trial and contains the following modifications:

- Added another cohort (cohort 4) to the study
- In the evaluation table: Weeks 8 and beyond, collections/assessments may occur ±2 days from specified time points

Version 6.0 (Dated 13 December 2016) of this protocol is the 7th amendment to this clinical trial and contains the following modifications:

- Revised original cohort 4 to smaller number of subjects and after initial infusion time
- Added 2 other cohorts (cohorts 5 and 6) to the study

Version 7.0 (Dated 24 April 2017) of this protocol is the 8th amendment to this clinical trial and contains the following modification:

- Addition of relapse assessment into the study evaluation table in section 7. This was erroneously left out.
- Added the option for subjects completing the 48 week study, and fulfilling entry criteria, to enter into an open label extension study (this will be submitted as separate protocol: TG1101-RMS201E). This is mentioned in Synopsis: Study Duration, Section 4 (Duration of Therapy), Section 7 (Study Evaluation Table), and Section 7.1 (Overview).

Version 8.0 (Dated 10 October 2017) of this protocol is the 9th amendment to this clinical trial and contains the following modification:

- Include information regarding a new vial size and concentration for ublituximab
- Minor typographical errors

Study Title	**A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis.**
Study Rationale	Over the past decade, the understanding of the role of B and 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 has been shown to regulate the formation and function of T cells, which can aid in the demyelinating events seen with multiple sclerosis.[13] 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 or ofatumumab, both currently approved anti-CD20 antibodies in oncologic diseases and rheumatoid arthritis (rituximab only). 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 cells targeted immunotherapy. Rituximab was the first anti-CD20 monoclonal antibody (mAb) tested in relapsing forms of Multiple Sclerosis (RMS) patients. More recently, ocrelizumab, a humanized anti-CD20 monoclonal antibody has shown promising results in its 2 Phase III trials (OPERA I and OPERA II). In OPERA I and II, patients treated with ocrelizumab had significantly lower annualized relapse rates (0.156 and 0.155, respectively) compared to patients treated with IFNβ-1a 44µg (0.292 and 0.29, respectively). Further, in OPERA I and II, patients treated with ocrelizumab had 40% reduction in clinical disease progression compared to those treated with IFNβ-1a 44µg. [14] To date, a B-cell targeted therapy has not been approved for the treatment of RMS. Although an ublituximab phase I has been completed in chronic lymphocytic leukemia (CLL) and in non-Hodgkin's lymphoma (NHL) patients with no MTD reached up through 1200 mg, a dose ranging study has not been initiated in the MS population. It is important determine the optimal dose of ublituximab use to treat MS patients as well as understand the safety and tolerability profile of ublituximab in this population. Thus, the primary purpose of this study is to identify the recommended Phase 3 dose and infusion time as well as explore the safety of ublituximab in patients with relapsing forms of MS.
Products	Ublituximab is a recombinant chimeric monoclonal antibody against the CD20 antigen, available as a 10 mg/mL or 25mg/mL concentrate for solution for infusion, supplied by TG Therapeutics, Inc.

Phase	Phase IIa
Study Sponsor	TG Therapeutics, Inc. (New York, NY, USA)
Study Chair	**RMS Group Study Chair** [redacted], MD, PhD [redacted]
Study Objectives	**Primary Objectives** • To determine the level of B cell depletion by ublituximab in subjects with RMS • To determine the optimal dose and infusion time for ublituximab in subjects with RMS **Secondary Objective** • To examine the effect of ublituximab on the development of new Gadolinium-(Gd) enhancing lesions and new or enlarging T2 lesions at 24 and 48 weeks • To evaluate the % of relapses in ublituximab-treated RMS subjects • To determine immunogenicity • To evaluate the safety of ublituximab, as determined by adverse events (AEs) and serious adverse events (SAEs), including MS worsening
Efficacy Endpoints	**Efficacy Endpoints** • Responders Rate defined as percent of subjects with ≥95% reduction of B cells (CD19+ cells) within 2 weeks after the second infusion (day 15) **Secondary efficacy endpoints** • Number of new Gd-enhancing lesions at 24 and 48 weeks • Number of new or enlarging T2 lesions at 24 and 48 weeks • Annualized relapse rate (ARR) • Relapse rate reduction (RRR) • Percent of relapse free subjects • Reduction in B cells (CD19+), memory (CD19+CD27+) and naïve (CD19+CD27-) B cells at baseline, day 1 (pre dose), 2, week 2, Day 15 (pre-dose), week 4 and every 4 weeks thereafter until the next infusion at weeks 24 (pre-dose and 2 days post dose) 25, 28, 36, 40, 44 and 48. • Additional immune profiling (CD4+, CD8+, IL10 and NK cells) at baseline, day 1 (pre dose), 2, week 3, 15 (pre-dose), week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 dose post-dose) 25, 28, 36, 40, 44 and 48. • PK (ADME) profile of ublituximab at day 1 and 15 and weeks 4, 24 and 25
Safety Endpoints	All AEs will be reported and evaluated during the treatment period using National Cancer Institute (NCI) version 4.0 grading system; the number and severity of infusion-associated events, defined as AEs reported during or within 24 hours 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 52-week trial.
Study Design	This is a 52-week, phase IIa, placebo-controlled, multi-center study that is primarily designed to assess the optimal dosing, optimal infusion time as well as safety/tolerability of ublituximab (TG1101; UTX) in patients with RMS.

Subjects may be screened up to 4 weeks before first dosing date. Qualified subjects will receive ublituximab on Days 1, 15, and week 24. There will be at least four treatment cohorts in the study with 8 subjects (2 placebo and 6 ublituximab treatment; please see treatment schema) enrolled in each cohort. Subjects within each cohort will receive either placebo or study drug dosing on Days 1 and 15 and week 24 per dosing schema (please see table below). Additional dose ranging cohorts may be explored and expansion cohorts at selected doses are contemplated.

A Data and Safety Monitoring Board (DSMB) will be established to safe guard the wellbeing of the subjects and to advise the Sponsor whether it is appropriate to expand the enrollment to a dosing cohort or to initiate next dosing cohort. The DSMB may recommend to the Sponsor to terminate the enrollment to a treatment cohort for safety concerns or otherwise. For example, the DSMB may recommend early termination of enrollment to a dosing cohort that is higher than the optimal treatment cohort after the optimal dosing is determined or a cohort that is considered without meaningful clinical benefit.

Once a subject is qualified, the Site will contact the Sponsor or its designee for cohort assignment (treatment assignment). The Sponsor or its designee will issue the cohort assignment for the subject using the following procedures. If DSMB deems that a cohort is not appropriate (e.g., due to safety), enrollment to that cohort and all higher cohorts will be terminated and all future subjects will be enrolled to the lowest incomplete cohort. Upon completion of first two patients in each cohort (one on placebo and one on study drug) through 21 days, the DSMB will review safety data and assuming no safety concern is raised, the remaining qualified subjects will be enrolled into such cohort.

MS Relapses during the study:

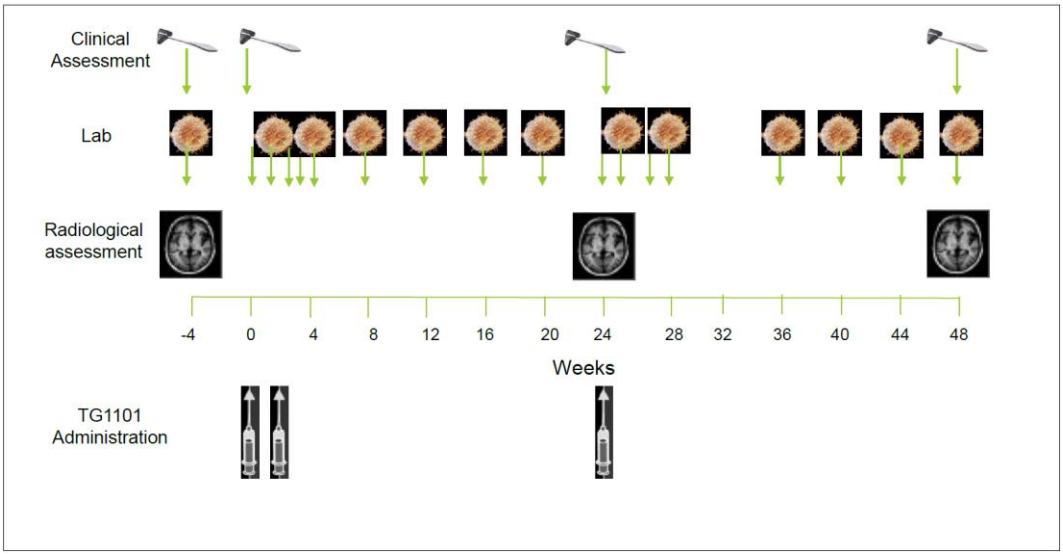
Any patient experiencing a multiple sclerosis relapse while on study will be allowed rescue therapy with intravenous methylprednisolone 1gm/day for up to 5 consecutive days. Subjects requiring rescue therapy will have an MRI scan 10 days after completion of treatment with steroids.

Re-consent criteria

In case of a confirmed diagnosis of MS relapse (as defined in the protocol, Appendix C), **or** in case of an increase in EDSS of 1.0 points or more, sustained for at least 3 months, during the study, the following actions will be taken:

1. 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.
2. The subject will be requested to re-sign an informed consent form if he/she chooses to continue to participate in the study, in the same treatment assignment.

Subjects enrolled into the study will be closely monitored through the study course by the Sponsor's personnel as well as by an external independent data monitoring committee (DSMB) in order to ensure subjects' welfare.

