Brief Title: Ublituximab for Acute Neuromyelitis Optica (NMO) Relapses

Document Date: August 3, 2017

Document: Protocol and Statistical Plan

ClinicalTrials.gov ID: NCT02276963

TABLE OF CONTENTS

1 BACKGROUND 13

1.1 rationale 13
1.2 Investigational Agent 14
1.3 magnetic resonance imaging in the trial 20
1.4 Use of plasma exchange 21

2 OBJECTIVES 23

2.1 Primary Objectives 23
2.2 Secondary Objectives 23

3 SUBJECT SELECTION 24

3.1 Eligibility Criteria 24

4 REGISTRATION PROCEDURES 27

4.1 Registration Process 27

5 TREATMENT PLAN 28

5.1 Agent Administration 28
5.2 General Concomitant Medication and Supportive Care Guidelines 28
5.3 Duration of Therapy 28
5.4 Duration of Follow Up 29

6 DOSING DELAYS/DOSE MODIFICATION 30
7 TRIAL ASSESSMENTS AND TREATMENT 31
8 PHARMACEUTICAL INFORMATION 34

8.1 Investigational Agent – ublituximab 34
8.2 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) 35

9 TRIAL CALENDAR/EVALUTION TABLE 39
10 MEASUREMENT OF EFFECT 40

10.1 Definitions 41

11 STATISTICAL CONSIDERATIONS 42

11.1 Sample Size 42
11.2 General Analysis Convention 42
11.3 Analysis populations 43
11.4 subject dIsposition 43
11.5 subject Demographics and Baseline Characteristics 43
11.6 prior and Concomitant Medications 43
11.7 medical history 43
11.8 extent of exposure 43
11.9 Efficacy Analyses 44

12 SAFETY REPORTING AND ANALYSIS 45

12.1 Safety Analyses 45
12.2 Adverse events 45
12.3 Adverse Event Characteristics 45
12.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions 45
12.5 Adverse events 45
12.6 Definitions of Adverse Events 46
12.7 Serious Adverse Events 47
12.8 Sponsor SAE Reporting Requirements 49
12.9 Recording of Adverse Events and Serious Adverse Events 49
12.10 Diagnosis vs. Signs and Symptoms 49

13 STOPPING RULES 53
14 CLINICAL DATA COLLECTION AND MONITORING 54

14.1 Site Monitoring Plan 54

15 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS 55

15.1 IRB Approval 55
15.2 Regulatory Approval 55
15.3 Insurance and Indemnity 55
15.4 Informed Consent 55
15.5 Confidentiality 56
15.6 Investigator and Staff Information 56
15.7 Financial Information 57

16 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL 58

16.1 Amendments to the Protocol 58
16.2 Documentation Required to Initiate Trial 58
16.3 Trial Documentation and Storage 59
16.4 Data Collection 60
16.5 Trial Monitoring, Auditing, and Inspecting 60
16.6 Quality Assurance and Quality Control 60
16.7 Disclosure and Publication Policy 60

17 REFERENCES 62
18 APPENDIX A 65

18.1 Quantifying the Level of Disability 66
18.2 EDSS Scoring 66
18.3 Functional Systems 66
18.4 Functional System Score 66
18.5 The Scale 69
Response to Non-Hold FDA Issues 97

TRIAL SYNOPSIS

Trial title	**Phase I, Open Label Safety Study of Ublituximab for the Treatment of Acute Optic Neuritis and/or Transverse Myelitis in Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD)**
Trial rationale	Ublituximab (UTX; also known as LFB-R603) is a monoclonal antibody that specifically binds to the trans-membrane antigen CD20. The binding induces an immune response that causes lysis of B cells. The rationale for using ublituximab is based on the known roles of B cells, antibody production and plasma cells in the pathophysiology of NMO. NMO is characterized by the presence of an anti-AQP4 antibody, which is produced by differentiation of B cells to plasma cells. Because these anti-AQP4 antibodies may be pathogenic, B cells recognizing AQP4 may be involved in the disease process as well. B cells also play a role as potent antigen presenting cells in NMO. The strongest evidence of the importance of B cells in NMO comes from studies of B cell depletion, most commonly with anti-CD20 monoclonal antibody, rituximab (Rituxan®). Rituximab has been shown in five retrospective and two prospective studies to be effective in reducing NMO relapses up to 90% and achieving remission in up to 80% of patients solely by its action on CD20+ B cells, despite no change in plasma cell population and anti-AQP4 antibody titers. These human studies strongly suggest a critical role for B cells in the pathophysiology of human disease. While typically used in the prevention of disease, B-cell depletion may be beneficial in the treatment of an acute relapse as well. Emerging evidence indicates that peripheral B cells are activated during a relapse and plasmablast production of anti-AQP4 antibodies spikes. B cells are also found within acute lesions of the spinal cord and optic nerve suggesting roles both in the blood and in the central nervous system during a relapse.
Product	Ublituximab, recombinant chimeric monoclonal antibody against CD20 antigen, concentrate for solution for infusion. Ublituximab is manufactured by LFB Biotechnologies (Les Ulis, France) and supplied by TG Therapeutics, Inc.
Phase	Phase I
Trial Sponsor	Michael Levy, MD, PhD (Investigator-Initiated Trial-Sponsor)
Trial Chair	Michael Levy, MD, PhD John Hopkins University
Trial Objectives	The overall objective is to assess the safety of ublituximab as add-on therapy to steroids for treatment of acute optic neuritis and/or transverse myelitis in NMO and NMOSD. **Primary Objective** To assess safety of acute B cell depletion in NMO subjects with acute relapse of optic neuritis and/or transverse myelitis who are treated with ublituximab + steroids beginning on dose administration and ending with repletion of circulating B cells. **Secondary Objectives** • To determine the B cell depletion pharmacokinetics of ublituximab in the NMO patient population by monthly B cell counts for up to 9 months. • To determine the frequency of adverse events with ublituximab in this patient population.

Efficacy Endpoints

Clinical secondary efficacy endpoints:

Clinical outcomes will be monitored for efficacy using three functional neurologic tests, the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk and High Contrast Visual Acuity (HCVA). These will be assessed days 1 and 5 of hospitalization, on Days 13 and 20 (if necessary) and at follow up in 90 day and 180 days.

Objective secondary efficacy endpoints:

- MRI lesion size
- Number of days in hospital
- Requirement for plasma exchange rescue therapy

Pharmacokinetics and Immunogenicity

- To determine the pharmacokinetics of ublituximab in NMO patients
- To assess for the effect of immunogenicity on the pharmacokinetics, pharmacodynamics, and safety of ublituximab.

Safety Endpoints

All AEs will be reported and evaluated during the treatment period using CTCAE v4.0.

Trial design

Given the severity and the consequences of relapse in NMO, use of an active treatment is considered mandatory. The potential of currently utilized drugs and techniques to reduce the inflammation in NMO has been established primarily through expert consensus and small open label and retrospective studies.

This is a Phase 1 open-label, standard-of-care, single treatment arm, unblinded, single center interventional trial in NMO/NMOSD patients in which experimental subjects will receive one (1) infusion of 450 mg of intravenous ublituximab at the onset of an NMO exacerbation in addition to standard of care treatment with daily intravenous methylprednisolone at a dose of 1000 mg for five days.

The trial phases and durations, as well as standard of care treatment and MRIs are shown in the table below. For those who complete the trial, it is comprised of 4 potential phases: Screen, Steroid Treatment, Plasma Exchange (PLEX; if necessary) Treatment and Follow-Up.

Table S1: Ublituximab in NMO Trial Phases and Timings of Treatments/MRIs

Phase:	**Screening 1 day**	**Steroid Treatment* 5 days**					**Plasma Exchange (If necessary)**	**Follow-up Monthly**	**Follow-up 90-Day Visit**	**Follow-up 6 Month Visit**
Day	0	1	2	3	4	5	6-20	30, 60, 90, 120, 150, 180, 210, 240, 270	90	180
Treatment		$T^{1,2}$	T^{1}	T^{1}	T^{1}	T^{1}				
Exam/Lab	E/L	E/L	L	L	L	E/L	E/L	L	E	E
MRI Brain/spine	M					M	M		M*	

T^{1}: Administration of methylprednisolone 1000 mg intravenously
T^{2}: Administration of 450 mg of ublituximab intravenously
E: Neurological examination
L: Lab testing
M: MRI, as indicated by standard of care; M*: MRI for research purposes

Screening Phase

The purpose of the Screening Phase is to assess subject eligibility. This process includes an MRI scan (standard of care) to identify a contrast enhancing lesion(s) in the optic nerve and/or spinal cord.

Subjects must have a minimum of circulating B cells comprising at least 0.5% of total lymphocyte count to enroll in the trial and receive ublituximab therapy. For those who have not received B cell depleting medications in the past 12 months (rituximab, ofatumumab, ocrelizumab, ublituximab), a normal B cell count of 5-20% of total lymphocytes must be present in the circulation, confirmed by a limited flow cytometry panel of CD3, CD4, CD19 and CD20. For those who have received a B cell depleting medication in the past 12 months, a minimum of 0.5% of total lymphocytes has to be B cells. The working hypothesis is that when a patient has an acute attack following preventive therapy with B cell depleting agents, the remaining or returning B-cells are very aggressive and may catalyze the attack.

Steroid Treatment Phase

High dose (1000 mg) intravenous methylprednisolone will be given to all subjects with MRI-confirmed active lesions at onset of the attack according to standard of care. As early as possible in the Steroid Treatment Phase, 450 mg of intravenous ublituximab will be administered once to each subject enrolled.

Effort will be focused on giving the ublituximab as early in the steroid treatment process as possible. If a subject's admission or transfer to the Johns Hopkins Hospital is delayed, standard of care therapy with steroids will begin as soon as possible at the outside hospital. The subject may then enroll in this trial and receive one dose of ublituximab on the first day of hospitalization at the Johns Hopkins Hospital if the transfer takes place within the Steroid Treatment Phase.

All subjects who fail to clinically respond by day 5 will be recommended for plasma exchange as per standard of care. A beneficial response is generally considered an improvement in the specific deficit(s) that led to the hospitalization. Depending on those specific deficits, the criteria that are routinely used at Johns Hopkins to indicate treatment response(s) in motor, sensory, autonomic and visual function are:

1. An improvement in strength by the Motor Research Council strength scale by at least 1 full point in at least two isolated muscles of at least one limb, or
2. An increase of two Rydel tuning fork units in at least one affected limb.
3. Improvement in bowel and/or bladder function from incontinence to at least partial voluntary control.
4. An improvement in visual acuity using bedside Snellen equivalent of ≥ 2 lines.

If subjects do not require rescue with plasma exchange because they fulfill the clinical criteria above, an MRI may be performed to confirm resolution of the inflammatory lesion to compare to admission MRI. Based on the MRI and other clinical factors, the treating physician may proceed to discharge the subject home or change the plan to escalate immunosuppression to plasma exchange for continued treatment of the acute exacerbation. Before discharge from the hospital, the subject will be scheduled for follow up in the NMO Clinic within 90 days and 6 months. Findings by MRI that may influence escalation to plasma exchange typically include extension of enhancement, involvement of new areas of the nervous system or an increase in the area of T2 hyperintensity. Historically among the NMO/NMOSD

	subjects treated at Johns Hopkins, approximately 50% of NMO/NMOSD subjects improve from a relapse with steroids alone. The other 50% require escalated care with plasma exchange. <u>Plasma Exchange Treatment Phase</u> Should subjects not meet above clinical criteria to be discharged home, escalation to treatment with plasma exchange is standard of care. The plasma exchange treatment phase begins at the end of the Steroid Treatment Phase and will last up to 14 days. During the Plasma Exchange Treatment Phase, subjects will undergo 1.0 – 1.5 volumes of plasma exchange every other day according to standard of care. At the end of this phase, a second MRI may be performed to compare to admitting MRI. If any further acute immunosuppressive treatment for the acute NMO flare is required and provided according to standard of care, the subject will continue to be followed for safety issues, but the clinical efficacy data will not be included in the statistical analysis. Historically among NMO/NMOSD patients treated at the Johns Hopkins Hospital, approximately 95% of NMO/NMOSD patients who complete plasma exchange are discharged following completion of the plasma exchange. <u>Follow-up</u> Every month after discharge, subjects will be followed with monthly B cell counts until their B cell counts replete to a minimum of 0.5% for patients who will continue to be treated with B-cell depleting agents for preventive care, according to standard of care, or to a minimum of 5% for patients who will use other preventive strategies. In addition, complete blood counts with differential to track neutrophil counts and complete metabolic profiles will be completed monthly as well. The secondary efficacy outcome is neurologic function at follow up 90 days and 6 months after initial hospitalization for the acute relapse. In addition to a thorough history and physical examination, including EDSS rating, visual examination and timed walk, a research MRI of the spine will be performed at day 90 to compare to the relapse lesion.
Trial visits	Screening (Day 0), Steroid Treatment Phase (Days 1 to 5), Plasma Exchange Treatment Phase, if necessary (Days 6 to 20), and Follow-up (monthly blood tests and visits on Days 90 and 180).
Baseline Lab Evaluation (Local Lab)	• CBC with differential (3 part differential is acceptable) • Serum chemistry • Serology HIV, HCV, HBV (See Appendix A) • Serum pregnancy test; at screening and at the end of treatment. • Fibrinogen level • B cell count by limited flow cytometry panel
Instrumental tests	• MRI of the affected area (brain, cervical spine, thoracic spine) with and without gadolinium contrast.
Dosing Regimen	All subjects will receive 5 days of intravenous 1000 mg methylprednisolone (referred to generically as “steroids”) as per the current standard of care. Subjects will all receive 450 mg/day of UTX infused over four hours as close to the onset of steroid treatment as possible, during the Steroid Treatment Phase. Therefore all subjects will receive UTX + steroids. All subjects will receive pre-medication prior to infusion of UTX.