Treatment Study Visits	**<u>Ublituximab (or Placebo) Regimen</u>**  • Ublituximab (IV): Infusions on Days 1 and 15 and week 24 • Placebo (IV): Infusions on Days 1 and 15 **<u>Laboratory Assessment Schedule:</u>** • For subjects initially treated with UTX: ○ Blood collection for CBC and serum chemistry at baseline, and day 1 (pre-dose), 2, 8, 15 (pre-dose), and weeks 4, 8, 12, 16, 20, 24 (pre-dose and 2 days post-dose), 25, 28, 36, 40, 44 and 48 ○ Blood collection for immune profiling at screening, baseline, and day 1 (pre-dose), 2, 8, 15 (pre-dose), and week 4, 8, 12, 16, 20, 24 (pre-dose and 2 days post dose), 25, 28, 36, 40, 44 and 48 • For subjects initially treated with placebo followed by UTX treatment ○ Blood collection for CBC and serum chemistry at baseline, and day 1 (pre-dose), 2, 8, 15 (pre-dose), and week 4. Once the subject starts UTX treatment, blood collection for CBC and serum chemistry on day 1 (pre-dose), 2, 8, 15 (pre-dose), and week 4, 8, 12, 16, 20, 24 (pre-dose and 2 days post-dose), 25, 28, 36, 40, 44 and 48 ○ Blood collection for immune profiling at screening, baseline, and day 1 (pre-dose), 2, 8, 15 (pre-dose), and week 4. Once the subject starts UTX treatment, blood collection for immune profiling will occur on day 1 (pre-dose), 2, 8, 15 (pre-dose), and week 4, 8, 12, 16, 20, 24 (pre-dose and 2 days post-dose), 25, 28, 36, 40, 44 and 48 **<u>MRI Schedule:</u>** Screening, weeks 24 (pre-dose) and 48 **<u>Clinical Assessment Schedule:</u>** Screening, baseline, weeks 24 (pre dose), and 48
Baseline Lab Evaluation (Local 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 7.1.1 for complete listing of laboratory assessments

Pharmacokinetic (PK)	• For subjects treated with UTX, serum samples will be drawn at the Baseline (Day 1) visit prior to the first infusion of UTX and 30 minutes after the completion of the infusion; week 2; Day 15 (prior to the infusion of UTX and 30 minutes after the completion of the infusion); week 4; week 24 (prior to the infusion of UTX and 30 minutes after the completion of the infusion) and week 25. • For subjects initially treated with placebo, serum samples will be drawn at Baseline (Day 1) visit prior to the first infusion of placebo and 30 minutes after the completion of the infusion; week 2; Day 15 (prior to the infusion of UTX and 30 minutes after the completion of the infusion); week 4. Upon week 4, placebo subjects will start ublituximab treatment and will thus follow the PK analysis timeline as UTX subjects starting from Day 1 of UTX treatment
Instrumental Tests	• MRI (≥1.5T; closed MRI only)

Dosing Regimen

Table 1: Ublituximab/Placebo (Dose Range)

Randomization		Treatment Period		
Cohort	**Subjects and treatment**	**Day 1/ infusion time**	**Day 15/ infusion time**	**Week 24/ infusion time**
1	Placebo (n=2)[b]	Placebo / 4h	Placebo / 3h	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	Placebo (n=2)[b]	Placebo / 4h	Placebo / 1.5h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	Placebo (n=2)[b]	Placebo / 4h	Placebo / 1h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h
4	Placebo (n=2)[b]	Placebo / 3h	Placebo / 1h	-
	UTX (n=6)	150 mg / 3h	600 mg / 1h	600 mg / 1h
5	Placebo (n=2)[b]	Placebo / 2h	Placebo / 1h	-
	UTX (n=6)	150 mg / 2h	600 mg / 1h	600 mg / 1h
6	Placebo (n=2)[b]	Placebo / 1h	Placebo / 1h	-
	UTX (n=6)	150 mg / 1h	600 mg / 1h	600 mg / 1h
Cohort expansion[a]	*Up to 100*	*To be explored at selected doses pending on the results of the above doses*		

[a] Additional cohorts may be evaluated at doses ranging from 25 mg up to 900 mg to further elucidate the level of B-cell depletion and recovery parameters in subjects with RMS

[b] Following completion of Day 28, all placebo subjects will enter their respective "a" cohort and receive active treatment as described in Table 2 below. Further, the study evaluation table (section 7) will be restarted for these patients upon the initiation of active treatment with ublituximab

Table 2: Treatment Schema for Placebo Subjects after Day 28

Cohort	Subjects	Day 1/ infusion time	Day 15/ infusion time	Week 24/ infusion time
1a	Pbo patients from Cohort 1	150 mg UTX / 4h	450 mg UTX / 3h	450 mg UTX / 1.5h
2a	Pbo patients from Cohort 2	150 mg UTX / 4h	450 mg UTX / 1.5h	450 mg UTX / 1h
3a	Pbo patients from Cohort 3	150 mg UTX / 4h	450 mg UTX / 1h	600 mg UTX / 1h
4a	Pbo patients from Cohort 4	150 mg UTX / 3h	600 mg UTX / 1h	600 mg UTX / 1h
5a	Pbo patients from Cohort 5	150 mg UTX / 2h	600 mg UTX / 1h	600 mg UTX / 1h
6a	Pbo patients from Cohort 6	150 mg UTX / 1h	600 mg UTX / 1h	600 mg UTX / 1h

Inclusion Criteria	Patients must meet all of 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. Active disease 5. EDSS 0-5.5 (inclusive) 6. B cell counts ≥5% of total lymphocytes 7. Neurologic stability ≥ 30 days prior to screening and baseline 8. 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 acceptable method of contraception throughout the study period and for 30 days after the last dose of either study drug. 9. Willingness and ability to comply with trial and follow-up procedures, give written consent
Exclusion Criteria	Patients 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 within last 12 months 2. Treated with alemtuzumab 3. Patients treated with teriflunomide within 12 months prior to screening. a. Exceptions to above are patients who have undergone accelerated/rapid elimination with oral activated charcoal or oral cholestyramine ≥ 90 days of screening 4. Prior DMT exposure within days of screening a. 90 days with fingolimod and natalizumab b. 30 days with glatiramer acetate, interferons, dimethyl fumarate, or glucocorticoids 5. Pregnant or nursing 6. ≥ 10 years disease duration with subjects EDSS ≤ 2.0 7. Contraindication for MRI and gadolinium 8. Known presence of other neurologic disorders that may mimic MS 9. Current evidence or known history of clinically significant infection including: a. Chronic or ongoing active 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 HIV 10. History of clinically significant CNS trauma (e.g. traumatic brain injury, cerebral contusion, spinal cord compression) 11. Past or current history of medically significant adverse effects (including allergic reactions) from: a. Corticosteroids

	b. Diphenhydramine c. Murine or mouse/human chimeric antibodies 12. Absolute neutrophil count *or* platelet count outside of normal range (as per reference laboratory) 13. Absolute lymphocyte counts less than 1000/microliter 14. 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 >470 msec c. Angina not well-controlled by medication d. 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 15. 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 16. Current participation in any other interventional clinical trial. Participation in non-interventional trial requires approval of the protocol by investigator 17. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol 18. Lack immunity to varicella as determined by screening. Patient may receive vaccine and be rescreened 19. Vaccination with live virus within 2 months of randomization
Populations	**Intention-To-Treat (ITT)** – all registered subjects who received at least one dose of ublituximab **Modified Intent to Treat (mITT)** – all subjects who received UTX and have one baseline and post-baseline MRI
Statistical Considerations	The primary efficacy analyses will be based on intent-to-treatment (ITT) population that will include all subjects who receive any study drugs and provide some post baseline efficacy values. Additional efficacy analyses based on modified intent-to-treat (mITT) population may also be performed. mITT are all subjects who received UTX and have one baseline and post-baseline MRI. All safety analyses will be based on the safety population that will include all subjects who received any study drugs. [redacted] All efficacy variables will be summarized. The primary efficacy variable, responders rate, will be analyzed for dose response (trend analysis). In this analysis, responders are subjects who have at least 95% reduction in B cells (CD19+ cells) within 2 weeks of second dose (day 15) of study drug.

	Safety profiles will be evaluated based on adverse events and laboratory outcomes. More details of efficacy and safety analyses can be found in Statistical Considerations sections of the protocol.
Estimated Study Duration	Approximately 52 weeks. Upon study completion, subjects may have the option of entering a 112 week open label extension study, with a continuation of treatment, relapse and safety monitoring.

Phase IIa

Ublituximab / Placebo

Table 3: Ublituximab/Placebo (Dose Range)

Randomization		Treatment Period		
Cohort	**Subjects and treatment**	**Day 1/ infusion time**	**Day 15/ infusion time**	**Week 24/ infusion time**
1	Placebo (n=2)[b]	Placebo / 4h	Placebo / 3h	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	Placebo (n=2)[b]	Placebo / 4h	Placebo / 1.5h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	Placebo (n=2)[b]	Placebo / 4h	Placebo / 1h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h
4	Placebo (n=2)[b]	Placebo / 3h	Placebo / 1h	-
	UTX (n= 6)	150 mg / 3h	600 mg / 1h	600 mg / 1h
5	Placebo (n=2)[b]	Placebo / 2h	Placebo / 1h	-
	UTX (n= 6)	150 mg / 2h	600 mg / 1h	600 mg / 1h
6	Placebo (n=2)[b]	Placebo / 1h	Placebo / 1h	-
	UTX (n= 6)	150 mg / 1h	600 mg / 1h	600 mg / 1h
Cohort expansion[a]	*Up to 100*	*To be explored at selected doses pending on the results of the above doses*		

[a] Additional cohorts may be evaluated at doses ranging from 25 mg up to 900 mg to further elucidate the level of B-cell depletion and recovery parameters in subjects with RMS

[b] Following completion of Day 28, all placebo subjects will enter their respective "a" cohort and receive active treatment as described in Table 4 below. Further, the study evaluation table (section 7) will be restarted for these patients upon the initiation of active treatment with ublituximab

Table 4: Treatment Schema for Placebo Subjects after Day 28

Cohort	Subjects	Day 1/ infusion time	Day 15/ infusion time	Week 24/ infusion time
1a	Pbo patients from Cohort 1	150 mg UTX / 4h	450 mg UTX / 3h	450 mg UTX / 1.5h
2a	Pbo patients from Cohort 2	150 mg UTX / 4h	450 mg UTX / 1.5h	450 mg UTX / 1h
3a	Pbo patients from Cohort 3	150 mg UTX / 4h	450 mg UTX / 1h	600 mg UTX / 1h
4a	Pbo patients from Cohort 4	150 mg UTX/ 3h	600 mg UTX/ 1h	600 mg UTX/ 1h
5a	Pbo patients from Cohort 5	150 mg UTX/ 2h	600 mg UTX/ 1h	600 mg UTX/ 1h
6a	Pbo patients from Cohort 6	150 mg UTX / 1h	600 mg UTX / 1h	600 mg UTX / 1h

LIST OF ABBREVIATIONS

Abbreviations and Definition of Terms	
Ab	Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
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
Cl	Clearance
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)
FL	Follicular Lymphoma
FU	Follow-up
GCP	Good Clinical Practice
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

Abbreviations and Definition of Terms	
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL	Interleukin
IRR	Infusion Related Reactions
ITT	Intent to Treat
IV	Intravenous
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
NCI	National Cancer Institute
NCI-WG	National Cancer Institute – Working Group
NK	Natural Killer
NHL	Non-Hodgkin's Lymphoma
OS	Overall survival
PCR	Polymerase Chain Reaction
PFS	Progression-Free Survival
PD	Pharmacodynamic or Progressive Disease
PHI	Patient Health Information
PI	Primary 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
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
SOC	System Organ Class
t1/2	Half-Life of Elimination
TB	Tuberculosis
TEAEs	Treatment Emergent Adverse Events
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal
V	Visit
Vd	Volume of distribution
WHO	World Health Organization

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1 INTRODUCTION

1.1 BACKGROUND

Multiple Sclerosis (MS) is a chronic demyelinating 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 higher incidences in females versus males. According to the Multiple Sclerosis Foundation, it estimates that >400,000 people in the United States and approximately 2.5 million people worldwide have been diagnosed with the disease.[1] Previously, MS has been classified into four clinical subtypes: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive relapsing MS (PRMS).[2] Most recently, 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), RRMS (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 patients 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 6 injectables, 3 orals and 3 infusions. The main target in the majority of these therapies has been on the T cells. Despite improvements in the available therapies in reducing relapses by up to 65% [4] and slowing the progression of the disease, patients continue to experience disease relapses and progression. Recent immunopathologic and clinical studies have demonstrated that B cells also play a significant role in the pathogenesis of the disease. 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 patient 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 in vitro ADCC against CLL cells, and a higher FcγRIIIA mediated interleukin (IL)-2 production by FcγRIIIA+ Jurkat cells (5). Ublituximab demonstrated high ADCC against both patient-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 100mg/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. These 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 patient 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 5.

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

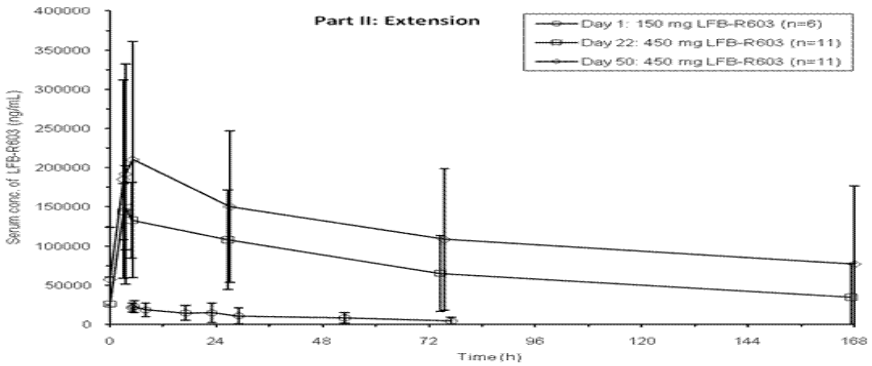


Table 5: Pharmacokinetic results after the 1st (150 mg), the 4th (450 mg) and the 8th (450 mg) infusion of ublituximab

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 patient 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 patients. The rituximab Phase I trial, a 72 week open-label study consisting of 26 enrolled RRMS patients, demonstrated that B-cell depletion was approximately 99.8% depleted by week 2 and sustained through week 48 when patients were treated with rituximab (500mg day 1; 500mg 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 weeks 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 patient was ocrelizumab. In its phase II study, similar to rituximab, there were significant reductions in both radiological and clinical activities.[11] In patients treated with ocrelizumab (600mg), there was an 89% reduction in total number of Gd-enhancing lesions for weeks 12, 16, 20 and 24 when compared to placebo. Clinically, ocrelizumab treated patients 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). In OPERA I and II, patients treated with ocrelizumab had significantly lower annualized relapse rates (0.156 and 0.155, respectively) compared to patients treated with IFNβ − 1a 44µg (0.292 and 0.29, respectively). Further, in OPERA I and II, patients treated with ocrelizumab had 40% reduction in clinical disease progression compared to those treated with IFNβ-1a 44µg. [14]

1.3.2 RATIONALE FOR THE TRIAL

Although an ublituximab phase I has been completed in chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL) patients with no MTD reached at doses explored up through 1200 mg, a dose ranging study has not been initiated in the MS population. It is important determine the optimal dose of ublituximab use to treat MS patients as well as understand the safety and tolerability profile of ublituximab in this population. Thus, the purpose of this phase IIa study is to explore the safety/tolerability and dose of ublituximab in subjects with relapsing forms of MS.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To determine the level of B cell depletion by ublituximab in subjects with RMS
- To determine the optimal dose and infusion time for ublituximab in subjects with RMS

2.2 SECONDARY OBJECTIVE

- To examine the effect of ublituximab on the development of new Gadolinium- (Gd) enhancing lesions and new or enlarging T2 lesions at 24 and 48 weeks
- To evaluate the % of relapses in ublituximab-treated RMS subjects
- To determine immunogenicity
- To evaluate the safety of ublituximab, as determined by adverse events (AEs) and serious adverse events (SAEs), including MS worsening

3 TRIAL POPULATION

3.1 INCLUSION CRITERIA

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. Active disease
5. EDSS 0-5.5 (inclusive)
6. B cell counts ≥5% of total lymphocytes
7. Neurologic stability ≥ 30 days prior to screening and baseline
8. 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 acceptable method of contraception throughout the study period and for 30 days after the last dose of either study drug.
9. Willingness and ability to comply with trial and follow-up procedures, give written consent

3.2 EXCLUSION CRITERIA

1. Treatment with Anti-CD20 or other B cell directed treatment within last 12 months
2. Treated with alemtuzumab
3. Subjects treated with teriflunomide within 12 months.
    a. Exceptions to above are patients who have undergone accelerated/rapid elimination with oral activated charcoal or oral cholestyramine ≥ 90 days of screening
4. Prior DMT exposure within days of screening
    a. 90 days with fingolimod and natalizumab
    b. 30 days with glatiramer acetate, interferons, dimethyl fumarate, or glucocorticoids
5. Pregnant or nursing
6. ≥ 10 years disease duration with subjects EDSS ≤ 2.0
7. Contraindication for MRI and gadolinium
8. Known presence of other neurologic disorders that may mimic MS
9. Current evidence or known history of clinically significant infection including:
    a. Chronic or ongoing active 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 HIV
    d. Prior history, suspicion, or documented positive TB test
10. History of clinically significant CNS trauma (e.g. traumatic brain injury, cerebral contusion, spinal cord compression)
11. Past or current history of medically significant adverse effects (including allergic reactions) from:
    a. Corticosteroids
    b. Diphenhydramine
    c. Murine or mouse/human chimeric antibodies
12. Absolute neutrophil count *or* platelet count outside of normal range (as per reference laboratory)

13. Absolute lymphocyte counts less than 1000/microliter
14. 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 >470 msec
    c. Angina not well-controlled by medication
    d. 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
15. 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
16. Current participation in any other interventional clinical trial. Participation in non-interventional trial requires approval of the protocol by investigator
17. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol
18. Lack immunity to varicella as determined by screening. Patient may receive vaccine and be rescreened
19. Vaccination with live virus within 2 months of randomization

3.3 DISCONTINUATION FROM TRIAL TREATMENT

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

- Disease progression, defined as 6 month confirmed disability progression (≥ 1 point increase in the EDSS score)
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Patient requests to withdraw consent or discontinue treatment
- Pregnancy (see Section 3.3.1)
- Inability of the patient to comply with trial requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Inter-current illness (this will be at the investigator's discretion)
- Non-compliance/lost to follow-up
- Discontinuation of the study by the Sponsor

If a patient withdraws from treatment during the first 4 weeks due to any reason other than DLT, that patient will be replaced.

After withdrawal from protocol treatment, subjects must be followed for AEs for 30 calendar days after their last dose of the trial drug. 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. In this case the investigators 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 CTCAE grade 3 or 4 laboratory abnormalities at the time of withdrawal must be followed until the laboratory values have returned to grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the subjects' medical records and as a comment on the eCRF.

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 treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

If an investigator suspects that a patient may be pregnant prior to administration of trial drug(s), the trial drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any trial drug(s), and must be discontinued from the trial.

If an investigator suspects that a patient may be pregnant after the patient has been receiving trial drug(s), the trial drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the trial drug(s) must be immediately and permanently stopped, the patient must be discontinued from the trial, and the investigator must notify the Study Chair or Medical Monitor as soon as possible. If a patient becomes pregnant while enrolled in the trial, an SAE form should be completed and faxed to the Sponsor expeditiously. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 10.11.6.

4 REGISTRATION/TREATMENT ASSIGNMENT PROCEDURES

4.1 REGISTRATION PROCESS

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. IRB approval of this protocol and consent form is required. Eligible subjects who wish to participate in the study will be enrolled into the trial.

To register a patient, the following documents should be completed by the research coordinator or data manager at the clinical trial site and faxed or emailed to the Sponsor (**See Study Manual for Registration Information**):

- Signed Eligibility Screening Worksheet
- Registration Form

The Sponsor will then verify eligibility. To complete the registration process, the Sponsor will:

- Assign a patient study number
- Assign a cohort and dose level for the patient
- Register the patient on the study
- Fax or e-mail the completed patient registration form to the participating site
- Call or email the research coordinator or data manager at the participating site and confirm registration.

4.2 TREATMENT ASSIGNMENT PROCESS

A DSMB will be established to safe guard the well-being of the subjects and to advise the Sponsor whether it is appropriate to expand the enrollment to a dosing cohort or to initiate next dosing cohort. The DSMB may also recommend to the Sponsor to terminate the enrollment to a treatment cohort. For example, the DSMB may recommend early termination of enrollment to a dosing cohort that is higher than the optimal treatment cohort after the optimal dosing is determined or a cohort that is considered without meaningful clinical benefit.

Once a subject is qualified, the Site will contact the Sponsor or its designee for cohort assignment (treatment assignment). The Sponsor or its designee will issue the cohort assignment for the subject using the following procedures. If DSMB deems that a cohort is not appropriate (e.g., due to safety), enrollment to that cohort and all higher cohorts will be terminated and all future subjects will be enrolled to the lowest incomplete cohort. Assuming that no safety concern is raised after the DSMB has completed its review based on the safety data from the first two subjects (one placebo and one UTX treatment) in a cohort, the next qualified subject will be enrolled, if applicable. If, however, the new subject is qualified before the DSMB has the opportunity to review the safety data, the new subject will be enrolled to the lowest incomplete cohort. For example, the first two subjects of the study will be enrolled to Cohort 1. If the fourth subject is qualified before the DSMB has the chance to review the safety data from the first two subjects, the subject will be enrolled to Cohort 1.