	Premedication: Approximately 30 minutes prior to the infusion of 450 mg/day of UTX, subjects will be pre-medicated with an antihistamine (diphenhydramine 25 mg or equivalent). Use of oral acetaminophen 650 mg (or equivalent) will be allowed for subjects who experience fever or pyrexia, or as clinically warranted.
Inclusion and Exclusion criteria	Subjects eligible for enrollment must meet all of the following criteria: 1. Able and willing to provide written informed consent. 2. 18-100 years of age. 3. New acute optic neuritis and/or transverse myelitis. A new clinical event is defined as a clinically significant neurologic deficit(s) on physical exam, not attributable to another disease process, which is different from baseline neurological exam, and attributable to a lesion in the spinal cord, optic nerve or brainstem. New symptoms must be reported within 10 days of onset. 4. Confirmed or highly suspected diagnosis of NMO according to the 2006 revisions of the Wingerchuk diagnostic criteria for NMO (Wingerchuk, 2006), or AQP4 positive NMOSD per the EFNS Guidelines. For NMO, subjects must have two absolute criteria: a. optic neuritis b. myelitis **and** at least two of three supportive criteria: c. presence of a contiguous spinal cord MRI lesion extending over three or more vertebral segments, d. MRI criteria NOT satisfying the revised McDonald diagnostic criteria for MS [Polman, 2011] e. NMO-IgG (AQP4) in serum. For NMOSD, subjects must have longitudinally extensive transverse myelitis (LETM) recurrent isolated optic neuritis (RION)/bilateral optic neuritis (BON), or opticospinal multiple sclerosis (OSMS) that is NMO-IgG or AQP4 antibody positive. 5. The B cell count must be normal (5-20% of total lymphocytes) in subjects who have not received another B cell depleting therapy in the past year. For those on B cell depleting therapy within the past year, a B cell count of at least 0.5% of total lymphocytes is necessary. 6. A female subject is eligible to enter the trial if she is: o Not pregnant or nursing; o Of non-childbearing potential (i.e. women who have had a hysterectomy, are post-menopausal, which is defined as >2 years without menses or, in female subjects who have been post-menopausal for <2 years, must be confirmed with Follicle Stimulating Hormone (FSH) and estradiol levels), have both ovaries surgically removed or have current documented tubal ligation) OR

Of child-bearing potential (i.e. women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea (even severe), women who are perimenopausal or have just begun to menstruate.

- Subject has a negative serum pregnancy test at screening and agrees to one of the following:
  a. Complete abstinence from intercourse for the period from consent into the trial until 6 months after the last dose of investigational product; or,
  b. Consistent and correct use of one of the following acceptable methods of birth control for the period from consent into the trial until 6 months after the last dose of investigational product:
     i. Oral contraceptives (either combined or progesterone only)
     ii. Injectable progesterone
     iii. Levonorgestrel implants
     iv. Estrogenic vaginal ring
     v. Percutaneous contraceptive patches
     vi. Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of <1% per year
     vii. Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the trial; this male must be the sole partner for the subject
     viii. Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).

Exclusion Criteria

Subjects meeting any of the following criteria are **not** eligible and cannot enroll in the trial:

1. 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: progressive multifocal leukoencephalopathy (PML), chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis, or active hepatitis C.
   b. Previous serious opportunistic or atypical infections.
   c. History of positive serology for hepatitis B.
   d. Prior history, or suspicion, of tuberculosis (TB).
   e. History of positive serology for HIV.
2. History of clinically significant CNS trauma (e.g. traumatic brain injury, cerebral contusion, spinal cord compression)
3. Past or current history of medically significant adverse effects (including allergic reactions) from:

	a. Corticosteroids b. Diphenhydramine c. Murine or mouse/human chimeric antibodies 4. Past or current malignancy, except for a. Cervical carcinoma Stage 1B or less b. Non-invasive basal cell and squamous cell skin carcinoma c. Cancer diagnoses with a duration of complete response (remission) >5 years **A history of hematologic malignancy excludes a subject from participation, regardless of response.** 5. 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. 6. Use of an investigational drug or other experimental therapy for a condition other than NMO within 4 weeks, 5 pharmacokinetic half lives or duration of biological effect (whichever is longer) prior to screening. 7. Current participation in any other interventional clinical trial. Participation in non-interventional trial requires approval of the protocol by investigator. 8. Subjects who are concurrently receiving any other investigational agents, or have participated in an interventional clinical trial within the last 21 days, or subjects who have been vaccinated with a live vaccine < 2 months prior to trial inclusion. 9. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ublituximab breastfeeding should be discontinued if the mother is enrolled.
Number of subjects	Five (5) subjects will be enrolled to receive UTX + steroids.
Populations	**Intention-To-Treat (ITT)** – all subjects who received one dose of trial medication (UTX) **Per Protocol (PP)** – all subjects who performed all visits in accordance with protocol without significant protocol deviations or violations **Safety Population** – all subjects that receive one dose of trial drug (UTX)
Statistical issues	Primary Safety Assessments: A summary of the number and percentage of subjects with any adverse event (AE), any serious adverse event (SAE), adverse events leading to permanent discontinuation of trial drug and trial drug-related adverse events will be reported. Secondary Efficacy Assessments: Change in neurologic outcomes on the EDSS, Timed 25-Foot Walk and HCVA scales from admission to discharge (Day 5 or 21), and follow up (Days 90 and 180) will be analyzed by paired t-tests with significant p-values considered less than 0.05. A clinical neurologic improvement is commonly

	observed in > 66% of NMO subjects treated at the Johns Hopkins Hospital. The degree of improvement in this trial population has not been adequately quantified historically. By MRI, length of T2 hyper-intensity and length of T1-post contrast enhancement should be stable or reduced by discharge. A paired t-test will be used to compare these values with significance considered at p-values less than 0.05.
Sample size	The sample size of 5 subjects in this single arm study (UTX + steroid) is based on feasibility and logistical considerations on the number of subjects that will ensure a reliable safety report of ublituximab-mediated B cells depletion in the NMO patient population. An independent Data and Safety Monitoring Board (DSMB) will be composed of five members with at least one member who is an Infectious Disease Specialist, Hematologist, Neurologist, Statistician, and another independent expert with experience on assessing safety. Three of the DSMB members will be on staff at the Johns Hopkins University. The DSMB will be reviewing the safety data after the first two subjects are enrolled and completing the Steroid Treatment Phase to determine if it safe to continue the trial. The DSMB will submit their findings to the Sponsor after every meeting and to the IRB. DSMB meetings can be in-person or via teleconference or a combination of the both. The data to be used for review by the DSMB will be actual raw data recorded in the database. The clinical data will be monitored by TG Therapeutics and will be query-free prior to review by the DSMB.
Duration of Subject Participation	Up to 9 months

Abbreviations and Definition of Terms	
Ab	Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AQP4	Aquaporin-4
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Class
BON	Bilateral Optic Neuritis
Ca	Calcium
CBC	Complete Blood cell Count
CDC	Complement-Dependent Cytotoxicity
CLL	Chronic Lymphocytic Leukemia
CRF	Case Report Form
CNS	Central Nervous System
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
D, d	Day
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDDS	Expanded Disability Status Scale
Fab	Fragment antigen binding (region)
Fc	Fragment crystallizable (region)
FU	Follow-up
GCP	Good Clinical Practice
HCVA	High Contrast Visual Acuity
IEC/IRB	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Ig	Immunoglobulin
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
kD	kilo Dalton
LDH	Lactate Dehydrogenase
LETM	Longitudinally Extensive Transverse Myelitis
LLT	Lowest Level Term
MRT	Mean Residence Time
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NCI-WG	National Cancer Institute – Working Group
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
OSMS	Opticospinal sclerosis

Abbreviations and Definition of Terms	
PD	Pharmacodynamic or Progressive Disease
PML	Progressive Multifocal Leukoencephalopathy
PPS	Per Protocol Set
PT	Preferred Term
PN	Preferred Name
RCT	Randomized Clinical Trial
RION	Recurrent Isolated Optic Neuritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPE	Serum Protein Electrophoresis
t1/2	Half-Life of Elimination
V	Visit
WHO	World Health Organization

1 BACKGROUND

1.1 RATIONALE

Neuromyelitis Optica (NMO) is a severe, demyelinating autoimmune disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Although historically considered a subtype of multiple sclerosis (MS) with overlapping symptoms, NMO is distinct radiologically and prognostically and has a pathophysiology unresponsive to typical MS treatments [Weinshenker 2007; Kimbrough, et al., 2012]. In 2004, an antibody targeting the water channel protein, aquaporin-4, was found to be associated with NMO. Compared to MS, NMO exhibits an older age at onset, a poorer prognosis, and a rarity of cerebrospinal fluid oligoclonal IgG bands. NMO attacks typically produce moderate to severe disability that leads to accumulation of disability with each attack; between attacks, patients generally remain neurologically stable without evidence of progressive deterioration. Therefore, it is crucial that aggressive treatment for each relapse is optimized to prevent disability.

NMO affects predominantly females, with a female to male ratio of 6.5:1. The relative frequency of NMO among demyelinating disorders is quite variable, being higher in Asian, Hispanic and African populations compared to whites. The few population-based prevalence studies of NMO conducted provide prevalence rates of 0.32 to 3.1 per 100,000 in the non-white population [Nandhagopal, et al., 2010]

Clinically definite NMO is defined by a history of optic neuritis and history of transverse myelitis with a non-MS brain MRI, longitudinally extensive myelitis lesions and/or presence of the NMO-IgG biomarker. Seronegative NMO patients with transverse myelitis and optic neuritis must have longitudinally extensive myelitis and a brain MRI that is not typical for multiple sclerosis. NMO Spectrum Disorder (NMOSD) is defined as AQP4 antibody positive individuals with *either* optic neuritis or transverse myelitis.

NMOSD comprise the spatially limited syndromes of longitudinally extensive transverse myelitis (LETM), recurrent isolated optic neuritis (RION)/bilateral optic neuritis (BON), and Asian opticospinal multiple sclerosis (OSMS), as long as patients test positive for the anti-AQP4 antibody [Sellner, et al., 2010]. Bizzoco, et al., reported that 7 of 13 (56%) NMOSD patients from Tuscany developed clinically definite NMO after a follow-up time of at least 2 years with the other six (46%) remaining NMOSD. Weinshenker et al., prospectively studied 29 patients with a first event of LETM. Within 1 year, 6 of the 11 seropositive (AQP4+) patients had a relapse of myelitis (indicative of recurrent transverse myelitis) or developed optic neuritis (indicative of neuromyelitis optica). By contrast, no seronegative patients relapsed over 1–7 years follow-up. NMO and Asian OSMS have similar neuroimaging, serological, and immunopathological characteristics, and the difference is primarily one of classification as in Japan these individuals are diagnosed with MS, but in North America and Europe, these patients are diagnosed with NMO [Matsuoka, et al., 2007; Wingerchuk et al., 2007].

The current standard of care for treatment of acute NMO attacks of both optic neuritis and transverse myelitis is a 5-day course of high dose methylprednisolone (1000 mg daily)(Kimbrough 2012). In some patients, this course of steroid treatment is sufficient to suppress CNS inflammation and reverse some neurologic dysfunction. Factors that may predict success with steroids alone include a small CNS lesion caught early in the process and concurrent preventive immunosuppression. In many patients, steroids are not sufficient to suppress CNS inflammation, and treatment escalation to plasma exchange is necessary. Five cycles of 1.0 – 1.5 volume exchanges require an additional 2-week inpatient hospitalization and a central line catheter. Plasma exchange carries a 4-10% risk of line infection or thrombotic complications. Despite these risks, plasma exchange is standard of care in steroid-unresponsive patients because it is 50-70% effective in reducing active CNS inflammation and reducing inflammatory damage in this patient population

(Szczepiorkowski 2010). Ultimately, neurologic recovery after high dose steroids and plasma exchange can be stratified into three groups: a group that does not improve at all, a group that improves some but maintains a significant neurologic deficit and a group that improves well if not back to baseline.

The rationale for using ublituximab is based on the known roles of B cells, antibody production and plasma cells in the pathophysiology of NMO. NMO is characterized by the presence of an anti-AQP4 antibody, which can only be produced by differentiation of B cells to plasma cells. Because these anti-AQP4 antibodies may be pathogenic, B cells recognizing AQP4 may be directly involved in the disease process as well. B cells also play a role as potent antigen presenting cells in NMO. The strongest evidence of the importance of B cells in NMO comes from studies of B cell depletion, most commonly with anti-CD20 monoclonal antibody, rituximab (Rituxan®). Rituximab has been shown in five retrospective and two prospective studies to be effective in reducing NMO relapses up to 90% and achieving remission in up to 80% of patients solely by its action on CD20+ B cells, despite no change in plasma cell population and anti-AQP4 antibody titers. These human trials strongly suggest a critical role for B cells in the pathophysiology of human disease. While typically used in the prevention of disease, B-cell depletion may be beneficial in the treatment of an acute relapse as well. Emerging evidence indicates that peripheral B cells are activated during a relapse and plasmablast production of anti-AQP4 antibodies spikes. B cells are also found within acute lesions of the spinal cord and optic nerve suggesting roles both in the blood and in the central nervous system during a relapse.

1.2 INVESTIGATIONAL AGENT

Background

Ublituximab is a novel third generation chimeric anti-CD20 monoclonal antibody bioengineered for enhanced activity, exhibiting a unique glycosylation profile with a low fructose content. Ublituximab has been designed to introduce superior antibody-dependent cell-mediated cytotoxicity (ADCC) while maintaining competitive complement-dependent cytotoxicity (CDC). Ublituximab has also been demonstrated to induce programmed cell death (PCD). Ublituximab has a unique protein sequence, targeting epitopes on CD20 not targeted by rituximab or ofatumumab.

Preclinical Evaluations of Ublituximab

In Vitro Activity

The monoclonal antibody, ublituximab, demonstrated an enhanced ability to kill chronic lymphocytic leukemia (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-2 (IL2) production by FcγRIIIA+ Jurkat cells [de Romeuf et al. 2008]. 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. [Baritaki et al., 2011]

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. [Esteves et al., 2011]

Toxicology

The non-clinical toxicology program was performed according to ICH S6 guideline "Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals" (Investigator Brochure). The toxicity studies performed to establish the safety of ublituximab were conducted according to Good Laboratory Practice (GLP) requirements, including validation of the analytical method used for the serum analysis of ublituximab. The clinical toxicology studies conducted to date with ublituximab are summarized in Table 1 below.