5 TREATMENT PLAN

5.1 DOSING SCHEMA

Table 6: Ublituximab/Placebo (Dose Range)

Randomization		Treatment Period		
Cohort	**Subjects and treatment**	**Day 1/ infusion time**	**Day 15/ infusion time**	**Week 24/ infusion time**
1	Placebo (n=2)[b]	Placebo / 4h	Placebo / 3h	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	Placebo (n=2)[b]	Placebo / 4h	Placebo / 1.5h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	Placebo (n=2)[b]	Placebo / 4h	Placebo / 1h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg /1h
4	Placebo (n=2)[b]	Placebo / 3h	Placebo / 1h	-
	UTX (n=6)	150 mg / 3h	600 mg / 1h	600 mg /1h
5	Placebo (n=2)[b]	Placebo / 2h	Placebo / 1h	-
	UTX (n=6)	150 mg / 2h	600 mg / 1h	600 mg /1h
6	Placebo (n=2)[b]	Placebo / 1h	Placebo / 1h	-
	UTX (n=6)	150 mg / 1h	600 mg / 1h	600 mg /1h
Cohort expansion[a]	*Up to 100*	*To be explored at selected doses pending on the results of the above doses*		

[a] Additional cohorts may be evaluated at doses ranging from 25 mg up to 900 mg to further elucidate the level of B-cell depletion and recovery parameters in subjects with RMS

[b] Following completion of Day 28, all placebo subjects will enter their respective "a" cohort and receive active treatment as described in Table 7 below. Further, the study evaluation table (section 7) will be restarted for these patients upon the initiation of active treatment with ublituximab

Table 7: Treatment Schema for Placebo Subjects after Day 28

Cohort	Subjects	Day 1/ infusion time	Day 15/ infusion time	Week 24/ infusion time
1a	Pbo patients from Cohort 1	150 mg UTX / 4h	450 mg UTX / 3h	450 mg UTX / 1.5h
2a	Pbo patients from Cohort 2	150 mg UTX / 4h	450 mg UTX / 1.5h	450 mg UTX / 1h
3a	Pbo patients from Cohort 3	150 mg UTX / 4h	450 mg UTX / 1h	600 mg UTX / 1h
4a	Pbo patients from Cohort 4	150 mg UTX / 3h	600 mg UTX / 1h	600 mg UTX / 1h
5a	Pbo patients from Cohort 5	150 mg UTX / 2h	600 mg UTX / 1h	600 mg UTX / 1h
6a	Pbo patients from Cohort 6	150 mg UTX / 1h	600 mg UTX / 1h	600 mg UTX / 1h

5.1.1 DOSE-LIMITING TOXICITY

Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE).

Toxicity will be considered dose-limiting if it occurs during the first 4 weeks of treatment and is considered at least possibly related to ublituximab. Any event defined below, unless the investigator considers the event clearly unrelated to study drug or due to extraneous causes, will be considered a dose-limiting toxicity.

Dose-limiting toxicities will be defined as the following:

- Grade 4 anemia; Grade 4 neutropenia or thrombocytopenia lasting >7 days; Grade ≥3 febrile neutropenia; and Grade ≥3 thrombocytopenia with Grade >2 hemorrhage;
- Grade ≥ 3 non-hematologic toxicity unresponsive to standard supportive care measure with the exception of:
    - Grade ≥3 ALT/AST elevation that resolves to ≤ Grade 2 within 7 days;
    - Infusion related reactions (IRR's) Grade ≥ 3 related to ublituximab occurring at the 1st infusion, which does not affect continuation to subsequent infusions
- Treatment delay of ≥14 days due to unresolved toxicity; and
- Non-hematologic toxicity of Grade 2 (at any time during treatment) that, in the judgment of the Investigators, Study Chair, and the Medical Monitor, is dose-limiting.

Adverse events meeting the above definitions but are clearly unrelated to study drug will not be considered DLTs. In rare instances an event may fall within the definition of a DLT as defined above but the event may not be considered a DLT (i.e., not clinically meaningful/significant). If this occurs, a meeting with the Investigator(s), the Medical Monitor, and the Study Chairs, will take place to thoroughly review the event and supporting data, and the reasons for not considering the event a DLT will be clearly documented with supporting rationale. In addition, other events may occur which do not meet the definition of a DLT but are concerning to the Investigator(s), Medical Monitor, and Study Chairs, and may be then considered to be DLTs.

5.1.2 DETERMINATION OF DOSE-LIMITING TOXICITY

The patient population used for determination of DLT will consist of subjects who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT. Minimum safety requirements will be met if, during the first 4 weeks of treatment of the study, the patient completes all required safety evaluations, and is observed for at least 4 weeks following the first dose of ublituximab. Subjects who experience a DLT will be considered evaluable regardless of the number of doses received.

Subjects who discontinue treatment early due to disease progression or withdrawal will be asked to have all end-of-treatment safety evaluations performed as described in the protocol. If a patient withdraws from treatment during the first 4 weeks due to any reason other than a DLT, that patient may be replaced.

5.1.3 STOPPING RULES

The DSMB (Study Chairs, Medical Monitor and Sponsor Representative) will be in charge of reviewing safety data after the first 4 weeks of therapy for the last patient in each cohort, and will decide whether or not it is possible to proceed to the next cohort according to the dosing schema described in Section 5.1 These events will be reviewed by the DSMB and potentially other study Investigators at the end of each cohort and routinely thereafter during the course of the study. All other serious and non-serious adverse events will be documented, managed including possible reductions in dose according to investigator discretion, followed until resolution or stabilization, and will also be reviewed by the DSMB at the end of each cohort and routinely thereafter during the course of the study.

The Data Review Group will look at the total safety data in determining whether it is possible to proceed to the next dose cohort and have discretion to apply the following:

Suspension of Patient Enrollment:

In the event of one (1) death attributed to the study drug(s), study accrual will be suspended pending further investigation, and will only be resumed at the recommendation of the DSMB and the Investigators. The DSMB will have discretion to terminate the trial if an additional death occurs that can be attributed to either or both of the study drugs.

5.2 AGENT ADMINISTRATION

Treatment will be administered in the MS center. The MS centers must have skilled personnel and adequate equipment to provide emergency treatment should the subject experience anaphylaxis, hypotension or respiratory distress. Subjects will be enrolled into a specified cohort. A single dose of 150 mg of ublituximab on Day 1 with an infusion rate of 4 hours, 450 or 600 mg on Day 15 at different infusion rates (see dosing scheme), and at week 24, a single dose of 450 or 600 mg of ublituximab with different infusion rates will be administered to the respective cohorts. Additionally, 2 subjects in each cohort will be randomized to a placebo group. On day 28, the placebo subjects will begin active treatment with ublituximab in its respective cohort (see dosing scheme). Administration of ublituximab and placebo will be under the direction of the study investigators. Additional dosing cohorts may be explored.

It is required the absolute neutrophil counts and the platelet count should be within normal range before the infusion of ublituximab.

If the liver enzymes (ALT and/or AST) are > 5 times the upper limit of normal (ULN) of the normal range, or if the neutrophil count and platelets counts are below acceptable levels as described, the dose of ublituximab will be held for up to 48 hours until the laboratory values return to within acceptable range. If all labs above do not return to within the acceptable range within 48 hours, the subject will not receive the ublituximab infusion and will be withdrawn from the study. Subjects who are withdrawn will be asked to enter the follow-up evaluation period of the study.

5.2.1 GUIDELINES FOR ADMINISTRATION OF UBLITUXIMAB

- *Necessity of MS Center:* Center must have personnel and equipment necessary to provide adequate emergency treatment for anaphylaxis, hypotension and respiratory distress.
- *Method of Administration:* Ublituximab must be administered as an intravenous infusion through a dedicated intravenous line and will be done under the supervision of the study investigator
- *Potential Drug Interactions*: No drug interactions have been reported to date.
- *Pre-medications:* Pre-medicate approximately 30 minutes prior to each dose of ublituximab with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to patient 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.

- *Hypersensitivity and Infusion Reaction Precautions*: Medication and resuscitation equipment utilized by a trained personnel must be available per institutional guidelines prior to ublituximab administration for the emergency management of potential anaphylactic reactions
- *Subject Care Implications*:
    - Ublituximab should not be administered as an IV push or bolus.
    - Ublituximab should only be diluted in 0.9% NaCl.
    - Diluted ublituximab should be checked before administration for cloudiness, color, or deposits. Ublituximab 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 be administered immediately after dilution.
    - No other treatment may be co-administered with ublituximab (other than for immediate intervention for adverse event).

5.2.1.1 INFUSION RELATED REACTIONS AND INFUSION RATE GUIDANCE

Infusion related reactions, including severe reactions, have been reported with ublituximab administration in subjects with CLL and NHL. Guidelines are provided below for subjects who experience such reactions. Symptomatic infusion reactions, despite premedication, may be treated at the discretion of the Principal Investigators using the following or other appropriate treatments: oral acetaminophen 650 mg, corticosteroids, antihistamines, oxygen, and bronchodilators.

The following are recommended infusion rate reduction/delay guidelines for subjects who experience severe Infusion Related Reactions (IRR's) that require treatment interruption. The final decision for the infusion rate reduction/delay or discontinuation resides with the treating investigator. Infusion rates should be considered targets for each respective cohort. If the treating investigator 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 Interruption:

- Stop the infusion, and closely monitor the subject. Institute symptomatic medical management until resolution of IRR symptoms.
- Following the judgment of the investigator and provided the subject is stable, the infusion may be resumed at no more than half the previous rate.

If the subject does not experience any further IRR symptoms, the infusion may be resumed at the increments and intervals as appropriate for the treatment dose.

If there is a second interruption of treatment due to IRR symptoms, ublituximab infusion must be stopped. The treating physician may decide whether to attempt completion of the infusion on a second day.

5.2.1.2 DISPENSING OF UBLITUXIMAB

Before dispensing, the site pharmacist or his/her representative must check that the ublituximab product received is in accordance with the product specifications and the re-test/expiration date.

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

The pharmacist or his/her representative should complete the accountability forms with information concerning the dispensation of ublituximab. Preparation should be done by the pharmacist or his/her representative according to instructions for sterile dilution provided below.

The pharmacist or his/her representative should record the date dispensed and the subject's study identification number and initials, as well as complete the accountability forms with information concerning the dispensation of ublituximab. Preparation should be done by the pharmacist or his/her representative according to instructions for sterile dilution.

5.3 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

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

- No glucocorticoids may be administered outside of protocol requirements for premedication or AE management, except low doses of steroids stabilized at $\leq$ 10 mg per day of prednisone or equivalent, and started at least 7 days prior to study entry.

Neutropenia: Granulocyte colony stimulating factor (G-CSF; filgrastim or pegfilgrastim) may be used during the course of the study after the first 28 days during the dose-escalation portion, at the investigator discretion. The drug(s) should be used at a dose/schedule specified in the package insert. During the cohort expansion, GCSF may be used at the discretion of the investigator.

Antiemetics: Ublituximab is considered to be of low emetogenic potential that may be adequately prevented with prochlorperazine. Other antiemetics may be used at the discretion of the treating physician if nausea and/or vomiting is not adequately controlled/prevented.

Infusion Reactions with ublituximab: Infusion related reactions have been reported with ublituximab, more profound in patients with hematologic malignancies. All subjects treated with ublituximab require pre-medication approximately 30 minutes prior to each dose of ublituximab with an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent). Symptomatic infusion reactions despite premedication, 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.

MS Relapses during the study:

Any patient experiencing a multiple sclerosis relapse while on study will be allowed rescue therapy with intravenous methylprednisolone 1gm/day for up to 5 consecutive days. Subjects requiring rescue therapy will have an MRI scan 10 days after completion of treatment with steroids.