Table 1: Toxicology

Type of study	Test system	Method of administration	Doses	Report n°	GLP
Single dose toxicity	Cynomolgus monkey	IV	Single dose 2 weeks observation 0, 0.3, 10 and 100 mg/kg	CIT 32879 TAP	Yes
Repeated dose toxicity	Cynomolgus monkey	IV	Weekly for 4 weeks 0, 10 and 50 mg/kg	CIT 32880 TSP	Yes
Cytokine release	Cynomolgus monkey	IV	5, 20, 60 minutes and 6 hours 10 and 50 mg/kg	CIT32880TSP	Yes
Local tolerance	Cynomolgus monkey	IV	4 weeks 10 and 50 mg/kg	CIT 32880 TSP	Yes
Local tolerance	New Zealand white rabbit	IA and PV	Single dose 10 mg/kg	CERB 20070605TL	Yes
Mutagenicity (Ames test)	Salmonella typhimurium	In vitro	N/A 0, 1, 3, 10, 30 and 100 µg/plate	IPL 070522	Yes
Immunogenicity	Cynomolgus monkey	IV	Single dose, 2-week observation 0.3, 10 and 100 mg/kg	CIT 32879 TAP	Yes
Immunogenicity	Cynomolgus monkey	IV	4-week 10 and 50 mg/kg	CIT 32880 TSP	Yes

CIT: Centre International de Toxicologie *(International Toxicology Centre),* **CERB**: Centre de Recherches Biologiques (*Centre for Biological Research*). **IPL**: Institut Pasteur de Lille (*Lille Pasteur Institute*)

In single-dose toxicology studies, 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 (Investigator Brochure).

A repeated-dose GLP toxicology study treated cynomolgus monkeys with ublituximab intravenously at doses of 0, 10 or 50 mg/kg weekly for 4 consecutive weeks. At 10 mg/kg, no evidence of treatment-related toxicity was observed except for the expected pharmacological effect on white blood cell and lymphocyte counts (small decrease due to loss of B cells); no toxicological effects on the hematological or blood biochemistry parameters evaluated were observed. At 50 mg/kg dose, two animals presented with poor general clinical signs (hypothermia, hypoactivity and prostration). The female showed these symptoms starting on day 15 and was prematurely sacrificed on day 20 after the third administration of ublituximab, whereas the male presented with these clinical signs after the fourth infusion and recovered with symptomatic treatment.

In relation to the primary activity of ublituximab, lymphoid depletion was induced in the spleen and lymph nodes at both the 10 mg/kg and 50 mg/kg doses. In some animals, a decrease in thymus and spleen weights was observed. Histopathological examination showed spleen and lymph node atrophy, more pronounced at the 50 mg/kg dose. Additional changes affecting the hematolymphopoietic compartment (CD20-expressing cells) were found in the lungs, liver, kidneys, adrenals (leukocytosis, extramedullary hematopoiesis) and bone marrow (increased myeloid/erythroid ratio). In different organs of some animals, many immature cells were observed within the vessels.

Hepatic inflammation was demonstrated at the 10 mg/kg dose in 1 of 6 animals. Histopathology demonstrated a "cluster" of hepatic lesions: minimal single cell necrosis, slightly activated Kupffer cells and minimal inflammatory changes. It should be noted that the B-cell depletion in the peripheral blood as well as in bone marrow was particularly marked in this animal; upon necropsy, reduction of B-cells was 99% in the bone marrow, whereas this value reached approximately 68% in the other monkeys treated with 10 mg/kg. At the 50 mg/kg dose single-cell necrosis was minimal (n=2) or slight (n=2) for 4 of the 6 monkeys and activation of the Kupffer cells was slight (n=2) or moderate (n=1) in 3 out of these 4 animals. Some inflammatory changes were noted.

A possible hypothesis to the observed minimal hepatic lesions is the resurgence of pathogens caused by the immunosuppressed state of the animal. As the liver enzyme activities (AST, ALT) were not modified and since ublituximab did not cross-react with the liver in the tissue-cross reactivity assay, this finding was considered a non-adverse effect. Based on these toxicology studies in non-human primates, the liver could be a target organ and special attention should be paid to hepatic monitoring, and to subclinical infections, which can impact hepatic parameters such as chronic hepatitis.

Clinical Development of Ublituximab

To date, 33 patients with relapsed or refractory CLL have been treated in a first-in human dose escalation study (protocol CD20-0703). Patients received either one weekly infusion of single agent ublituximab for 4 doses at 5 different dose levels (part I) or a weekly 8-dose regimen at one dose level (part II). Part II used an initial dose of 150 mg followed by 7 doses of 450 mg (total dose 3300 mg).

Pharmacokinetics

After injection of ublituximab with a 150 mg dose followed by seven weekly injection with 450 mg, results suggested non-linear pharmacokinetics with dose (450 mg vs 150 mg) and time (week 4 vs week 8): 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 eighth infusion of ublituximab are presented in Figure 1. A summary of non-compartmental PK parameters after the first, the fourth and the eighth infusion of ublituximab are presented in Table 2.

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

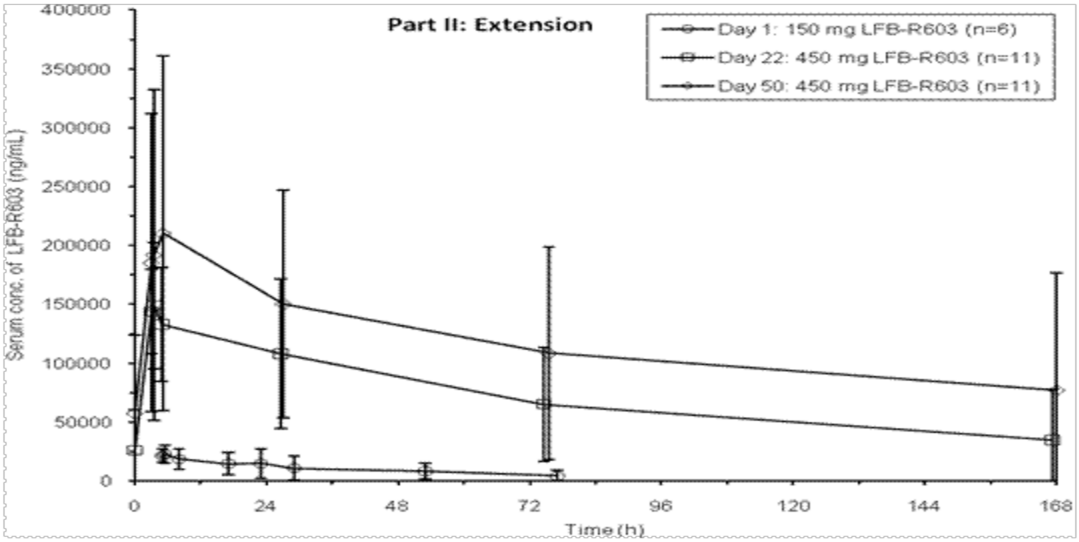


Table 2: Pharmacokinetic results after the 1st (150 mg), the 4th (450 mg) and the 8th (450 mg) infusion of ublituximab

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

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

Concentration was still measurable in at least one 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.

Safety

A total of 315 adverse events (AEs) were experienced by the 33 patients, 170 (54%) of them deemed related to ublituximab. Among these 170 drug-related AEs, 149 (88%) occurred from the time of the first infusion to one week after the last infusion of ublituximab, 28 (16%) were grade 3 (according to the NCI-CTCAE v3.0) and 11 (6%) were grade 4 AEs.

At least one drug-related AE occurred after the first ublituximab infusion in each patient, after the second infusion in 19 patients (58%), after all subsequent infusions in 16 patients (48%) and more than one week after the last infusion in 11 patients (33%). Twenty (61%) patients (12/21 in part I, 8/12 in part II) presented with at least one grade 3 drug-related AE and 9 (27%) patients (5/21 in part I, 4/12 in part II) presented with at least one grade 4 drug-related AE. No drug related mortality was recorded.

The most frequent drug-related AEs were infusion-related reactions (20 patients; 61%), pyrexia (19 patients; 58%), neutropenia (15 patients; 45%), thrombocytopenia (10 patients; 30%), infections (9 patients; 27%), headache (8 patients, 24%), chills (7 patients; 21%), elevated liver enzymes (6 patients; 18%), nausea (4 patients; 12%), asthenia (4 patients; 12%), and pancytopenia

(3 patients; 9%). Late drug-related AEs, i.e. occurring more than one week after the last infusion of ublituximab, consisted essentially of infections (n=12) and neutropenia (n=4).

Twenty-three infusion-related reactions (IRRs) were reported in 20 patients, 16 of them grade 2 and 7 (3 in part I, 4 in part II), grade 3. Sixteen of these 23 IRRs occurred after the first infusion of ublituximab, 3 after the second infusion and 4 after subsequent infusions. Grade 3 infusion-related reactions required infusion interruption and resolved without sequelae after symptomatic treatment such as corticosteroid, antihistamines, oxygen therapy, and bronchodilators in case of bronchospasm.

Twenty three episodes of drug-related pyrexia were reported in 20 patients; mild (< 39°C) for 20 episodes and moderate (from 39 to 40°C) for 3 episodes. Headaches, chills, nausea and asthenia were all reported as mild to moderate AEs.

Fifteen drug-related infections were reported in 9 patients. Ten of these AE's were mild to moderate respiratory tract infections, herpes recurrences or anal abscesses. One grade 3 listeriosis was diagnosed at the time of the 4th infusion followed by a grade 3 bronchopulmonary aspergillosis 2 months later. One grade 3 varicella was reported in one patient and required IV treatment with acyclovir. Another patient with a medical history of aortic valve replacement and staphylococcal endocarditis receiving ublituximab presented with 2 grade 4 episodes, *Streptococcus agalactiae* sepsis then *Staphylococcus aureus* sepsis with endocarditis. Evolution was favorable after antibiotic therapy. All these infections resolved without sequelae except *Staphylococcus aureus* sepsis complicated with endocarditis, which resolved after valve replacement.

Twenty episodes of drug-related neutropenia were observed in 15 patients as well as 2 additional cases of febrile neutropenia. Eight episodes (40%; 4 in part I and 4 in part II) were grade 3 neutropenia and 7 episodes (35%; 3 in part I and 4 in part II) were grade 4. In part I, all episodes but one occurred within 8 days after the first dose and resolved spontaneously despite continuation of the treatment with ublituximab. By contrast, in part II, grade 3-4 neutropenia was observed after the third infusion in 3 cases, after the 7th or 8th infusion in 3 cases, and later in the last two cases. Treatment with granulocyte colony stimulating factor (G-CSF) was started in 4 cases leading to recovery to normal value within 1 to 3 days. Four cases resolved spontaneously.

Eleven episodes of drug-related thrombocytopenia were reported in 10 patients consisting of 10 grade 1-2 and 1 grade 3. Nine of the episodes reported occurred less than 48h after the start of ublituximab infusion.

Drug-related pancytopenia was reported in 3 patients (1 grade 3 and 2 grade 4 episodes). For all of them, mild to moderate pre-existing pancytopenia was present at baseline. All but one patient fully recovered. The last one was prematurely withdrawn from the study due to diagnosis of a concomitant secondary leukemia.

Six patients each experienced one drug-related elevated liver enzyme event, (i.e. increase over 2x in ALT alone, or ALT/Alkaline Phosphatase ratio > or equal to 5) (see Table 3). Five out of these 6 episodes were grade 3 AEs whereas the 6th was grade 2. Four episodes occurred soon after the first infusion, one occurred after the second infusion, and the last one was observed after the 4th infusion in a patient with a medical history of chronic mixed hepatocellular and cholestatic liver disorder. All of them were asymptomatic, isolated, and transient. Neither increased level of bilirubin nor impaired protein synthesis were reported. Recovery was spontaneous without recurrence after a subsequent ublituximab infusion.

Table 3: Grade 2-3 elevated liver enzyme suspected to be related to ublituximab

Cohort	Patient number	Grade

A	01-01	3
C	07-03	3
E	02-02	2
E	03-03	3
II	03-06	2
II	01-06	3

No patients were found to be positive for anti-ublituximab antibodies up to 12 months after the start of the study.

Among the 315 aforementioned AEs, 39 were reported as serious adverse events (SAE), 23 of them being suspected to be related to the study drug (see Table 4). It is to note that these 23 SAEs occurred in 15 patients. All of these SAEs resolved without sequelae except *Staphylococcus aureus sepsis* (patient 04-04) and a case of pancytopenia due to a secondary leukemia for which the patient was prematurely withdrawn from the study.

Table 4: Drug-related serious adverse events listing

Cohort	Patient number	SAE	Grade*
A	05-01	Infusion related reaction	3
A	07-01	Listeriosis	3
A	07-01	Bronchopulmonary aspergillosis	3
D	01-03	Pyrexia	2
D	04-04	Streptococcal sepsis	4
D	04-04	Staphylococcal sepsis complicated with endocarditis	4
E	01-04	Febrile neutropenia	3
E	02-02	Acute infusion reaction	3
E	02-02	Pancytopenia	4
E	03-04	Acute infusion reaction	3
E	03-04	Varicella	3
II	02-03	Neutropenia	4
II	02-03	Pyrexia	1
II	03-06	Elevated Liver Enzymes	3
II	03-06	Neutropenia 1	4
II	03-06	Neutropenia 2	4
II	03-07	Pyrexia	2
II	03-09	Acute infusion reaction	3
II	04-05	Acute infusion reaction	3
II	06-06	Acute infusion reaction	3
II	03-08	Neutropenia	4
II	01-06	Pancytopenia	4
II	01-06	Febrile neutropenia	3

* according to CTCAE v3

None of the aforementioned AEs has been considered as a dose-limiting toxicity according the judgment of the study Safety Committee. Therefore, the maximum tolerated dose has not been reached yet.

Efficacy

Demographic data for the patients enrolled in the study were as follows. The median age of the 33 patients was 64 years (range 43-77). Patients had received 3 (range 1-8) lines of anticancer therapy prior to study entry, 6 of them refractory to their most recent treatment. Eighteen patients (55%) were previously treated with a rituximab-containing therapy at the time of inclusion into the study. All patients but one presented with lymph node enlargement, 11 (33%) of them having a bulky (>5cm) lymphadenopathy. Twenty one patients (68%) presented with splenomegaly and 5 (15%)

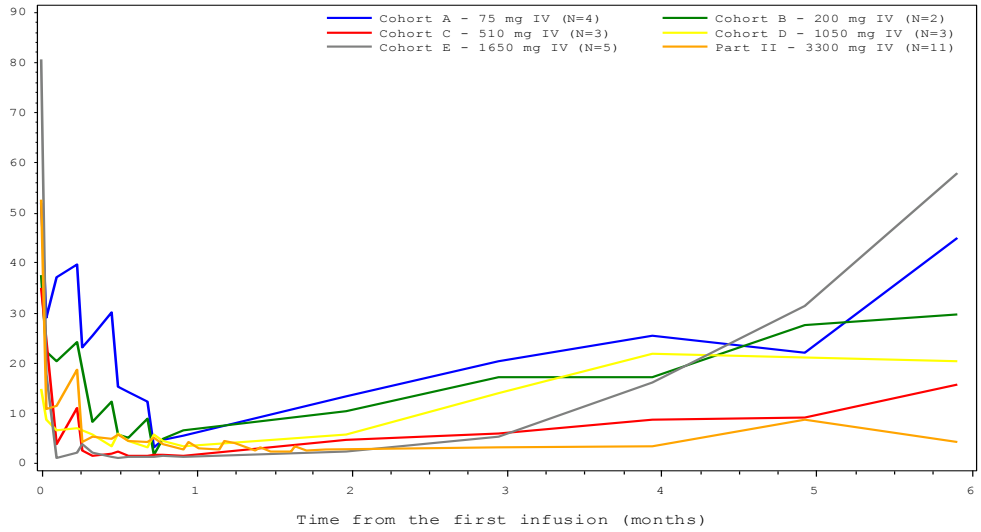
with hepatomegaly. Median blood lymphocyte count was 36.7 x 109/L (range 4.37-214). Median hemoglobin and platelet levels were 11.9 g/dl and 107 x 109/L, respectively. Thirteen (39%) patients had an IgG value <6 g/L.

Clinical response was based on the criteria established by the National Cancer Institute (NCI)-Working Group updated in 2008 (5). Response data were available for 29 patients, 18 out of 21 in part I and 11 out of 12 in part II. No complete responses were observed whatever the cohorts. Twelve (41%) patients were in partial response (PR) at month 4, 5/18 in part I, and 7/11 in part II. PR was confirmed 2 months later in 8 (28%) patients, 3/5 in part I and 5/7 patients in part II.

Immune Effects

Significant blood lymphocyte depletion was observed in all patients reflecting the intended biological activity of ublituximab. In the 4-dose part of the study, lymphocyte depletion was maximal one week after the 4th dose of ublituximab with a median lymphocyte count of 0.9 x 109/L in cohort E, corresponding to 97% relative change, persisting one month later (see Figure 2). In the 8-dose part of the study, the lymphocyte count nadir was unchanged but a profound (close to 90%) depletion was sustained until 6 months after start of therapy.

Figure 2: Mean Blood Lymphocyte Count



Studies in Special Populations

Ublituximab has not been evaluated in pediatric populations, or in pregnant woman.

1.3 MAGNETIC RESONANCE IMAGING IN THE TRIAL

The trial will utilize MRI for spine imaging with and without contrast during the trial for relapses, as per standard of care on admission and for research purposes on follow-up. In cases of poor creatinine clearance, contrast will not be used.

For purposes of this trial, trial staff will review standard of care MRIs of the spine and/or optic nerves; the following characteristics will be recorded for research purposes:

1. Length of sagittal spine T2 lesion in centimeters in all subjects who obtain MRIs, and
2. Length of sagittal spine T1-post contrast lesion in centimeters and/or orbital T1-post contrast lesion in millimeters in those subjects who additionally receive gadolinium contrast.

A single reader will review the MRI for research purposes and will be independent of the trial. The reader will also be blinded to the time sequences of the scans.

1.4 USE OF PLASMA EXCHANGE

All subjects who fail to clinically respond by Day 5 in the Steroid Treatment Phase will be recommended for plasma exchange as per standard of care. A beneficial response is generally considered an improvement in the specific deficit(s) that led to the hospitalization. Depending on those specific deficits, the criteria that are routinely used at Johns Hopkins to indicate treatment response(s) in motor, sensory, autonomic and visual function are:

1. An improvement in strength by the Motor Research Council strength scale by at least 1 full point in at least two isolated muscles of at least one limb, or
2. An increase of two Rydel tuning fork units in at least one affected limb.
3. Improvement in bowel and/or bladder function from incontinence to at least partial voluntary control.
4. An improvement in visual acuity using bedside Snellen equivalent of ≥ 2 lines.

If subjects do not require escalation to plasma exchange because they fulfill the clinical criteria above, an MRI may be performed to confirm resolution of the inflammatory lesion(s) compared to admission MRI. Based on the MRI and other clinical factors, the treating physician may proceed to discharge the subject home or change the plan to escalate immunosuppression to plasma exchange for continued treatment of the acute exacerbation.

Before discharge from the hospital, the subject will scheduled for follow up in the NMO Clinic for the 90 and 180 day visits. Findings by MRI that may influence escalation to plasma exchange typically include extension of enhancement, involvement of new areas of the nervous system or an increase in the area of T2 hyperintensity. Historically among the NMO/NMOSD patients treated at Johns Hopkins, approximately 50% of NMO/NMOSD patients improve from a relapse with steroids alone. The other 50% require escalated care with plasma exchange.

Plasma Exchange Treatment Phase

Should subjects not meet above clinical criteria to be discharged home, escalation to treatment with plasma exchange is standard of care.

The plasma exchange treatment phase begins at the end of the Steroid Treatment Phase and will last up to 14 days. During the Plasma Exchange Treatment Phase, subjects will undergo 1.0 – 1.5 volumes of plasma exchange every other day according to standard of care. At the end of this phase, a second MRI may be performed to confirm resolution of the lesion. If any further acute immunosuppressive treatment for the acute NMO flare is required and provided according to standard of care, the subject will continue to be followed for safety issues, but the clinical efficacy data will not be included in the statistical analysis. Historically among NMO/NMOSD patients treated at the Johns Hopkins Hospital, approximately 95% of NMO/NMOSD patients who complete plasma exchange are discharged following completion of the plasma exchange.

Plasma exchange will likely clear remaining circulating ublituximab. However, by the time plasma exchange is initiated on day 6 of hospitalization, 5 days after the drug infusion, most, if not all, of the circulating B cells will already have been eliminated as shown in Figure 2. Although there is no experimental pharmacokinetic data in patients who undergo plasma exchange 5 days after receiving ublituximab, experience with rituximab, a similar B cell depleting agent, used in this patient population suggests that acute B cell depletion prior to plasma exchange is not harmful but the effect of rituximab may wear off sooner than in patients without plasma exchange. This may be due to effects of rituximab outside of the circulation (e.g., bone marrow) that normally leads to 6-8 months of circulatory B cell depletion. As with rituximab, plasma exchange may also shorten the duration of circulatory B cell depletion due to ublituximab in NMO patients. These effects will be monitored by monthly B cell counts.

2 OBJECTIVES

The overall objective is to assess the safety of ublituximab as add-on therapy to steroids for treatment of acute optic neuritis and/or transverse myelitis in NMO and NMOSD.

2.1 PRIMARY OBJECTIVES

To assess safety of acute B cell depletion in NMO subjects with acute relapse of optic neuritis or transverse myelitis who are treated with ublituximab + steroids beginning on dose administration and ending with repletion of circulating B cells.

2.2 SECONDARY OBJECTIVES

- To determine the B cell depletion pharmacokinetics of ublituximab in the NMO patient population with monthly B cell counts.
- To determine the pharmacokinetics of ublituximab in NMO patients.
- To determine the frequency of adverse events with ublituximab in the NMO patient population.
- To follow clinical endpoints for preliminary evidence of efficacy. Clinical outcomes will be monitored for efficacy using three functional neurologic tests, the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk and High Contrast Visual Acuity (HCVA) during admission to the hospital and two follow up visits, 90 days and 6 months after hospitalization. Additional clinical endpoints will include:
    - MRI lesion size
    - Number of days in hospital
    - Requirement for plasma exchange rescue therapy
- To assess for the effect of immunogenicity on the pharmacokinetics, pharmacodynamics, and safety of ublituximab.

3 SUBJECT SELECTION

3.1 ELIGIBILITY CRITERIA

Subjects eligible for enrollment must meet all of the following criteria:

1. Able and willing to provide written informed consent.
2. 18-100 years of age.
3. New acute optic neuritis and/or transverse myelitis. A new clinical event is defined as a clinically significant neurologic deficit(s) on physical exam, not attributable to another disease process, which is different from baseline neurological exam, and attributable to a lesion in the spinal cord, optic nerve or brainstem. New symptoms must be reported within 10 days of onset.
4. Highly suspected or confirmed diagnosis of NMO according to the 2006 revisions of the Wingerchuk diagnostic criteria for NMO (Wingerchuk, 2006), or AQP4 positive NMOSD per the EFNS Guidelines. For NMO, subjects must have two absolute criteria:

    a. optic neuritis
    b. myelitis

    and at least two of three supportive criteria:

    c. presence of a contiguous spinal cord MRI lesion extending over three or more vertebral segments,
    d. MRI criteria NOT satisfying the revised McDonald diagnostic criteria for MS [Polman, 2011]
    e. NMO-IgG (AQP4) in serum.

    For NMOSD, subjects must have longitudinally extensive transverse myelitis (LETM) recurrent isolated optic neuritis (RION)/bilateral optic neuritis (BON), or opticospinal multiple sclerosis (OSMS) that is AQP4 antibody positive
5. The B cell count must be normal (5-20% of total lymphocytes) in subjects who have not received another B cell depleting therapy in the past year. For those on B cell depleting therapy within the past year, a B cell count of at least 0.5% of total lymphocytes is necessary.
6. A female subject is eligible to enter the trial if she is:

    a. Not pregnant or nursing;
    b. Of non-childbearing potential (i.e. women who have had a hysterectomy, are post-menopausal, which is defined as >2 years without menses or, in female subjects who have been post-menopausal for <2 years, must be confirmed with Follicle Stimulating Hormone (FSH) and estradiol levels), have both ovaries surgically removed or have current documented tubal ligation)

    OR

    Of child-bearing potential (i.e. women with functional ovaries and no documented impairment of oviductal or uterine function that would cause sterility). This category includes women with oligomenorrhoea (even severe), women who are perimenopausal or have just begun to menstruate. Women of child-bearing potential must have a negative serum pregnancy test at screening and agrees to one of the following:

    1. Complete abstinence from intercourse for the period from consent into the trial until 6 months after the last dose of investigational product; or,

2. Consistent and correct use of one of the following acceptable methods of birth control for the period from consent into the trial until 6 months after the last dose of investigational product:
    a. Oral contraceptives (either combined or progesterone only)
    b. Injectable progesterone
    c. Levonorgestrel implants
    d. Estrogenic vaginal ring
    e. Contraceptive patches
    f. Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of <1% per year
    g. Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the trial; this male must be the sole partner for the subject
    h. Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).

Exclusion Criteria

Subjects meeting any of the following criteria are **not** eligible and cannot enroll in the trial:

1. 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, or active hepatitis C.
    b. Previous serious opportunistic or atypical infections.
    c. History of positive serology for hepatitis B.
    d. Prior history, or suspicion, of tuberculosis (TB).
    e. History of positive serology for HIV.
2. History of clinically significant CNS trauma (e.g. traumatic brain injury, cerebral contusion, spinal cord compression)
3. Past or current history of medically significant adverse effects (including allergic reactions) from:
    a. Corticosteroids
    b. Diphenhydramine
    c. Murine or mouse/human chimeric antibodies
4. Past or current malignancy, except for
    a. Cervical carcinoma Stage 1B or less
    b. Non-invasive basal cell and squamous cell skin carcinoma
    c. Cancer diagnoses with a duration of complete response (remission) >5 years

    A history of hematologic malignancy excludes a subject from participation, regardless of response.

5. Absolute neutrophil count less than 1000/microliter *or* platelet count less than 50,000/microliter of blood.
6. 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.
7. Use of an investigational drug or other experimental therapy for a condition other than NMO within 4 weeks, 5 pharmacokinetic half-lives or duration of biological effect (whichever is longer) prior to screening.
8. Current participation in any other interventional clinical trial. Participation in non-interventional trial requires approval of the protocol by investigator.
9. Subjects who are concurrently receiving any other investigational agents, or have participated in an interventional clinical trial within the last 21 days, or subjects who have been vaccinated with a live vaccine < 2 months prior to trial inclusion.
10. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ublituximab breastfeeding should be discontinued if the mother is enrolled.

4 REGISTRATION PROCEDURES

4.1 REGISTRATION PROCESS

To register a subject, the following documents should be completed by the research coordinator and signed by Michael Levy, MD, PhD.:

- Signed Eligibility Screening Worksheet
- Registration Form

Dr. Levy will then verify eligibility. To complete the registration process, Dr. Levy will:

- Assign a subject trial number
- Register the subject on the trial
- Start the infusion of UTX as per the protocol

After the first two (2) subjects are enrolled and completed infusion with trial drug (UTX) or after the first six months, whichever is first, the DSMB will meet to review safety. No further subjects may be enrolled into the trial until the DSMB has reviewed the study data and submitted their conclusion to the Sponsor and IRB. The DSMB will inform the Sponsor that the study may proceed as follows, to reduce the dose, or to terminate the study due to safety concerns as noted below.

DSMB Permits the Trial to Continue

If the DSMB permits the study to continue, an additional three (3) subjects will be enrolled and infused with trial drug (UTX). Upon completion of the infusion of trial drug into these additional subjects, the DSMB will meet again to review the safety data from these three subjects and the cumulative safety from this trial. The DSMB will inform the Sponsor of any safety concerns.

DSMB Terminates Trial

The Sponsor (Dr. Levy) may challenge this decision as per the DSMB charter. However, no subject may be enrolled into the trial during the challenge.