Re-consent criteria

In case of a confirmed diagnosis of MS relapse (as defined in the protocol, Appendix C), **or** in case of an increase in EDSS of 1.0 points or more, sustained for at least 3 months, during the study, the following actions will be taken:

1. 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.
2. The subject will be requested to re-sign an informed consent form if he/she chooses to continue to participate in the study, in the same treatment assignment.

Subjects enrolled into the study will be closely monitored through the study course by the Sponsor's personnel as well as by an external independent data monitoring committee (DSMB) in order to ensure subjects' welfare.

5.4 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment should continue through first 24 weeks and beyond unless one of the following criteria applies:

- Disease progression or inter-current illness that prevents further treatment,
- Patient decides to withdraw from the study, or changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

The first efficacy assessment should be approximately 24 weeks after Day 1 (± 7 days) and approximately another 24 weeks thereafter (± 7 days) through the first 48 weeks following initiation of therapy.

The reason for study removal and the date the patient was removed must be documented in the Case Report Form. Subjects who discontinue therapy due to an adverse event should be followed until disease progression.

5.5 END OF STUDY/OPEN LABEL EXTENSION STUDY

Subjects who are in good health with stable disease and has completed the treatments and scheduled assessments through the final study visit may have the option of entering a 112 week open label extension study, with a continuation of treatment, and relapse and safety monitoring. The criteria for entering the open label extension study will be clearly stated in a separate protocol (TG1101-RMS201E).

6 DOSING DELAYS/DOSE MODIFICATION - RECOMMENDATIONS

Subjects should be assessed clinically for toxicity at each visit using the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE) grading scale.

Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.

Dose modification and or intervention with supportive care recommendations for ublituximab is provided below, however final discretion lies with the treating investigator in regards to more or less aggressive intervention, if the investigational agent needs to be reduced, and actual dose reductions, as well as the number of dose reductions.

6.1 CRITERIA FOR ONGOING TREATMENT

Repeat treatment should be administered per protocol provided that:

- Renal function should continually be assessed, with appropriate dose modifications as needed
- Recovered from grade 3-4 non-hematologic toxicity to grade 2 or less.
- Treatment may be delayed to recover from toxicity or per investigator discretion.
- No clinical or radiographic evidence of disease progression.

6.2 IMPORTANT DOSE MODIFICATIONS

For RMS subjects, the hematologic dose modifications are graded by the CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE).

6.2.1 DOSE MODIFICATIONS OF UBLITUXIMAB

If toxicity, in the opinion of the investigator, is attributable to ublituximab, the following guidelines for neutropenia, thrombocytopenia, anemia, and elevated liver enzymes are recommended below (for Infusion Related Reactions, see Section 6.2.1.2). Final discretion lies with the treating investigator in regards to more or less aggressive dose reductions, as well as the number of dose reductions.

6.2.1.1 LAB ABNORMALITIES

If cytopenias are deemed related to the underlying disease rather than ublituximab, dose reductions are not required, or are per investigator discretion.

Worst CTCAE Grade Toxicity	**Action to be Taken**
Neutropenia	
Grade	**Management**
≤ Grade 1	No action required.
Grade 2	No action required; consider growth factor support.
Grade 3 or 4 1st Occurrence	Hold until < Grade 3. Consider growth factor support per protocol requirement. Resume ublituximab at current dose cohort. Hold until < Grade 3. Consider growth factor support per protocol requirement. Resume ublituximab at current dose cohort.
Grade 3 or 4 subsequent Occurrences	Hold until < Grade 3. Consider growth factor support. Resume ublituximab at current dose cohort.
Management of neutropenia are per institution guidelines and if in the opinion of treating investigator, are appropriate for patient care.	

Worst CTCAE Grade Toxicity	Action to be Taken
Thrombocytopenia or Anemia	
Grade	**Management**
≤ Grade 1	No action required.
Grade 2	No action required.
Grade 3 or 4 1st Occurrence	Hold until < Grade 3, or at subjects previous baseline. Resume ublituximab at current dose cohort.
Grade 3 or 4 subsequent Occurrences	Hold until < Grade 3, or at subjects previous baseline. Resume ublituximab at current dose cohort.
Management of thrombocytopenia and anemia are per institution guidelines and if in the opinion of treating investigator, are appropriate for patient care.	

Worst CTCAE Grade Toxicity	Action to be Taken
Elevated Liver Enzymes	
Grade	**Management**
≤ Grade 1	No action required.
Grade 2	No action required.
Grade 3 or 4 1st Occurrence	Hold until < Grade 1, or at subjects previous baseline. Resume ublituximab at current dose cohort.
Grade 3 or 4 subsequent Occurrences	Hold until < Grade 3, or at subjects previous baseline. Resume ublituximab at current dose cohort.
Management of elevated liver enzymes are at the discretion of the investigator and should be discussed with TG Therapeutics.	

6.2.1.2 INFUSION RELATED REACTIONS

Infusion related reactions have been reported with ublituximab. All subjects treated with ublituximab require pre-medication approximately 30 minutes prior to each dose of ublituximab or placebo with an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent). Symptomatic infusion reactions, despite premedication, may be treated at the discretion of the treating physician, including but not limited to: oral acetaminophen 650 mg (or equivalent), corticosteroids, antihistamines, oxygen and bronchodilators.

6.2.1.2.1 INFUSION RATE REDUCTIONS DUE TO INFUSION RELATED REACTIONS

The following are recommended infusion rate reduction/delay guidelines for subjects who experience severe Infusion Related Reactions (IRR's) in which treatment must be interrupted. Infusion rates should be considered targets for each respective cohort. If the treating investigator 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.

1st Dose Interruption:

- The patient must be closely monitored until resolution of symptoms.
- Following the judgment of the Investigator, and provided vital signs are stable and normal saline has infused for at least 30 minutes, the infusion may be resumed at maximum 50% of previous rate.
- The rate should be increased by 50% every 30 minutes to the max rate of 100 mL/hr as long as tolerated.

2nd Dose Interruption (same day):

- Wait approximately 2 hours. The patient should be closely monitored until resolution of symptoms.

If there is a second interruption of treatment due to IRR symptoms, ublituximab infusion must be stopped. The treating physician may decide whether to attempt completion of the infusion on a second day.

- If the dose discontinued is the Day 1 infusion, administration of the remainder of the dose on Day 2 is permitted as follows:
    - On Day 2, if patient symptoms have resolved, estimate remaining dose needed and prepare accordingly for infusion.
    - Begin infusion of remaining dose according to the infusion rate guidelines presented above for the first infusion of ublituximab.

If the patient has a dose interruption on Day 2, discontinue the infusion. The patient should again be monitored for all symptom resolution prior to release from trial site. The patient should start their next scheduled infusion at the protocol specific dose (Day 15) and infusion rate. If infusion rate reductions should be needed for the Day 15 infusion, please refer to the above recommendations. Final decision for infusion rate or discontinuation resides with the treating investigator.

7 STUDY EVALUATION TABLE

Baseline evaluations / laboratory tests are to be conducted within 28 days prior to Day 1. MRI scans used to identify measurable/evaluable disease are required to be done within 30 days prior to Day 1. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next infusion.

	Screen-ing	Baseline																Study End
Procedure		**W1**	**W1**	**W2**	**W3**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W24**	**W25**	**W28**	**W36**	**W40**	**W44**	**W48**
	D (-28 to 0	**D1**	**D2**		**D15**							**(2 days post week 24 dose)**						
Patient consent	X																	X[12]
Medical history	X																	
Serum Pregnancy test[1]	X																	
Urine Pregnancy Test[5]					X						X							
EDSS and Neurological Assessment[4,11]	X	X									X							X
Physical exam[8] & Vital signs (pulse rate, BP, temperature)[3,4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Relapse Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI[4]	X										X							X
12 Lead ECG[9]	X	X			X						X							
Blood collection for CBC and serum chemistry[3,4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood collection for Immunological analyses[3,4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fibrinogen [4,5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK analysis [4, 6]		X		X	X	X					X		X					
Ublituximab Dose		X			X						X							
Serology: HIV, HCV, HBV, varicella[2]	X																	
Anti-drug Abs[3,7, 10,4]		X			X	X		X			X				X			X
PT/INR		X																
Quantitative Immunoglobulin[3,4]		X						X			X				X			X
Adverse events (CTC v4.0)[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] For women of child bearing potential completed within 5 days prior to Day 1

[2] To confirm negative HIV 1 and 2, HBV and HCV

[3] Pre-dose on any day of infusion

[4] Weeks 8 and beyond, collections/assessments may occur ±2 days from specified time points

[5] Prior to each dosing

[6] Prior to and 15-30 minutes after each dosing on UTX treatment days; for non-treatment days, 1 PK sample should be obtained

[7] To confirm potential development of human anti-chimeric antibodies

[8] Physical exam will occur on all visits except Days 2 and 15 and weeks 2, 24 and 25

[9] Pre-dose and post-dose on any day of infusion

[10] Anti-drug antibodies are antibodies developed against ublituximab

[11] EDSS Assessment will be assessed based on a slightly modified neurological examination as fatigue will not contribute to the EDSS assessment

[12] Consent for open label extension study

7.1 OVERVIEW

All subjects should visit the study center on the days specified within this protocol. The complete schedule of assessments is shown in Section 7. The baseline physical examination with vital signs, medical history, evaluation of concomitant medications, EDSS (will be assessed based on a slightly modified neurological examination as fatigue will not contribute to the EDSS assessment), 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 Day 1. MRI scans should be performed ≤30 days prior to initiation of treatment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next infusion. Subjects who are in good health with stable disease and has completed the treatments and scheduled assessments through the final study visit may have the option of entering a 112 week open label extension study, with a continuation of treatment, and relapse and safety monitoring. Entry into the open label extension will require patient consent and fulfillment of entry criteria per the TG1101-RMS201E open label extension protocol.