5 TREATMENT PLAN

5.1 AGENT ADMINISTRATION

Given the severity and the consequences of relapse in NMO, use of an active treatment is considered mandatory. The potential of currently utilized drugs and techniques to reduce the inflammation in NMO has been established primarily through expert consensus and small open label and retrospective studies.

Treatment will be administered in an inpatient hospital setting and absolute neutrophil count must be > 1000/μL and platelet count must be > 50,000/μL before infusing UTX.

Guidelines for Administration of Ublituximab

- *Method of Administration:* ublituximab will be administered as an intravenous infusion.
- Potential Drug Interactions: No drug interactions have been reported to date.
    - *Pre-medications:* All subjects receiving an infusion of UTX must be pre-medicated approximately 30 minutes prior to the dose of ublituximab with an antihistamine (diphenhydramine 25 - 50 mg or equivalent) and oral acetaminophen 650 mg (or equivalent).

NMO/NMOSD subjects will be given an infusion of 450 mg/day of UTX over four (4) hours consecutively on the first day while at the Johns Hopkins Hospital.

5.2 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's acute NMO relapse.

No steroids may be administered outside of protocol requirements for acute treatment as outlined.

Infusion Reactions with ublituximab: Infusion related reactions have been frequently reported with ublituximab. All subjects treated with ublituximab require pre-medication approximately 30 minutes prior to the dose of ublituximab with an antihistamine (diphenhydramine 25 - 50 mg or equivalent) and oral acetaminophen 650 mg. Symptomatic infusion reactions, despite pre-medication, may be treated at the discretion of the treating physician, including but not limited to: additional antihistamines, oxygen and bronchodilators.

Symptomatic treatment for neuropathic or muscular pain and muscle spasms may be treated using concomitant medication as per standard of care.

5.3 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment will begin on Day 1 with UTX and with steroids on day 1 and continue to day 5, unless one of the following criteria applies:

- Delay in transfer to the Johns Hopkins Hospital from an outside institution. In the event that an NMO patient interested in participating in the trial presents with an acute relapse to outside institution, there should be no delay in beginning treatment with standard of care steroid therapy. The subject may enroll in this trial and receive one dose of ublituximab on the first day of hospitalization at the Johns Hopkins Hospital if the transfer takes place within 5 days of presentation. Steroid treatment will continue at Johns Hopkins to ensure a total of 5 days of steroids.

- Intercurrent illness that prevents administration of treatment,
- Unacceptable adverse event(s) during the infusion of steroids or UTX,
- Subject decides to withdraw from the trial, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

The reason for trial removal and the date the subject was removed must be documented in the Case Report Form. Subjects who discontinue therapy due to an adverse event will be followed until resolution or stabilization of the adverse event.

5.4 DURATION OF FOLLOW UP

After discharge from the hospital, subjects will be followed as an outpatient clinically at days 90 and 180. In addition, subjects will be monitored monthly for B cell counts for as long as it takes for B cells to replete to a minimum of 0.5% for patients who will continue to be treated with B-cell depleting agents for preventive care, according to standard of care, or to a minimum of 5% for patients who will use other preventive strategies. For most subjects, the duration of B-cell depletion with UTX is up to 9 months. Subjects removed from the trial for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. In addition, subjects will be checked by complete blood count with differential and complete metabolic profile for evidence of toxicity to other cells (e.g., neutrophils) or organs such as kidney or liver function.

6 DOSING DELAYS/DOSE MODIFICATION

A single dose of 450 mg of ublituximab will be administered under the direction of the Principal Investigator, Dr. Michael Levy while the subject is in the hospital. It is required that the absolute neutrophil count be $\geq$ 1000/μL and the platelet count be $\geq$ 50,000 μL before the infusion. If the liver enzymes (ALT and/or AST) are > 5 times the upper limit of normal (ULN) of the normal range at the John Hopkins medical laboratory 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 acceptable range within 48 hours, the subject will not receive the ublituximab infusion and will be withdrawn from the study.

7 TRIAL ASSESSMENTS AND TREATMENT

Given the severity and the consequences of a relapse in NMO, use of an active treatment is considered mandatory. The potential of currently utilized drugs and techniques to reduce the inflammation in NMO has been established primarily through expert consensus and small open label and retrospective studies.

This is Phase 1, unblinded safety trial in NMO/NMOSD subjects in which subjects will receive one (1) infusion of 450 mg of intravenous ublituximab at the onset of an NMO exacerbation in addition to standard of care treatment with daily intravenous methylprednisolone at 1000 mg for five days.

The trial phases and durations, as well as standard of care treatment and MRIs are shown in the table below. For those who complete the trial, it is comprised of 4 potential phases: Screen, Steroid Treatment, Plasma Exchange (if necessary) Treatment and Follow-Up.

Table S1: Ublituximab in NMO Trial Phases and Timings of Treatments/MRIs

Phase:	**Screening 1 day**	**Steroid Treatment* 5 days**					**Plasma Exchange (if necessary)**	**Follow-up Monthly**	**Follow-up 90-Day Visit**	**Follow-up 6 Month Visit**
Day	0	1	2	3	4	5	6-20	30, 60, 90, 120, 150, 180, 210, 240, 270	90	180
Treatment		T[1,2]	T[1]	T[1]	T[1]	T[1]				
Exam/Lab	E/L	E/L	L	L	L	E/L	E/L	L	E	E
MRI of affected area	M					M	M		M*	

T1: Administration of methylprednisolone 1000 mg intravenously
T2: Administration of 450 mg of ublituximab intravenously
E: Neurological examination
L: Lab testing
M: MRI, as indicated by standard of care; M*: MRI for research purposes

Screening Phase

The purpose of the Screening Phase is to assess subject eligibility. This process includes an MRI scan (standard of care) to identify a contrast enhancing lesion(s) in the optic nerve and/or spinal cord.

Subjects must have circulating B cells to enroll in the trial and receive ublituximab therapy. For those who have not received B cell depleting medications in the past 12 months (rituximab, ofatumumab, ocrelizumab, ublituximab), a normal B cell count of 5-20% of total lymphocytes must be present in the circulation, confirmed by a limited flow cytometry panel of CD3, CD4, CD19 and CD20. For those who have received a B cell depleting medication in the past 12 months, a minimum of 0.5% of total lymphocytes must be B cells. The working hypothesis is that when a subject has an acute attack following preventive therapy with B cell depleting agents, the remaining or returning B-cells are very aggressive and may catalyze the attack.

Steroid Treatment Phase

High dose (1000 mg) intravenous methylprednisolone with be given to all subjects with MRI-confirmed active lesions at onset of the attack according to standard of care. During the first day of steroid treatment or as early as possible in the steroid treatment course, 450 mg of intravenous ublituximab will be administered to all subjects.

Effort will be focused on giving the ublituximab as early in the steroid treatment process as possible. If a subject's admission or transfer to the Johns Hopkins Hospital is delayed, standard of care therapy with steroids will begin as soon as possible. The subject may enroll in this trial and receive ublituximab on the first day of hospitalization at the Johns Hopkins Hospital if the transfer takes place within the Steroid Treatment Phase.

Prior to the infusion, a complete cell count with differential and complete metabolic panel screening for abnormalities in neutrophil count, platelet count and liver enzymes.

All subjects who fail to clinically respond by day 5 will be recommended for plasma exchange as per standard of care. A beneficial response is generally considered an improvement in the specific deficit(s) that led to the hospitalization. Depending on those specific deficits, the criteria that are routinely used at Johns Hopkins to indicate treatment response(s) in motor, sensory, autonomic and visual function are:

1. An improvement in strength by the Motor Research Council strength scale by at least 1 full point in at least two isolated muscles of at least one limb, or
2. An increase of two Rydel tuning fork units in at least one affected limb.
3. Improvement in bowel and/or bladder function from incontinence to at least partial voluntary control.
4. An improvement in visual acuity using bedside Snellen chart of ≥ 2 lines.

If subjects do not require escalation to plasma exchange because they fulfill the clinical criteria above, an MRI may performed to confirm resolution of the inflammatory lesion, according to standard of care at Johns Hopkins. Based on the MRI and other clinical factors, the treating physician may proceed to discharge the subject home or change the plan to escalate immunosuppression to plasma exchange for continued treatment of the acute exacerbation.

Findings by MRI that may influence escalation to plasma exchange typically include extension of enhancement, involvement of new areas of the nervous system or an increase in the area of T2 hyperintensity. Historically among the NMO/NMOSD subjects treated at Johns Hopkins, approximately 50% of NMO/NMOSD subjects improve from a relapse with steroids alone. The other 50% require escalated care with plasma exchange.

Before discharge from the hospital, the subject will be scheduled for follow up in the NMO Clinic in 90 and 180 day visits. In addition, subjects will be sent to a local lab for monthly CD19 monitoring until the B cell counts replete to a minimum of 0.5% for patients who will continue to be treated with B-cell depleting agents for preventive care, according to standard of care, or to a minimum of 5% for patients who will use other preventive strategies. These results will be reviewed by the PI, Dr. Levy.

Plasma Exchange Treatment Phase

Should subjects not meet above clinical criteria to be discharged home, escalation to treatment with plasma exchange is standard of care.

The plasma exchange treatment phase begins at the end of the Steroid Treatment Phase and will last up to 14 days. During the Plasma Exchange Treatment Phase, subjects will undergo 1.0 – 1.5 volumes of plasma exchange every other day according to standard of care. At the end of this phase, a second MRI may be performed to confirm resolution of the lesion, according to standard of care. If any further acute immunosuppressive treatment for the acute NMO flare is required and provided according to standard of care, the subject will continue to be followed for safety issues, but the clinical efficacy data will not be included in the statistical analysis. Historically among NMO/NMOSD

subjects treated at the Johns Hopkins Hospital, approximately 95% of NMO/NMOSD subjects who complete plasma exchange are discharged following completion of the plasma exchange.

Follow-up

The primary outcome is safety for the duration of the period of B cell depletion. Secondary efficacy outcomes will be assessed at follow up 90 and 180 days after initial hospitalization for the acute relapse. In addition to a thorough history and physical examination, including EDSS rating, visual examination and timed walk, a research MRI of the spine will be performed at day 90 to compare to the relapse lesion. In addition, subjects will be sent to a local lab for monthly CD19 monitoring until the B cell counts replete to a minimum of 0.5% for patients who will continue to be treated with B-cell depleting agents for preventive care, according to standard of care, or to a minimum of 5% for patients who will use other preventive strategies. These results will be reviewed by the PI, Dr. Levy.

Withdrawal

For subjects who discontinue or withdraw from the trial, investigators will continue to monitor subjects who have ongoing neurologic deficits while the subject remains in the hospital. This involves periodic neurologic exams and close observation in collaboration with the treating physician.

Subjects unable to tolerate ublituximab will be withdrawn from the trial. A tolerability issue for the purpose of withdrawing to alternative treatment is defined as a moderate or severe side-effect or complication related to treatment, which is unacceptable to the subject; or a clinically significant change in hematologic, hepatic, or renal laboratory parameters that, in the opinion of the investigator, would require a change in treatment.

Definition of Completer and Maximum Duration of Participation

A completer is defined as a subject who has completed all of the clinically necessary phases of the trial, as per standard of care, and has followed up in the NMO Clinic for all follow up visits. The maximum duration of participation is up to 9 months for most subjects.

Magnetic Resonance Imaging in the Trial

The trial will utilize MRI for spine imaging with and without contrast during the trial for relapses, as per standard of care and for research purposes on 90-day follow-up. In cases of poor creatinine clearance, contrast will not be used. According to standard of care, MRI scans in the trial will be performed at the initiation of the relapse. On follow up, the MRI is a research procedure.
For purposes of this trial, standard of care MRIs of the spine will be reviewed by trial staff; the following characteristics will be recorded for research purposes:

1. Length of sagittal spine T2 lesion in centimeters in all subjects who obtain MRIs, and
2. Length of sagittal spine T1-post contrast lesion in centimeters and/or orbital T1-post contrast lesion in millimeters in those subjects who additionally receive gadolinium contrast.

A single blinded Independent Reader will review the MRI for research purposes. The reader will be blinded to the treatment assignments and time sequences of the scans.

8 PHARMACEUTICAL INFORMATION

8.1 INVESTIGATIONAL AGENT – UBLITUXIMAB

8.1.1 Ublituximab

Chemical Name:	ublituximab
Other Names:	TGTX-1101, LFB-R603
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 3 mL (30 mg) and 15 mL (150 mg) single-use glass vials.
Storage:	Storage Conditions Ublituximab must be stored in a secured limited-access area at a temperature ranging +2°C / + 8°C. Ublituximab must not be frozen.
Stability:	Stability Conditions Once a vial of ublituximab has been opened and/or diluted it must be used immediately. After dilution in polyvinyl chloride (PVC) infusion bags, 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 18 months based on available stability data.
Route of Administration:	Intravenous
Packaging:	Ublituximab is packed in unit boxes. Each unit box contains: • Five 3 mL or one 15 mL vial(s) containing 10 mg/mL solution of ublituximab • Instructions for dilution in Sodium Chloride 0.9% • A temperature control system including a leaflet with instructions for use The unit boxes containing the 3 mL vial are grouped by 5 in outer package boxes, which will be provided to the clinical trial sites. The unit boxes containing the 15 mL vial are not grouped in outer package boxes and they will be provided individually to the clinical trial sites.

The container closure system of ublituximab is a Type I glass vial closed by a siliconized bromobutyl rubber stopper and a tamperproof protective cap crimped to the neck of the vial.

Availability: Ublituximab is available from TG Therapeutics

8.2 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS (CAEPRS)

8.2.1 Very Common ≥10%

- **Blood and lymphatic system disorders:** Neutropenia, Thrombocytopenia
- **Gastrointestinal disorders:** Nausea
- **General disorders and administration site conditions:** Fever[1], Infusion-Related Reactions, Asthenia, Chills
- **Infections and infestations:** Bronchitis, Nasopharyngitis, Rhinitis, Sinusitis, Oral herpes
- **Investigations:** GGT increased, ALT increased, AST increased
- **Nervous system disorders:** Headache
- **Respiratory, thoracic and mediastinal disorders:** Cough

[1] "Fever" includes preferred terms "pyrexia" and "hyperthermia"

8.2.2 Common ≥1% and <10%

- **Blood and lymphatic system disorders:** Anemia, Pancytopenia, Febrile neutropenia, Autoimmune hemolytic anemia, Macrocytic anemia, Evans syndrome
- **Cardiac disorders:** Cardiac flutter, Nodal arrhythmia
- **Ear and labyrinth disorders:** Tinnitus
- **Endocrine disorders:** Thyroid cyst
- **Eye disorders:** Conjunctivitis, Lacrimation decreased
- **Gastrointestinal disorders:** Lip edema, Gingival bleeding, Oral paresthesias, Stomatitis, Esophagitis, Abdominal pain, Upper Abdominal pain, Gastric ulcer, Constipation, Colonic polyp, Diverticulum intestinal, Diarrhea
- **General disorders and administration site conditions:** Chest pain, Fatigue, Injection site hemorrhage, Peripheral edema
- **Hepatobiliary disorders:** Cholestasis, Cholecystitis acute, Mixed liver injury
- **Immune system disorders:** Drug hypersensitivity, Hypogammaglobulinemia
- **Infections and infestations:** Influenza, Lung infection, Upper respiratory tract infection, Tracheitis, Laryngitis, Tonsillitis, Parotitis, Otitis media, Urinary tract infection, Anal abscess, Bronchopulmonary aspergillosis, Febrile infection, Listeriosis, Septic shock, Staphylococcal sepsis, Streptococcal sepsis, Hepatitis C, Genital herpes, Herpes zoster,
- **Injury, poisoning and procedural complications:** Wrong technique in drug usage process, Head injury, Postoperative hernia, Subcutaneous hematoma
- **Investigations:** Weight decreased, Serum IgA increased, O2 saturation decreased
- **Metabolism and nutrition disorders:** Diabetes mellitus inadequate control, Hypercholesterolemia, Hyperglycemia, Hyperuricemia
- **Musculoskeletal and connective tissue disorders:** Back pain, Musculoskeletal pain, Muscle spasms, Myalgia, Arthralgia, Tendonitis
- **Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Squamous cell carcinoma, Basal cell carcinoma, Leukemia, Neuroendocrine carcinoma of the skin
- **Nervous system disorders:** Somnolence, Paraesthesia, Syncope vasovagal, Ischemic stroke
- **Psychiatric disorders:** Anxiety, Aggression, Depression, Insomnia
- **Renal and urinary disorders:** Hematuria

- **Reproductive system and breast disorders:** Genital prolapse, Vulva cyst
- **Respiratory, thoracic and mediastinal disorders:** Epistaxis, Throat irritation, Bronchopneumopathy
- **Skin and subcutaneous tissue disorders:** Erythema, Urticaria, Allergic dermatitis, Perivascular dermatitis, Skin hemorrhage, Hyperhidrosis, Night sweats
- **Vascular disorders:** Hypertension, Hypotension, Hot flush

8.2.3 Uncommon ≥0.1% and <1%

Safety data for ublituximab is only available from administration in 33 patients in the recently completed Phase I clinical trial in relapsed and refractory CLL. As such, due to statistical limitations, no uncommon adverse events (occurring in ≥0.1% and <1% of patients) can be described.

8.2.4 Ordering Ublituximab

Once the clinical trial site receives IRB/EC approval and FDA approval as an Investigator-Initiated (Sponsor) IND a pre-determined quantity of trial drug (UTX) will be shipped from TG Therapeutics to the Investigational Pharmacy at John Hopkins.

Upon receipt of treatment supplies, the Pharmacist or the appropriate person of the site will complete the acknowledgement of receipt and send it back to the TG Therapeutics or designee and update the accountability forms for TG Therapeutics.

If any abnormality on the supplied boxes is observed, the Pharmacist or the appropriate person must document that on the acknowledgement of receipt before sending it to TG Therapeutics or its designee.

8.2.5 Randomization

There is no randomization in this unblinded, open-label safety study.

8.2.6 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, subject's medical records, and/or in the drug accountability records. Batch numbers of ublituximab must be reported within the CRF.

The Pharmacist or his/her representative will record the date dispensed and subject's number and initials on the labels. He/she will complete the accountability forms with information concerning the dispensation of ublituximab. Preparation will 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:

<u>Dilutions of ublituximab</u>

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.

Dose of ublituximab for infusion (cohort)	Volume of ublituximab (10 mg/mL)	Volume of NaCl 0.9% to be removed	Final volume in perfusion bag
450 mg	45 mL	45 mL	250 mL

8.2.7 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 TG Therapeutics.
- In accordance with Section 5.1, a list of pre-medication will be administered before infusion of ublituximab.
- Since infusion-related hypotension may occur, **antihypertensive medications may 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 over four (4) hours.

The flow rate is specified in the tables below.

8.2.7.1 Flow Rate for

- T0 to T30': 2% of the total volume
- T30' to T1H: 4% of the total volume
- T1H to T2H: 14% of the total volume
- T2h to T4H: 80% of the total volume

Infusion rate of ublituximab

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

8.2.8 Agent Hypersensitivity

Ublituximab Hypersensitivity and Infusion Reactions*:* Available at the bedside prior to ublituximab administration will be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and resuscitation equipment for the emergency management of

anaphylactic reactions. Ublituximab should be administered intravenously through a dedicated line.

9 TRIAL CALENDAR/EVALUTION TABLE

Table 6: Schedule of Events

Phase:	**Screen (1 day)**	**Steroid Treatment (5 days)**					**Plasma Exchange (if necessary)**	**Follow up**		
								Monthly	**90 day**	**6 month**
Day	0	1	2	3	4	5	6-20	30, 60, 90, 120, 150, 180, 210, 240, 270	90	180
MRI of the affected area (brain, c/t spine)	M					M	M		M	
Administration of treatment		Steroids on days 1-5 UTX: 1 dose on day 1 or as early as possible in this phase								
Informed Consent	X									
Eligibility	X									
Demographic, NMO and Medical History	X								X	X
Prior NMO treatments	X									
Vital signs, weight	X	X	X	X	X	X	X		X	X
Neurological Exam	X	X	X	X	X	X	X		X	X
Laboratory assessment	X	X	X	X	X	X		X		X
HCVA		X				X	X		X	X
EDSS		X				X	X		X	X
Timed 25-Foot Walk		X				X	X		X	X
Adverse Events		X	X	X	X	X	X		X	X
Concomitant Meds	X	X	X	X	X	X	X			

10 MEASUREMENT OF EFFICACY

This is a primary safety study, but we are interested in recording potential measures of efficacy. These will be assessed as secondary clinical endpoints. Primary outcome measures for safety are detailed in section 12 below.

Efficacy Endpoints
Clinical outcomes will be monitored for efficacy using three functional neurologic tests, the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk and High Contrast Visual Acuity (HCVA). These will be assessed days 1 and 5 of hospitalization and weekly thereafter for the first three weeks (Days 13 and 20 during PLEX period as needed). In addition, we will use quantifiable MRI parameters as a secondary endpoint as described below.

EDSS

The Kurtzke Expanded Disability Status Scale (EDSS) was developed to measure the disability status of subjects with multiple sclerosis. It allows an objective quantification of the level of functioning that could be widely and reproducibly used by researchers and health care providers. The EDSS provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The range of main categories include (0) = normal neurologic exam; to (5) = ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities; to (10) = death due to MS. In addition, it also provides eight subscale measurements called Functional System (FS) scores. These subscale categories are listed in Appendix 2.

HCVA

High Contrast Visual Acuity: High-contrast Sloan letter charts are readily available and provide a practical, quantitative, and standardized assessment of visual function. Each chart consists of rows of black letters (decreasing in size from top to bottom) on a white background.

For this trial, 100% monocular high contrast visual acuity will be measured on days 1 and 5 during the steroid phase and weekly during the plasma exchange phase. Charts will be read at a 2-meter distance by trained examiners in the hospital room with constant lighting of 80-100 foot-candles accomplished using standard fluorescent hospital room overhead lighting. Binocular testing will be recorded as total number of letters identified correctly (maximum 60).

Timed 25-Foot Walk

Timed 25-foot walking trials will be assessed on days 1 and 5 during the steroid phase and weekly in the plasma exchange phase. The Timed 25-Foot Walk test is a quantitative measure of lower extremity function. If required, the subject may use an appropriate assistive device to walk as quickly as he/she can from one end to the other end of a clearly marked, unobstructed, 25-foot course. Every effort will be made to use the same testing hallway for every Timed 25-Foot Walk test. Potential for external distractions should be kept to a minimum as much as possible. A subject will stand with the toes of his/her shoes on the starting line (identified by a taped mark on the floor) and timing will begin when any part of the subject's foot crosses the tape. Timing will end when any part of the subject's foot crosses the finish line (identified by a taped mark on the floor). Time will be recorded in seconds and rounded to the nearest tenth of a second using a stopwatch provided for this trial. The task is immediately administered again by having the subject walk back the same distance. The average of the two values will be recorded in the case report form.

Objective Efficacy Endpoints

MRIs will be performed for standard of care and research purposes and will be used to make clinical decisions about escalation of immunosuppressive treatment. For this trial, the MRIs will also be analyzed for two parameters: length and T2 hyperintensity in the spinal cord and optic nerve and length of T1 post-contrast enhancement if available.

Number of days in the hospital and requirement for plasma exchange will also be recorded on the CRFs.

10.1 DEFINITIONS

Intent-to-Treat. All subjects who receive one dose of trial drug will be included in the intent-to-treat group.

Per-Protocol. All subjects who performed all visits in accordance with protocol without significant protocol deviations or violations.

All Subject Treatment Group. All subjects who received one dose of trial drug (UTX).

11 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.

11.1 SAMPLE SIZE

Hypothesis
This trial is exploring the safety of ublituximab in the treatment of NMO/NMOSD relapses. The hypothesis is that the ublituximab regimen proposed in this trial is safe and tolerable in the NMO/NMOSD patient population. The objectives of the trial will be assessed through the use of summary statistics.

Sample Size Considerations
The sample size of 5 subjects is based on feasibility and logistical considerations on the number of subjects that will reveal a significant risk or tolerability issue of using ublituximab + steroids. It is anticipated that 1 subject will fail screening and 1 will drop out over the course of the trial, for a total of 4 subjects who are expected to complete the trial. Subjects who withdraw will not be replaced.

11.2 GENERAL ANALYSIS CONVENTION

Interim Analysis

There will be no interim analysis.

Statistical Analysis

A summary of the number and percentage of subjects with any adverse event, any serious adverse event, adverse events leading to permanent discontinuation of trial drug, and trial drug-related adverse events will be reported.

Change in neurologic outcomes on the EDSS, Timed 25-Foot Walk and HCVA scales from admission to discharge will be analyzed by paired t-tests with significant p-values considered less than 0.05.

By MRI, length of T2 hyperintensity and length of T1-post contrast enhancement should be stable or reduced by discharge. A paired t-test will be used to compare changes in these values with significance considered at p-values less than 0.05.

Continuous data will be described using the following descriptive statistics: n, mean, median, minimum and maximum. Data will be displayed in all listings sorted by subject number.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where necessary to account for dropouts and missing values. Unless otherwise specified, the denominator for percentages will be the number of subjects with a non-missing assessment within the analysis population of interest.

SAS Version 9.2 will be used to perform all analyses.

11.3 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population will used for the official analysis.

The Safety Population will include all subjects who received one dose of trial drug (UTX). All safety assessments including toxicity will be performed on the Safety Population.

The Per-Protocol Population (PP) will consist of all ITT subjects without a major protocol deviation or protocol violation. The criteria for a major protocol deviation or violation will be determined and documented prior to data base lock. Subject exclusion from the PP population will also be determined and documented prior to database lock. Supportive analyses may be performed based on the PP population.

11.4 SUBJECT DISPOSITION

The disposition of subjects includes the number and percentage of subjects for the following categories: subjects treated (safety population), subjects in the ITT population, subjects completed, and subjects discontinued from the trial. All percentages will be based on the number of subjects enrolled. The reasons for trial discontinuation will also be summarized in this table. Only one reason for trial discontinuation will be recorded. However, all reasons will be presented in the listing.

A listing will present data concerning subject disposition.

11.5 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 performed for the ITT Population.

11.6 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be summarized for the Safety population by World Health Organization (WHO) and MedDRA dictionary. Subjects may have more than one medication per drug class and preferred term. At each level of summarization, a subject is counted once if he/she reported one or more medications at that level.

Prior medications are defined as medications with a stop date occurring before the date of receiving first trial treatment. Concomitant medications are defined as medications with start dates occurring on or after date of receiving first trial treatment. Medications with start and stop dates which bracket the date of first dose will be summarized as both prior and concomitant medications.

11.7 MEDICAL HISTORY

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

11.8 EXTENT OF EXPOSURE

The dose (mg) of trial drug administered (UTX), and the duration of treatment will be summarized with descriptive statistics. The proportion of subjects completing the infusion of trial drug (UTX) will be summarized.

11.9 EFFICACY ANALYSES

Secondary endpoints of clinical outcomes will be monitored for efficacy using three functional neurologic tests, the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk and High Contrast Visual Acuity (HCVA). These will be assessed days 1 and 5 of hospitalization and weekly thereafter for the first three weeks (Days 13 and 20, if needed). The primary analysis will be a change from baseline to Day 90 and the secondary analyses will be a change from baseline to Days 5, 20, and 6 months.

For this secondary efficacy endpoint, the MRIs will be analyzed for two parameters: length of T2 hyperintensity in the spinal cord and optic nerve and length of T1 post-contrast enhancement if available. The secondary analyses for MRI will be a change from baseline to discharge on Day 5 or 20, as well as a change from baseline to follow up at day 90.

Number of days in the hospital and requirement for plasma exchange will be assessed using descriptive statistics.

12 SAFETY REPORTING AND ANALYSIS

12.1 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 subject's physical examination, vital signs, and clinical laboratory results. Safety analyses will be performed using the safety population. Safety variables will be tabulated and presented. Exposure to trial treatment and reasons for discontinuation of trial treatment will also be tabulated.

12.2 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 8.2) will determine whether the event requires expedited reporting in addition to routine reporting.

12.3 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.