7.1.1 LABORATORY EVALUATION

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

    a. For subjects initially treated with UTX:
        i. Blood collection for CBC and serum chemistry at baseline, and day 1 (pre-dose), 2, 8, 15 (pre-dose), and week 4, 8, 12, 16, 20, 24 (pre-dose and 2 days post-dose), 25, 28, 36, 40, 44 and 48

    b. For subjects initially treated with placebo followed by UTX treatment
        i. Blood collection for CBC and serum chemistry at baseline, and day 1 (pre-dose), 2, 8, 15 (pre-dose), and week 4. Once the subject starts UTX treatment, blood collection for CBC and serum chemistry on day 1 (pre-dose), 2, 8, 15 (pre-dose), and week 4, 8, 12, 16, 20, 24 (pre-dose and 2 days post dose), 25, 28, 36, 40, 44 and 48

2. Serum chemistry should be obtained at the same schedule for hematologic profile (outlined above)

Serum Chemistry		
Albumin	Creatinine	SGOT [AST]
Alkaline phosphatase	Glucose	SGPT [ALT]
Bicarbonate	LDH	Sodium
BUN	Magnesium	Total bilirubin
Calcium	Phosphorus	Total Protein

Chloride	Potassium	Uric acid

3. Serum pregnancy test should be obtained within 5 days prior to the initiation of therapy for women of childbearing potential.
4. PT/INR should be drawn on Day 1 prior to administration.
5. Quantitative immunoglobulin (IgG, IgM, IgA) test should be analyzed by a local laboratory on Day 1 (pre-dose), week 12, week 24 (pre-dose), and weeks 36 and 48.
6. Coagulant (Fibrinogen) tests will be obtained at the same schedule for hematologic profile (outlined above)

[redacted]

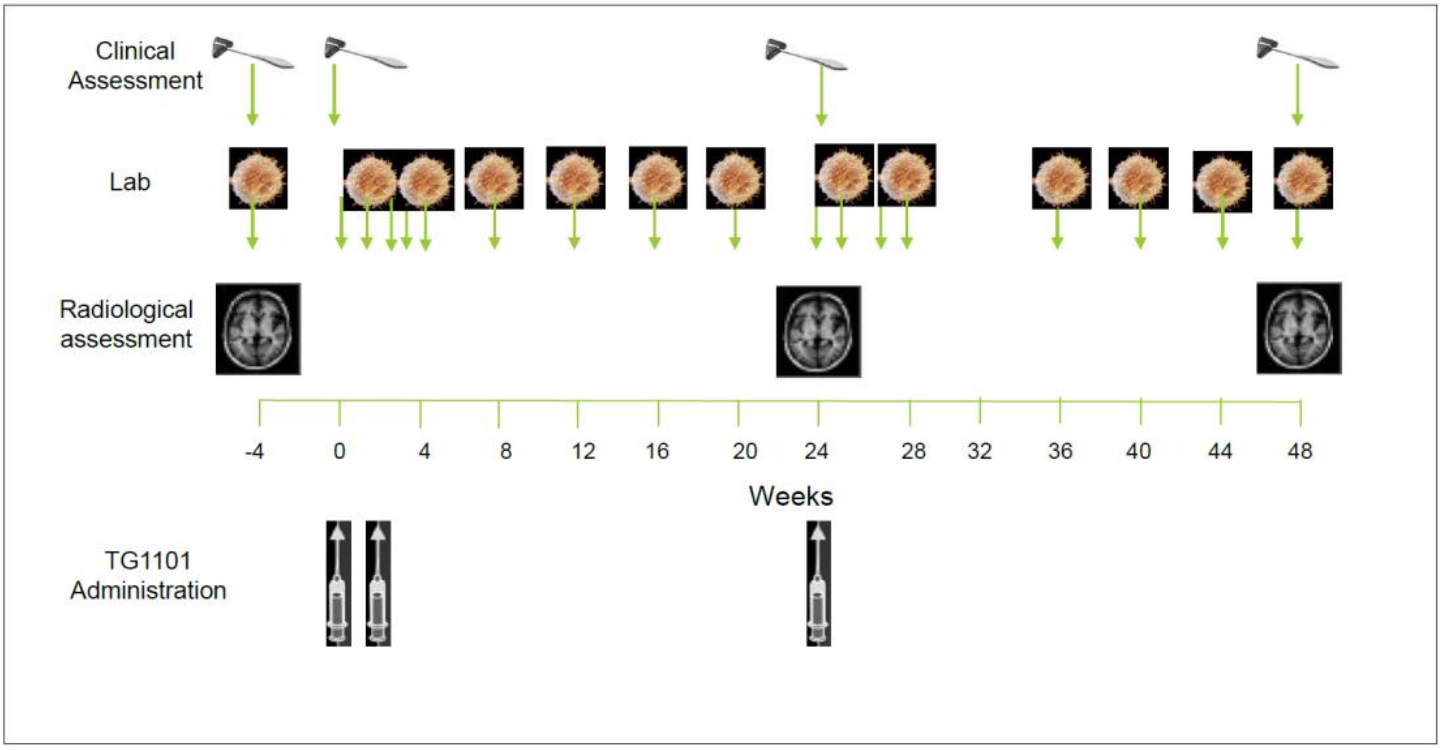
a. Samples will be drawn from all subjects at Baseline (Day 1) prior to the first infusion of UTX and 15-30 minutes after the completion of the infusion; on Day 15 prior to the infusion of UTX and 15-30 minutes after the completion of the infusion; on Day 180 (week 24) prior to the infusion of UTX and 15-30 minutes after the completion of the infusion;

[redacted]

[redacted]

[redacted]

[redacted]



7.1.2 RADIOLOGICAL EVALUATION

Assessment of effect on Gd enhancing lesion and new and enlarging T2 lesions will be evaluated as outlined in the schedule of events. For subjects initially treated with placebo, they will obtain a MRI at baseline and on week 4 (prior to start of UTX treatment).

Additionally, all study MRIs will undergo safety review by the site radiologist to 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 provide a report of the MRI to the treating physician.

7.1.3 NEUROLOGICAL EVALUATION

Assessment of effect on relapse rate will be evaluated as outlined in the schedule of events. For subjects initially treated with placebo, they will obtain a neurological evaluation at baseline and on week 4 (prior to start of UTX treatment). EDSS will be assessed based on a slightly modified neurological examination as fatigue will not contribute to the EDSS assessment.

7.1.4 RELAPSE ASSESSMENT

Relapses are defined as the occurrence of new or worsening neurological symptoms attributable to MS, and immediately preceded by a stable or improving neurological state of at least 30 days. Symptoms that persists for more than 24 hrs in the absence of fever and be accompanied by objective neurological worsening consistent with an increase ≥0.5 on the EDSS (subjects with baseline EDSS of >1.0) or an increase ≥1.0 on the EDSS (subjects with baseline EDSS=0).

Subjects will be assessed for relapse by the treating investigator at each study visit as outlined in the study evaluations table and, if necessary, at unscheduled visits. If a protocol defined relapse does occur, it will be documented in the eDC.

MS Relapses during the study:

Any patient experiencing a multiple sclerosis relapse while on study will be allowed rescue therapy with intravenous methylprednisolone 1gm/day for up to 5 consecutive days. Subjects requiring rescue therapy will have an MRI scan 10 days after completion of treatment with steroids.

Re-consent criteria

In case of a confirmed diagnosis of MS relapse (as defined in the protocol, Appendix C), **or** in case of an increase in EDSS of 1.0 points or more, sustained for at least 3 months, during the study, the following actions will be taken:

3. 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.
4. The subject will be requested to re-sign an informed consent form if he/she chooses to continue to participate in the study, in the same treatment assignment.

7.2 DEFINITIONS

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

7.3 DISEASE PARAMETERS

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

7.4 DURATION OF RESPONSE

Duration of stable disease:

Stable disease is measured from the start of the treatment 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.

7.5 RESPONSE REVIEW

Subjects will be assessed for relapse by the treating investigator at each study visit as outlined in the study evaluations table and, if necessary, at unscheduled visits.

Relapses are defined as the occurrence of new or worsening neurological symptoms attributable to MS, and immediately preceded by a stable or improving neurological state of at least 30 days. Symptoms that persists for more than 24 hrs in the absence of fever and be accompanied by objective neurological worsening consistent with an increase ≥0.5 on the EDSS (subjects with baseline EDSS of >1.0) or an increase ≥1.0 on the EDSS (subjects with baseline EDSS=0).

8 PHARMACEUTICAL INFORMATION

8.1 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. Ublituximab must not be frozen.

Stability: Once a vial of ublituximab has been opened and/or diluted it must 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 24 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
- Unit kit of 6 vials per kit with each vial 15 mL

OR

- Six 6 mL vial containing 25 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 6 mL is a type I glass vial closed by a siliconized chlorobutyl rubber stopper sealed with an aqua plastic aluminum cap.

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 a white plastic and aluminum cap.

Availability: Ublituximab is available from TG Therapeutics.

8.1.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

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

8.1.1.1 COMMON (>20%)

- **Blood and lymphatic system disorders:** Neutropenia, Thrombocytopenia
- **General disorders and administration site conditions:** Infusion-related reaction, Pyrexia, Chills
- **Nervous system disorders:** Headache

8.1.1.2 LESS COMMON (10-20%)

- **Blood and lymphatic system disorders:** Anaemia
- **Gastrointestinal disorders:** Diarrhoea, Nausea, Abdominal Pain Upper
- **General disorders and administration site conditions:** Fatigue, Asthenia

8.1.1.3 UNCOMMON (ADVERSE EVENTS REPORTED IN AT LEAST 2 PATIENTS BUT < 10%)

- **Blood and lymphatic system disorders:** Febrile neutropenia, Pancytopenia
- **General disorders and administration site conditions:** Pain
- **Infections and infestation:** Bronchitis
- **Investigations:** Blood bilirubin increase, Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Elevated liver enzymes
- **Musculoskeletal and connective tissue disorders:** Muscle weakness
- **Nervous system disorders: Dysgeusia**
- **Respiratory, thoracic and mediastinal disorders:** Throat irritation/tightness, Dyspnea
- **Skin and subcutaneous tissue disorders:** Pruritus
- **Vascular disorders:** Hypertension

8.1.2 DISPENSING

Before dispensing, the site pharmacist or his/her representative must check that ublituximab is in accordance with the product specifications and the validity is within the re-test and expiry date.

The exact dose and the date and time of administration of ublituximab must be recorded within the CRF, patient's medical records, and/or in the drug accountability records.

The Pharmacist or his/her representative should record the date dispensed and patient's number and initials on the labels. He/she should complete the accountability forms with information concerning the dispensation of ublituximab. Preparation should be done by the Pharmacist or his/her representative according to instructions for sterile dilution included within the unit boxes of ublituximab. Dilution for ublituximab is as follows:

8.1.2.1 DILUTIONS OF UBLITUXIMAB

Ublituximab must not be mixed with other medicinal products. Ublituximab should only be diluted in 0.9% NaCl before use. No data are available for other solutions such as 5% dextrose and 5% mannitol.

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

[redacted]

Dose of ublituximab for infusion	[redacted]
150 mg	
450 mg	
600 mg	

[redacted]

Dose of ublituximab for infusion	[redacted]
150 mg	
450 mg	
600 mg	

8.1.3 ADMINISTRATION

- IV administration only. Ublituximab should not be administered as an IV push or bolus.
- Ublituximab must be checked before being administered for cloudiness, color, soapy aspect, or deposits.
- Ublituximab must not be administered if does not conform to the specifications. The Investigator or his/her representative must immediately inform the Monitor/Sponsor.
- In accordance with Section 5.3, a list of pre-medication will be administered before infusion of ublituximab.
- Since infusion-related hypotension may occur, **antihypertensive medications should be withheld** 24 hours prior to and throughout infusion of ublituximab
- No other treatment may be co-administered with ublituximab (other than for immediate intervention for adverse event).
- It is recommended that ublituximab be administered immediately after dilution.

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

- 1st infusion ➔ in approximately 4 hours
- 2nd and 3rd infusion ➔ in approximately 1 to 3 hours, depending on the cohort

The flow rate is specified in the tables below.

8.1.3.1 FLOW RATE RECOMMENDATIONS FOR UBLITUXIMAB ADMINISTRATION

1st infusion over 4 hours for all cohorts

1ST INFUSION OF UBLITUXIMAB OR PLACEBO

Cohorts	Ublituximab Dose	Total volume to be infused	Infusion rate			
			T0 to T30'	T30' to T1H	T1H to T2H	T2H to T4H
1-3	150 mg	250 mL	10 mL/H	20 mL/H	35 mL/H	100 mL/H

Cohorts	Ublituximab Dose	Total volume to be infused	Infusion rate			
			T0 to T30'	T30' to T1H	T1H to T2H	T2H to T3H
4	150 mg	250 mL	10 mL/H	20 mL/H	85 mL/H	150 mL/H

Cohorts	Ublituximab Dose	Total volume to be infused	Infusion rate		
			T0 to T30'	T30' to T1H	T1H to T2H
5	150 mg	250 mL	10 mL/H	40 mL/H	225 mL/H

Cohorts	Ublituximab Dose	Total volume to be infused	Infusion rate	
			T0 to T30'	T30' to T1H
6	150 mg	250 mL	50 mL/H	450 mL/H

2nd infusion

2ND INFUSION OF UBLITUXIMAB OR PLACEBO

Cohort	Ublituximab Dose	Total volume to be infused	Infusion rate		
			T0 to T1H	T1H to T2H	T2H to T3H
1	450	250 mL	25 mL/H	75 mL/H	150 mL/H

Cohort	Ublituximab Dose	Total volume to be infused	Infusion rate	
			T0 to T30 min	T30 min to T90min
2	450	250 mL	100 mL/H	200 mL/H

Cohort	Ublituximab Dose	Total volume to be infused	Infusion rate	
			T0 to T30min	T30min to T60min
3	450 mg	250 mL	100 mL/H	400 mL/H

Cohort	Ublituximab Dose	Total volume to be infused	Infusion rate	
			T0 to T30min	T30min to T60min
4-6	600 mg	250 mL	100 mL/H	400 mL/H

3rd infusion

3RD INFUSION OF UBLITUXIMAB

Cohort	Ublituximab Dose	Total volume to be infused	Infusion rate	
			T0 to T30min	T30min to T90min
1	450	250 mL	100 mL/H	200 mL/H

Cohort	Ublituximab Dose	Total volume to be infused	Infusion rate	
			T0 to T30min	T30min to T60min
2	450	250 mL	100 mL/H	400 mL/H

Cohorts	Ublituximab Dose	Total volume to be infused	Infusion rate	
			T0 to T30min	T30min to T60min
3 -6	600mg	250 mL	100 mL/H	400 mL/H

8.1.3.2 AGENT HYPERSENSITIVITY

Ublituximab Hypersensitivity and Infusion Reactions: Available at the bedside prior to ublituximab administration will be medications and resuscitation equipment for the emergency management of anaphylactic reactions per institution guidelines. Ublituximab should be administered intravenously through a dedicated line.

8.1.3.3 INFUSION RATE REDUCTIONS DUE TO INFUSION RELATED REACTIONS

The following are recommended infusion rate reduction/delay guidelines for subjects who experience severe Infusion Related Reactions (IRR's) in which treatment must be interrupted. The final decision for the infusion rate

reduction/delay or discontinuation resides with the treating investigator. Infusion rates should be considered targets for each respective cohort. If the treating investigator 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.

1st Dose Interruption:

- The patient must be closely monitored until complete disappearance of symptoms.
- Following the judgment of the Investigator, and provided vital signs are stable and normal saline has infused for at least 30 minutes, the infusion may or may not be resumed at maximum 50% of previous rate.
- The rate should be increased by 50% every 30 minutes to the max rate of 100 mL/hr as long as tolerated.

2nd Dose Interruption (same day):

- Wait a minimum of 2 hours
- After 2 hours, the patient must again be closely monitored until complete disappearance of symptoms.
- Following the judgment of the Investigator, and provided vital signs are stable and normal saline has infused for at least 30 minutes, the infusion may or may not be resumed at maximum 50% of previous rate.
- The rate should be increased by 50% every 30 minutes to the max rate of 100 mL/hr as long as tolerated.

If there is a second interruption of treatment due to IRR symptoms, ublituximab infusion must be stopped. The treating physician may decide whether to attempt completion of the infusion on a second day. Clinical investigators and clinical monitors familiar with the clinical course of MS must use their judgement and determine the tolerability of a given dose of ublituximab.

- If the dose is discontinued on Day 1, administration of the remainder of the dose on Day 2 is permitted as follows:
    - On Day 2, if patient symptoms have resolved, estimate remaining dose needed and prepare accordingly for infusion.
    - Begin infusion of remaining dose according to the infusion rate guidelines presented above for the first infusion of ublituximab.

If the patient has a dose interruption on Day 2, discontinue the infusion. The patient should again be monitored for all symptom resolution prior to release from trial site. The patient should start their next scheduled weekly infusion at the protocol specific dose (Day 15), at the infusion rate indicated in Section 8.1.3.1 for 2nd and 3rd infusions. If infusion rate reductions should be needed for the week 24 infusion, please refer to the above recommendations. Final decision for infusion rate reduction/delay or discontinuation resides with the treating investigator. Clinical investigators and clinical monitors familiar with the clinical course of MS must use their judgement and determine the tolerability of a given dose of ublituximab.

8.2 ORDERING INVESTIGATIONAL AGENTS

Once the clinical trial site receives regulatory approval (IRB/IEB), and the Sponsor and/or Sponsor designee performs the Site Initiation Visit and inspection of pharmacy, and determines the site to be officially open for enrollment, an automatic shipment of pre-determined quantity of both drugs will be shipped to the clinical trial site.

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

If any abnormality on the supplied boxes is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt and contact that Sponsor and/or Sponsor designee.

9 STATISTICAL CONSIDERATIONS

This section describes the statistical methods to be used to analyze the efficacy and safety endpoints. A formal statistical analysis plan (SAP), which must be finalized before database lock, will provide additional details for data handling procedures, statistical methods, and data presentations (e.g., table, listing, and figure shells). The final clinical study report will describe deviations from the SAP, if any.

9.1 SAMPLE SIZE AND POWER

[redacted]

9.2 GENERAL ANALYSIS CONVENTION

Unless otherwise stated, all analyses will be performed using SAS Version 9.2 or higher and all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

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. In general, mean, standard deviation, median, 25th and 75th percentiles, minimum, maximum, and percentages will be presented with one decimal.

9.3 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population will consist of all subjects who receive at least one dose of study drug and provide some efficacy values. The primary efficacy analyses will be performed based on the ITT population.

The Safety Population will include all subjects who receive at least one dose of study drug. All safety assessments including toxicity will be performed on the Safety Population.

The modified intent-to-treat Population (mITT) will consist of all subjects who have received UTX and have one baseline and post-baseline MRI without a major protocol deviation. The criteria for a major protocol deviation will be determined and documented prior to data base lock. Subject exclusion from the mITT population will also be determined and documented prior to database lock. Supportive analyses may be performed based on the mITT population.

9.4 SUBJECT DISPOSITION

The disposition of subjects includes the number and percentage of subjects for the following categories: subjects enrolled, subjects treated (safety population), subjects in the ITT population, Subjects in the mITT population, if applicable, subjects completed, and subjects discontinued from the study. The reasons for study discontinuation will also be summarized in this table. Only one primary reason for study discontinuation will be reported in the summary. However, all reasons will be presented in the listing.

A listing will present data concerning subject disposition.

9.5 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 ITT Population.

9.6 MEDICAL HISTORY

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

9.7 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. The number and percentage of subjects whose dose is modified at any time will be summarized by infusions and overall. The proportion of subjects completing each infusion of treatment will be summarized.

9.8 EFFICACY ANALYSES

The study is not designed (powered) to detect treatment differences. All efficacy variables will be summarized at all-time scheduled points where they are assessed. If appropriate, dose response or treatment differences may be analyzed. If p-values are presented, they will be nominal p-values without adjustment for multiple tests.

9.8.1 PRIMARY EFFICACY VARIABLE

The primary efficacy variable will be responder rate at week 4 (2 weeks after the second infusion (day 15)), where responders are subjects who have reduced B-cell depletion by ≥95%. The percentages of the responders will be presented. The 95% confidence intervals of the percentages may be presented, if appropriate, using exact method due to small sample size. Logistic analysis may be used to perform trend tests to assess dose response.

9.8.2 SECONDARY EFFICACY VARIABLE

The secondary efficacy variables include:

- Number of new Gd-enhancing lesions at 24 and 48 weeks
- Number of new or enlarging T2 lesions at 24 and 48 weeks
- Annualized relapse rate (ARR)
- Relapse rate reduction (RRR)
- Percent of relapse free subjects
- Reduction in B cells (CD19+), memory (CD19+CD27+) and naïve (CD19+CD27-) B cells at baseline, day 1 (pre dose)and 2; week 2; Day15 (pre-dose); week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 days post-dose) 25, 28, 36, 40, 44 and 48
- To examine sustained B cell reduction during the first and third infusions
- Additional immune profiling (CD4+, CD8+, IL10 and NK cells) at baseline, day 1 (pre dose) and 2; week 2, Day 15 (pre-dose); week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 days post dose) 25, 28, 36, 40, 44 and 48
- PK (ADME) profile of ublituximab at day 1 (pre-dose); week 2; day 15 (pre-dose); weeks 4, 24 (pre-dose) and 25

All these variables will be summarized. Dose response and treatment difference may be analyzed as appropriate. Additional efficacy variables may be included as appropriate.

10 SAFETY REPORTING AND ANALYSIS

10.1 SAFETY ANALYSES

Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the patient'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 the dose of ublituximab 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.

10.2 ADVERSE EVENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs and the characteristics of an observed AE (Section 8.1.1) will determine whether the event requires expedited reporting in addition to routine reporting.

10.3 ADVERSE EVENT CHARACTERISTICS

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

10.4 PROTOCOL-SPECIFIC EXPEDITED ADVERSE EVENT REPORTING EXCLUSIONS

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (i.e., MedWatch). The following AEs are considered expected and do not require expedited reporting.