12.4 PROTOCOL-SPECIFIC EXPEDITED ADVERSE EVENT REPORTING EXCLUSIONS

There are no exclusions for expedited adverse event reporting. All adverse events, including death, will be considered unexpected and subject to expedited reporting.

12.5 ADVERSE EVENTS

All AEs and SAEs occurring on trial will be listed by subject. 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 trial medication and through the end of the trial or up through 30 days after the last dose of trial treatment, or
- Is considered treatment-related regardless of the start date of the event, or
- Is present before first dosing of trial medication but worsens in intensity or the investigator subsequently considers treatment-related.

TEAEs that are considered at least possibly related to trial 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 trial medication will not be summarized but will be listed.

At each level of summarization, a subject 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 trial drug, within each level of AE, SOC, or PT experienced, the one with the closest relationship to the trial drug will be included.

12.6 DEFINITIONS OF ADVERSE EVENTS

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

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; limiting age-appropriate instrumental ADL*.
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

The Investigator must also assess the relationship of any adverse event to the use of trial drug, based on available information, using the following guidelines:

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

12.6.1 Recording of Adverse Events

All adverse events of any subject 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). If the adverse event is serious, it should be reported as soon as possible and no greater than 24 hours

to TG Therapeutics and the Chair of DSMB. The Johns Hopkins IRB must also be notified as required by Johns Hopkins IRB guidelines. 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 the signature of the informed consent form, until 30 calendar days after discontinuation or completion of protocol-specific treatment as defined by the protocol for that subject, are to be recorded on the CRF.

12.6.2 Abnormal Laboratory Values and Vital Signs

The reporting of abnormalities of vital signs as adverse events should be avoided. Abnormalities of vital signs should not be reported unless any criterion for an SAE is fulfilled, the vital signs abnormalities cause the subject to discontinue trial treatment, or the investigator insists that the abnormality should be reported as an AE. Any grade 3 or 4 laboratory abnormality or any clinically significant grade 1 or 2 hematology or biochemistry laboratory value(s) should be recorded as an AE. 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 on the relevant CRF.

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. Subject incidence of laboratory toxicity will be summarized and assigned a maximum grade for each laboratory test.

12.6.3 Handling of Adverse Events

All adverse events resulting in discontinuation from the trial should be followed until resolution or stabilization. Subjects must be followed for AEs for 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 subject'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.

12.7 SERIOUS ADVERSE EVENTS

12.7.1 Definitions of Serious Adverse Events

The definitions of serious adverse events (SAEs) are given below. The principal investigator is responsible for ensuring that all staff involved in the trial is 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 inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- causes a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require

intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Death due to disease progression will be recorded on the CRF. 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 "inpatient 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 (Dr. Michael Levy).

12.7.2 Serious Adverse Event Reporting by Investigators

It is important to distinguish between "serious" and "severe" adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea, which persists for several hours, may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only 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 IRB or other regulatory agencies 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 9-month 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 TG Therapeutics, the Johns Hopkins IRB and the Chair of the DSMB 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 TG Therapeutics and the Chair of the DSMB, but can simply be captured on the appropriate CRF as an SAE (death). The Johns Hopkins IRB should be notified as soon as possible.

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). Transmission of the SAE report 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).

12.8 SPONSOR SAE REPORTING REQUIREMENTS

The Sponsor (Dr. Levy) with assistance from TG Therapeutics are 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.

The Sponsor (Dr. Levy) with assistance from TG Therapeutics are responsible for reporting unexpected fatal or life-threatening events associated with the use of the trial drug 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 medication to TG Therapeutics and the Johns Hopkins IRBs by safety report within 14 calendar days of notification. TG Therapeutics is required to notify the FDA.

12.9 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Investigators will use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE CRF. Colloquialisms and abbreviations will be avoided.

All AEs, including those that meet SAE reporting criteria, will be recorded on the AE CRF; AEs that meet the definition of an SAE will additionally be reported following the procedures noted in Section 14.7.

12.10 IMMUNOGENICITY AND PHARMACOKINETICS

12.10.1 Pharmacokinetic (PK) Sampling:

Patients will have pharmacokinetic (PK) sampling (serum) performed as noted on the schedule below:

Time point
Pre-dose
1 min prior to EOI
30 min post EOI[1]
6 hour post EOI[2]

24 hour post EOI[3]
72 hour post EOI[3]
168 hour post EOI[3]

EOI: End of Infusion

[1]+/- 5 minutes
[2]+/- 30 minutes
[3]+/- 2 hours

PK Sampling Procedures - IMPORTANT

Stop and start times of UTX infusion must be recorded and actual time/dates of samples drawn must be provided. The subject will not receive any additional infusions of ublituximab.

All samples to be obtained for PK analysis of ublituximab will be serum. One 6-ml blood sample is required for each sample time point.

After centrifugation, 2 aliquots of 0.5 ml of serum should be stored at -20°C to 70°C at the site. One aliquot will be sent to TG Therapeutics and the second aliquot will be shipped to TG Therapeutics after the first sample is received by them. All samples must be sent within 14 days of being collected from the subject.

Approximately seven (7) samples over 7 days should be collected for the PK analysis of ublituximab.

12.10.2 PK Sample Collection and Processing:

a. Peripheral blood is to be drawn into heparinized vacutainer tubes. The patient's initials, time sample obtained, and date sample was obtained should be recorded on each tube as well as on the respective PK timesheet in the CRF.

b. Within 20 minutes of collection, centrifuge the blood samples at 900xg for 15 minutes to separate plasma.

c. For each sample collected, pipette duplicate aliquots of plasma, 2 ml each, in polypropylene cryovials (Nunc). Aliquot 1 is the sample and aliquot 2 is the duplicate.

d. Aliquots are to be frozen and stored at -20°C to _-70°C or lower until specimens are shipped to shipped to TG Therapeutics. All samples must be shipped within 14 days following collection for further storage and/or analysis.

e. Specimens can be batched for shipment once all samples have been collected for a patient within 14 days of being collected.

12.10.3 PK Sample Shipping

a. Samples may be stored at the site for up to 14 days. Samples are to be shipped overnight in sufficient dry ice to keep samples frozen.

b. One aliquot from each sample will be shipped and the duplicate samples can be sent once TG Therapeutics verifies they have received the first aliquot. Again, all samples must be shipped with 14 days.

c. Do not ship samples and duplicates in the same box. Save the duplicates and ship them after TG Therapeutics has verified they have received the first aliquot.

d. Place the patient flow sheets in a separate plastic bag and then place in the shipping box.

e. Please contact TG Therapeutics either by phone or by email before shipping samples. This is to assure that shipments can be received on that day. This is especially important if shipping on Thursday for a Friday delivery.

f. The laboratory is open to receive samples Monday through Friday. **NOTE**: DO NOT ship samples on Fridays or on days prior to holidays.

12.10.4 Immunogenicity

Serum samples will be screened for antibodies against ublituximab and neutralizing antibodies to ublituximab. Serum samples will be collected prior to the infusion of ublituximab and at 2, 30, and 60 days following the end of the infusion. A titer, if any, will be recorded for each sample and correlated with safety and efficacy data. Approximately 4 mL of blood will be collected per sample.

12.11 DIAGNOSIS VS. SIGNS AND SYMPTOMS

All AEs will be recorded individually in the subject'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 will 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 will be recorded as an AE or SAE as appropriate on the Case Report Form. If a diagnosis is subsequently established, it will 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 will be updated to reflect the diagnosis.

12.11.1 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such events will be recorded as "persistent" on the Case Report Form. If a persistent AE becomes more severe or lessens in severity, it will be noted as such on the Case Report Form.

A recurrent AE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent AEs will be recorded on the Case Report Form as "recurrent.".

12.11.2 Abnormal Laboratory Values

Any grade 3 or 4 laboratory abnormalities or any clinically significant grade 1 or 2 hematology or biochemistry laboratory value(s) will be recorded as an AE. 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 will be considered additional information that must be collected on the relevant CRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis will be recorded the Case Report Form.

12.11.3 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator for up to 30 days post the dose of trial drug will be recorded on the appropriate trial CRF. All on-trial deaths, regardless of attribution, will be expeditiously reported to the TG Therapeutics and to the Johns Hopkins IRB.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome will 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, "Death NOS" will be recorded on the CRF Adverse Event page.

12.11.4 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolonged hospitalization will be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

12.11.5 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions will be recorded on the trial's appropriate medical history CRF. A pre-existing medical condition will 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 Case Report Form, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

12.11.6 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest, as described below in section 12.11.7.

12.11.7 Protocol-Defined Events of Special Interest

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

Pregnancy, Abortion, Birth Defects/Congenital Anomalies
If a subject becomes pregnant while enrolled in the trial, TG Therapeutics will be notified expeditiously, regardless of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) will also be reported to TG Therapeutics.

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

Trial Drug Overdose
Symptomatic and non-symptomatic overdose will be reported in the CRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, even if not fulfilling a seriousness criterion, will be reported to TG Therapeutics immediately (within 24 hours) using the corresponding CRF page, and following the same process described for SAEs (see Section 14). If a trial drug overdose occurs, subjects will stop trial drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

13 STOPPING RULES

An independent DSMB will be in charge of reviewing safety data. In order to ensure safety and limit toxicity for enrolled subjects, the DSMB will meet at least once (prior to subject enrollment (organizational meeting)), after two subjects have been infused with trial drug and a final safety review meeting after the fifth subject completed the study. The following adverse events will be followed by the DSMB: neutropenia, thrombocytopenia, infection, and elevations in liver enzymes. These events will be reviewed by the DSMB when two (2) subjects enrolled have completed treatment with UTX and steroids or every six (months), whichever occurs first, during the course of the trial. All other serious and non-serious adverse events will be documented. The DSMB will look at the total safety data in determining whether it is possible to dose the next three (3) subjects in this trial.

14 CLINICAL DATA COLLECTION AND MONITORING

14.1 SITE MONITORING PLAN

The proposed clinical trial is being submitted to the FDA as Investigator-Initiated Trial to be performed at one clinical site (John Hopkins) and as an Investigator-Initiated IND maintained by Dr. Michael Levy of John Hopkins University School of Medicine.

The Sponsor (Dr. Levy) will be transferring the regulatory obligation for monitoring this trial and data management to TG Therapeutics, Inc. 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 TG Therapeutics SOPs, GCP/ICH and, when appropriate, regulatory guidelines. The Site Monitoring Plan shall define aspects of the monitoring process.

TG Therapeutics will visit Johns Hopkins 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 trial 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) and other pertinent trial materials will be reviewed with the investigator's research staff. During the course of the trial, TG Therapeutics 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 trial 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 subject confidentiality is maintained.

15 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).

15.1 IRB APPROVAL

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

The Sponsor (Dr. Levy) and/or designee will follow all necessary regulations to ensure initial and ongoing, IRB trial review. The Sponsor (Dr. Levy), as appropriate must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document.

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 14 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.

Safety updates for ublituximab will be prepared by the Sponsor or its representative (TG Therapeutics, Inc.) as required, for submission to the relevant IRB.

15.2 REGULATORY APPROVAL

As required by local regulations, the Sponsor (Dr. Levy) 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 (TG Therapeutics, Inc.) as required, for submission to the relevant regulatory authority.

15.3 INSURANCE AND INDEMNITY

Details of insurance and/or indemnity will be contained within the written agreement between Johns Hopkins and TG Therapeutics.

15.4 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 will include all of the relevant elements currently required by the responsible regulatory authority, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of

participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the subject's medical record. A copy of the informed consent form, to include the subject's signature, will be provided by the investigator to the subject.

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

15.5 CONFIDENTIALITY

15.5.1 Subject Confidentiality

Confidentiality of subject'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 subject must sign an authorization from the trial that he or she has been informed of following:

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

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

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

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

15.6 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 will take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

15.7 FINANCIAL INFORMATION

The finances for this trial will be subject to a separate written agreement between the TG Therapeutics and Johns Hopkins University. All Investigator financial disclosures as applicable to 21CFR Part 54 will be appropriately provided and reviewed by the Johns Hopkins IRB.

16 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

16.1 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. The written amendment must be submitted to the Johns Hopkins IRB for the board's approval.

Amendments specifically involving change to trial design, risk to subject, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, will 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 subject 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 subject
- Increase to dose or subject exposure to drug
- Subject number increase of more than 20%
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

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

16.2 DOCUMENTATION REQUIRED TO INITIATE TRIAL

Before the trial may begin, certain documentation required by FDA regulations will be provided by the Investigator. The required documentation will be kept by 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 the Johns Hopkins IRB and/or 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 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.

16.3 TRIAL DOCUMENTATION AND STORAGE

The PI will maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and will 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 will be included on this document. All entries in the subject's CRF will be supported by source documentation where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the subject's 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 of 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 will 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, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug including accountability records. Drug accountability records will, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, will 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 will be maintained and be readily available.

The Sponsor/investigator (Dr. Levy) will 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.

To enable evaluations and/or audits from regulatory authorities, the investigator additionally will 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, , source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above will 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). TG Therapeutics or its representative will notify Dr. Levy (or Johns Hopkins University) when the trial-related records are no longer required.

16.4 DATA COLLECTION

The trial CRF is the primary data collection instrument for the trial. A case report form (CRF) 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, subject number, initials and date of birth may be used to identify the subject in the CRF. If the subject's name appears on any other document (e.g. laboratory report), it will be obliterated on the copy of the document to be supplied to the investigator site and replaced instead with the subject number and subject's initials. The investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to enable records to be identified and verified as authentic. Subject data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

16.5 TRIAL MONITORING, AUDITING, AND INSPECTING

The investigator will permit trial-related monitoring, quality audits, and inspections by TG Therapeutics and government regulatory authorities 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.

16.6 QUALITY ASSURANCE AND QUALITY CONTROL

In addition to the Clinical Monitoring component of this protocol, the TG Therapeutics'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.

16.7 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.

A clinical trial report will be prepared upon completion of the trial. 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 TG Therapeutics and the Johns Hopkins IRB 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 trial, the Investigator affirms to TG Therapeutics that he or she will maintain, in strict confidence, information furnished by TG Therapeutics including data generated from this trial and preliminary laboratory results, except as exempted for regulatory purposes.