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution
Blood/bone marrow	Neutropenia <7 days without fever	4	No	Yes
Blood/bone marrow	Thrombocytopenia <7 days without bleeding	4	No	Yes

10.5 ADVERSE EVENTS (AE'S) AND TREATMENT EMERGENT ADVERSE EVENTS (TEAE'S)

All AEs and SAEs occurring on study will be listed by patient. The frequency and percentages of subjects with treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and PT, where treatment-emergent is defined as any AE that:

- Occurs after first dosing of study medication and through the end of the study or up through 30 days after the last dose of study treatment, or

- Is considered treatment-related regardless of the start date of the event, or
- Is present before first dosing of study medication but worsens in intensity or the investigator subsequently considers treatment-related.

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.

AEs that occur after informed consent but before first dosing of study medication will not be summarized but will be listed.

At each level of summarization, a patient will be counted only once for each AE, SOC, or PT experienced within that level. In the summation for AE severity, within each level of AE, SOC, or PT experienced, the one with the highest severity will be included. In the summation for AE's relationship to the study drug, within each level of AE, SOC, or PT experienced, the one with the closest relationship to the study drug will be included.

10.6 DEFINITIONS OF ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient 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.

In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no trial treatment has been administered. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 is to be used for the grading of severity of symptoms and abnormal findings. For adverse events not covered by the NCI-CTCAE Version 4.0 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.

10.7 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 drug but a definite cause cannot be ascertained.
3. **Possible**: There is still a reasonable possibility that the cause of the event was the study drug 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 drug but other causes cannot be completely excluded.
5. **Definite:** Clear cut temporal and/or mechanistic relation to the study drug. All other causes have been eliminated. Events classified as definite will often be confirmed by documenting resolution on discontinuation of the study drug and recurrence upon resumption.

In the summary of drug related AEs, Categories 1 and 2 will be considered as "Not Drug Related" and all other categories, including missing, will be considered as "Drug Related."

10.7.1 RECORDING OF ADVERSE EVENTS

All adverse events of any patient during the course of the trial will be reported on the case report 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). 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 treatment spanning from Day 1 until 30 calendar days after discontinuation or completion of either protocol-specific treatment as defined by the protocol for that patient, are to be recorded on the CRF.

10.7.2 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 patient 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 or prolong inpatient 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 4.0 when applicable. Patient incidence of laboratory toxicity will be summarized by treatment group and maximum grade for each laboratory test.

10.7.3 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 30 calendar days 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. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the CRF. After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

MS Relapses during the study: For subjects having MS disease activity including relapses (protocol defined or otherwise):

Any patient experiencing a multiple sclerosis relapse while on study will be allowed rescue therapy with intravenous methylprednisolone 1gm/day for up to 5 consecutive days. Subjects requiring rescue therapy will have an MRI scan 10 days after completion of treatment with steroids.

Re-consent criteria

In case of a confirmed diagnosis of MS relapse (as defined in the protocol, Appendix C), **or** in case of an increase in EDSS of 1.0 points or more, sustained for at least 3 months, during the study, the following actions will be taken:

1. 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.
2. The subject will be requested to re-sign an informed consent form if he/she chooses to continue to participate in the study, in the same treatment assignment.

Subjects enrolled into the study will be closely monitored through the study course by the Sponsor's personnel as well as by an external independent data monitoring committee (DSMB) in order to ensure subjects' welfare.

Investigators must obtain expert evaluations of brain MRI images of subjects with suspected opportunistic CNS infections including PML.

10.8 SERIOUS ADVERSE EVENTS

10.8.1 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 at least a 24-hour 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 patient 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
- Outpatient 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 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.

10.8.2 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 CRF.

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 30-day 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 CRF page.

All SAEs and medically confirmed deaths (regardless of causality assessment) occurring on trial treatment or within 30 days of last trial treatment must be reported to the sponsor as SAEs within the CRF and followed until resolution (with autopsy report if applicable).

Deaths occurring within 30 days after last trial treatment that are deemed 'possibly' or 'probably' related to ublituximab must be reported as SAEs within the CRF (with an autopsy report if available).

Deaths occurring within 30 days after last trial treatment and not attributed to trial treatment (e.g., disease progression) need not be reported in an expeditious manner to the Sponsor, but can simply be captured on the appropriate CRF as an SAE (death).

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 CRF 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 CRF. The detailed SAE reporting process will be provided to the sites in the Safety Monitoring Plan.

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

10.9 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 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 but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs associated with the use of the trial medications to the FDA, investigators, and central IRBs by a written safety report within 15 calendar days of notification. Investigators using local IRBs are responsible for sending written safety reports for these events to their IRBs within 15 calendar days.

10.10 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 CRF. Avoid colloquialisms and abbreviations.

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

10.11 DIAGNOSIS VS. SIGNS AND SYMPTOMS

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, 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 CRF). 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.

10.11.1 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE CRF. 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 CRF.

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

10.11.2 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 inpatient 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.

10.11.3 DEATHS

All on-trial deaths, regardless of attribution, will be recorded on an SAE Report Form 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 CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the CRF Adverse Event page.

10.11.4 HOSPITALIZATION, PROLONGED HOSPITALIZATION, OR SURGERY

Any AE that results in hospitalization of >24 hours 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 Section 10.8).

10.11.5 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 CRF. 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 CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

10.11.6 PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

The following are events of special interest, and will need to be reported expeditiously:

Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the trial, an SAE form should be completed and faxed/emailed to the Sponsor. Sponsor should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sponsor.

Congenital anomalies/birth defects **always** meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting.

Trial Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the CRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the corresponding CRF page, and following the same process described for SAEs (see Section 10). If a trial drug overdose occurs, subjects should stop trial drug dosing and be clinically monitored as appropriate.

Malignancies

Malignancies must be reported via a MedWatch expedited report (in addition to your routine AE reporting mechanisms). Any malignancy possibly related to treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in the protocol.

11 STOPPING RULES

An independent DSMB (data safety monitoring board) will be in charge of reviewing safety data. In order to ensure safety and limit toxicity for enrolled subjects, the DSMB will meet (by phone) at least once (prior to subject enrollment (organizational meeting)), after first two subjects have completed infusion (one with placebo and the other with ublituximab) in each cohort during the treatment phase of the study and at end of the completion of the infusion of ublituximab for the eighth subject in each cohort. The independent DSMB may meet more frequently at their discretion depending on the safety and/or efficacy data presented and may stop the study at any time for safety or any other reason after discussing their findings with the Principal Investigator. The independent DSMB will be comprised of at least three MDs, with one being a neurologist and one with experience in the use of anti-CD20 mAb.

11.1.1 SUSPENSION OF PATIENT ENROLLMENT:

In the event of one (1) death attributed to the study drug, study accrual will be suspended pending further investigation, and will only be resumed at the recommendation of the DSMB. The DSMB will have discretion to terminate the trial if an additional death occurs that can be attributed to the study drug.

11.1.2 LACK OF CLINICAL RESPONSE

The DSMB may recommend to the Sponsor early termination of a study group if the MRI at 24-weeks demonstrates disease worsening.

12 CLINICAL DATA COLLECTION AND MONITORING

12.1 SITE MONITORING PLAN

A Sponsor representative or designee will have made a site visit to each institution within 6 months prior to initiating the protocol to inspect the drug storage area, and fully inform the Investigator of his/her responsibilities for studies and the procedures for assuring adequate and correct documentation. A study initiation site visit or a teleconference will be performed to review investigator responsibilities, the protocol, and its requirements with the Investigator(s). During the initiation, the case report forms (CRFs)/ eCRF's and other pertinent study materials will be reviewed with the investigator's research staff. During the course of the study, the Sponsor will make visits to the sites as necessary in order to review protocol compliance, examine CRFs, and individual subject medical records, and ensure that the study is being conducted according to the protocol and pertinent regulatory requirements. Selected CRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

Site monitoring shall be conducted to ensure the human subject protection, trial procedures, laboratory, trial intervention administration, and data collection processes are of high quality and meet the Sponsor, GCP/ICH and, when appropriate, regulatory guidelines. The Site Monitoring Plan shall define aspects of the monitoring process.

13 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).

13.1 IRB APPROVAL

The trial protocol, ICF, IB, available safety information, patient documents (e.g., trial diary), patient 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 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 trial review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB 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.

If applicable, the PI will notify the IRB **within 90 days** of the end of the trial, or if the trial terminates early, the PI must notify the IRB **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.

13.2 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 will be prepared by the Sponsor (or its representative), as required, for submission to the relevant regulatory authority.

13.3 INSURANCE AND INDEMNITY

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

13.4 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 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 patient's medical record. A copy of the informed consent form, including the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the trial design or the potential risks to the subjects, the patient's consent to continue participation in the trial must be obtained.

13.5 CONFIDENTIALITY

Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and national data protection laws. HIPAA regulations require that, in order to participate in the trial, a patient 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 patient's medical records, but the patient 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 patient to revoke his or her authorization.

In the event that a patient 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 patient 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 patient 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 direct access to review the patient'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 initials will identify subjects on the CRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the CRF or database. No material bearing a patient's name will be kept on file by the Sponsor. Subjects will be informed of their rights within the ICF.

13.6 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.

13.7 FINANCIAL INFORMATION

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

14 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

14.1 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 and the Principal Investigator supporting the trial. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

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

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and specifically when an increase to dosing or patient exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and REC and/or FDA and Competent Authority approval include, but are not limited to, the following:

- Change to trial design
- Risk to patient
- Increase to dose or patient 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.

14.2 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.

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 approval of the trial and the IRB members list;
- Current Curricula Vita 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-approved consent form containing permission for audit by representatives of the Sponsor, the IRB, and the FDA;
- 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.

14.3 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 CRFs are to be included on this document. All entries in the patient's CRF 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 patient's CRF 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 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 CRFs, IRB approval documents, Financial Disclosure forms, patient 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 CRF 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 shall maintain adequate documentation / records of IRB 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 CRFs, 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.

14.4 DATA COLLECTION

The trial CRF is the primary data collection instrument for the trial. A case report form (CRF/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 trial number, patient number, initials and date of birth will identify the patient in the CRF. If the patient's name 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 patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

14.5 TRIAL MONITORING, AUDITING, AND INSPECTING

The investigator will permit trial-related monitoring, quality audits, and inspections by the sponsor, government regulatory authorities, the Sponsor or its representative(s) of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, 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.

14.6 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 Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for trial conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

14.7 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 trial report will be prepared upon completion of the study. The Sponsor will disclose the trial results, in the form of a clinical trial 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 trial report and its addendum will comply with ICH E3 guidelines for structure and content of a clinical trial report.

The financial disclosure information will be provided to the Sponsor 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.

15 REFERENCES

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Contraceptive Guidelines and 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 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.

Contraceptive Guidelines for Women of Child-Bearing Potential:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 30 days after stopping treatment. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the patient. 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 six 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 patient.
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 at baseline and a negative urine pregnancy test prior to each dosing.

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, and for an additional 4 weeks after study drug discontinuation, and should not father a child in this period.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to TG Therapeutics Inc. within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy 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.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to TG Therapeutics Inc. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug 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.

17 APPENDIX B

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.

18 APPENDIX C

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