All data generated during the conduct of this trial is owned by the Sponsor (Dr. Levy) and may be shared with TG Therapeutics as outlined in a separate contract between TG Therapeutics and Johns Hopkins.

All manuscripts, abstracts, or other presentation materials can be generated at the discretion of the Sponsor (Dr. Levy).

17 REFERENCES

Alter A, Duddy M, Hebert S et al., Determinants of Human B Cell Migration Across Brain Endothelial Cells, *J Immunol* 2003 170(9):4497-4505

Baritaki S, Militello L, Malaponte G, Spandidos DA, Salcedo M, Bonavida B. The anti-CD20 mAb ublituximab interrupts the dysregulated NF-kappaB/Snail/RKIP/PTEN resistance loop in B-NHL cells: role in sensitization to TRAIL apoptosis. Int J Oncol. 2011;38(6):1683-94

Bedi GS, et al., Impact of rituximab on relapse rate and disability in neuromyelitis optica *Multiple Sclerosis Journal* 17(10) 1225–1230

Bizzoco E, Lolli F, Repice AM, et al. Prevalence of neuromyelitis optica spectrum disorder and phenotype distribution. *J Neurol* 2009; 256: 1891–1898

Bleeker WK, Munk ME, Mackus WJM et al., Estimation of dose requirements for sustatined *in vivo* activity of a therapeutic human anti-CD20 antibody, *Br J Hæmatology* 2007:140:303-312

Buerke M., Murohara T., Lefer A.M. Cardioprotective effects of a C1 esterase inhibitor in myocardial ischemia and reperfusion. *Circulation* 1995;91:393-402

Capobianco, et al., Variable responses to rituximab treatment in neuromyelitis optica (Devic's disease), *Neurol Sci* (2007) 28:209–211

Clopper, C and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*, 1934; 26: pp 404-413

Cook SD, in *Handbook of multiple sclerosis,* ed. Cook SD 2006, 4th edn., Taylor & Francis:New York

Cree BAC, Lamb S, Morgan K, Chen A, Waubant E, Genain C., An Open Label Study of the Effects of Rituximab in Neuromyelitis Optica. *Neurology* 2005; 64: 1270–1272

de Romeuf C, Dutertre CA, Le Garff-Tavernier M, Fournier N, Gaucher C, Glacet A, et al. Chronic lymphocytic leukaemia cells are efficiently killed by an anti-CD20 monoclonal antibody selected for improved engagement of FcgammaRIIIA/CD16. British journal of haematology. 2008;140(6):635-43

Esteves I, Dumontet C, Herveau S et al. ublituximab a Third Generation Monoclonal Anti-CD20 Antibody Displays an Additive Antitumor Activity with Antileukemic Chemotherapeutic Agents in Mouse Xenograft Models. American Society of Clinical Oncology 2011 Poster Presentation

Fattouch K, Bianco G, Speziale G, et al. Beneficial effects of C1 esterase inhibitor in ST-elevation myocardial infarction in patients who underwent surgical reperfusion: a randomised double blind study. *Eur J Cardiothorac Surg* 2007; 32(2): 326-332

Greenberg BM, et al., Rituximab dosing and monitoring strategies in neuromyelitis optica patients: creating strategies for therapeutic success, *Multiple Sclerosis J* 2011, 0(0) 1–5

Hinson SR, Pittock SJ, Lucchinetti CF, et al. Pathogenic potential of IgG binding to water channel extracellular domain in neuromyelitis optica, *Neurology* 2007; 69:2221-2231

Jacob A, Matiello M, Weinshenker BG, et al. Treatment of neuromyelitis optica with mycophenolate mofetil: retrospective analysis of 24 patients. *Arch Neurol* 2009; 66: 1128–1133.

Jacob A, Weinshenker BG, Violich I, et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Arch Neurol* 2008; 65: 1443–1448

Igonin A, Protsenko DN, Galstyan GM, et al. C1-esterse inhibitor infusion increases survival rates for patients with sepsis. *Crit Care Med* 2012; 40(3): 770-777

Kimbrough D,, et al., Treatment of Neuromyelitis Optica: Review and Recommendations 2012 Pub Pending

Kim SH, et al., Repeated Treatment with Rituximab Based on the Assessment of Peripheral Circulating Memory B Cells in Patients with Relapsing Neuromyelitis Optica Over 2 Years, *Arch Neuro* 2011*, 154:E1 - E8*

Kinoshita M, Nakatsuji Y, Moriya M, et al. Astrocytic necrosis is induced by anti-aquaporin-4 antibody-positive serum, *NeuroReport* 2009; 20(5):508-512

Kuenz B, Lutterotti A, Ehling R et al., Cerebrospinal Fluid B Cells Correlate with Early Brain Inflammation in Multiple Sclerosis, *PLoS one* 2008:3(7):e2559

McKeon A, et al., CNS aquaporin-4 autoimmunity in children, *Neurology* 2008;71:93–100

Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004, 364:2106–2112

Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis otpica, *Brain* 2002; 125:1450-1461

Macallan, DC, Wallace D, Zhang Y et al. , Rapid Turnover of Effector Memory CD4+ T Cells in Healthy Humans, *J Exp Med* 2004:200(2):255 – 260

Marignier E, Nicolle A, Watrin C, et al. Oligodendrocytes are damaged by neuromyelitis optica immunoglobulin G via astrocyte injury, *Brain* 2010; 133:2578-2591
Matsuoka T, Matsushita T, Kawano Y, et al. Heterogeneity of aquaporin 4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese, *Brain* 2007; 130: 1206–23

Misu T, Fujihara K, Kakita A, Konno H, Nakamura M, Watanabe S, Takahashi T, Nakashima I, Takahashi H, Itoyama Y. Loss of aquaporin 4 in lesions of neuromyelitis optica: distinction from multiple sclerosis, *Brain* 2007; 130:1224-1234

Nandhagopal R, Al-Asmi A, Gujjar A, Neuromyelitis optica: an overview, *Postgrad Med J* 2010; 86:153-159

Pellkofer HL, et al., Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab *Neurology* 2011, 76:1310 - 1315

Petereit HF and Rubbert-Roth A, Rituximab levels in cerebrospinal fluid of patients with neurological autoimmune disorders, *Multiple Sclerosis* 2009:15(2):189-192

Polman C, et al., Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria, *Ann Neurol* 2011; 69:292–302

Roemer SF, Parisi JE, Lennon VA, et al. Pattern-specific loss of aquaporin-4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis, *Brain* 2007; 130:1194-1205

Saadoun A, Waters P, MacDonald C, et al. Neutrophil protease inhibition reduces neuromyelitis optica-immunoglobulin G-induced damage in mouse brain, *Annals of Neurology* 2012; 71(3):323-333

Sabater L, Giralt A, Boronat A, et al. Cytotoxic effect of neuromyelitis optica antibody (NMO-IgG) to astrocytes: An *in vitro* study, *Journal of Neuroimmunology* 2009; 215:31-35

Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R, Schwartz J, Weinstein R, Shaz BH; Apheresis Applications Committee of the American Society for Apheresis. Guidelines on the use of therapeutic apheresis in clinical practice--evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. *J Clin Apher*. 2010;25(3):83-177

Selner J, et al., EFNS guidelines on diagnosis and management of neuromyelitis Optica, *European J Neurol* 2010, 17:1019–1032

Shandelya S.M.L., Kuppusamy P., Weisfeldt M.L., Zweier J.L. Soluble complement receptor type 1 inhibits the complement pathway and prevents contractile failure in the postischemic heart; evidence that complement activation is required for neutrophil mediated reperfusion injury. *Circulation* 1993;88:2812-2826

Sormani MP, Bruzzi P, Rovaris M et al., Modelling new enhancing MRI lesion counts in multiple sclerosis, *Multiple Sclerosis* 2001:7:298-304

Teeling JL, et al. The Biological Activity of Human CD20 Monoclonal Antibodies Is Linked to Unique Epitopes on CD20, *J. Immunol.* 2006;177:362-371

Tourtellotte WW, 1975. What is multiple sclerosis? Laboratory criteria for diagnosis, *Multiple Sclerosis Research*, ed. Davison AN, Humphrey JH, Liversedge AL et al., p.9, HMSO:London

Weisman H.F., Bartow T., Leppo M.K., Marsh H.C., Carson G.R., Concino M.F. Soluble human complement receptor type 1 in vivo inhibitor of complement suppressing post-ischemic myocardial inflammation and necrosis. *Science* 1990;24:146-151

Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol* 2006; 59**:** 566–69

Weinshenker BG, Neuromyelitis Optica Is Distinct From Multiple Sclerosis *Arch Neurol* 2007; 64: 899-901

Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006; 66(10):1485–1489

Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. The spectrum of neuromyelitis optica, *Lancet Neurol* 2007; 6: 805–15

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

www.cdc.gov/hepatitis

Adapted From: Marsha L Tarver, PhD, VA Puget Sound Health Care System—Seattle

18.1 QUANTIFYING THE LEVEL OF DISABILITY

The Kurtzke Disability Status Scale (DSS) was developed by Dr. John Kurtzke in the 1950s to measure the disability status of people with multiple sclerosis. The purpose was to create an objective approach to quantify the level of functioning that could be widely used by health care providers diagnosing MS. The scale was modified several times to more accurately reflect the levels of disabilities clinically observed. The scale was renamed the Kurtzke Expanded Disability Status Scale (EDSS).

18.2 EDSS SCORING

The **EDSS** provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The range of main categories include (0) = *normal neurologic exam*; to (5) = *ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities*; to (10) = *death due to MS*. In addition, it also provides eight subscale measurements called Functional System (FS) scores. These subscale categories are listed below. The levels of function within each category refer to the eight functional systems affected by MS.

18.3 FUNCTIONAL SYSTEMS

The eight Functional Systems (FS) and their abbreviations are as follows:

1. Pyramidal (motor function) (P)
2. Cerebellar (Cll)
3. Brainstem (BS)
4. Sensory (S)
5. Bowel and Bladder (BB)
6. Visual (V)
7. Cerebral or Mental (Cb)
8. Other (O)

18.4 FUNCTIONAL SYSTEM SCORE

The Functional Systems (FS) are scored on a scale of 0 (low level of problems) to 5 (high level of problems) to best reflect the level of disability observed clinically. The “Other” category is not rated numerically, but measures disability related to a particular issue, like motor loss.

In contrast, the total EDSS score is determined by two factors: gait and FS scores. EDSS scores below 4.0 are determined by the FS scores alone. People with EDSS scores of 4.0 and above have some degree of gait impairment. Scores between 4.0 and 9.5 are determined by both gait abilities and the FS scores. For simplicity, many experts gauge the EDSS scores between 4.0 and 9.5 entirely by gait, without considering the FS scores.

Kurtzke Functional Systems Scores (FSS)

Pyramidal Functions
0 - Normal
1 - Abnormal signs without disability
2 - Minimal disability
3 - Mild to moderate paraparesis or hemiparesis (detectable weakness but most function sustained for short periods, fatigue a problem); severe monoparesis (almost no function)
4 - Marked paraparesis or hemiparesis (function is difficult), moderate quadriparesis (function is decreased but can be sustained for short periods); or monoplegia
5 - Paraplegia, hemiplegia, or marked quadriparesis
6 - Quadriplegia
9 - (Unknown)

Cerebellar Functions
0 - Normal
1 - Abnormal signs without disability
2 - Mild ataxia (tremor or clumsy movements easily seen, minor interference with function)
3 - Moderate truncal or limb ataxia (tremor or clumsy movements interfere with function in all spheres)
4 - Severe ataxia in all limbs (most function is very difficult)
5 - Unable to perform coordinated movements due to ataxia
9 - (Unknown)
Record #1 in small box when weakness (grade 3 or worse on pyramidal) interferes with testing.

Brainstem Functions
0 - Normal
1 - Signs only
2 - Moderate nystagmus or other mild disability
3 - Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
4 - Marked dysarthria or other marked disability
5 - Inability to swallow or speak
9 - (Unknown)

Sensory Function
0 - Normal
1 - Vibration or figure-writing decrease only in one or two limbs
2 - Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory (c/s figure writing) decrease alone in three or four limbs
3 - Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
4 - Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
5 - Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
6 - Sensation essentially lost below the head
9 - (Unknown)

Bowel and Bladder Function

(Rate on the basis of the worse function, either bowel or bladder)

0 - Normal

1 - Mild urinary hesitance, urgency, or retention

2 - Moderate hesitance, urgency, retention of bowel or bladder, or rare urinary incontinence (intermittent self-catheterization, manual compression to evacuate bladder, or finger evacuation of stool)

3 - Frequent urinary incontinence

4 - In need of almost constant catheterization (and constant use of measures to evacuate stool)

5 - Loss of bladder function

6 - Loss of bowel and bladder function

9 - (Unknown)

Visual Function

0 - Normal

1 - Scotoma with visual acuity (corrected) better than 20/30

2 - Worse eye with scotoma with maximal visual acuity (corrected) of 20/30-20/59

3 - Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60-20/99

4 - Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100-20/200; grade 3 plus maximal acuity of better eye of 20/60 or less

5 - Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less

6 - Grade 5 plus maximal visual acuity of better eye of 20/60 or less

9 - (Unknown)

Record #1 in small box for presence of temporal pallor

Cerebral (or Mental) Functions

0 - Normal

1 - Mood alteration only (does not affect EDSS score)

2 - Mild decrease in mentation

3 - Moderate decrease in mentation

4 - Marked decrease in mentation (chronic brain syndrome ñ moderate)

5 - Dementia or chronic brain syndrome ñ severe or incompetent

9 - (Unknown)

18.5 THE SCALE

The EDSS is widely used and accepted as a valid tool to clinically measure and evaluate MS patients' level of functioning. Below is the EDSS:

0	Normal neurological exam (all grade 0 in Functional Systems (FS); cerebral grade 1 acceptable).
1	No disability, minimal signs in one FS (i.e., one grade 1 excluding cerebral grade 1).
1.5	No disability, minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1).
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three-four FS grade 2, others 0 or 1).
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3 and one or two FS grade 2) or two FS grade 3, others 0 or 1, or five FS grade 2, others 0 or 1.
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 meters (0.3 miles).
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability. (Usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters (975 ft.).)
5.0	Ambulatory without aid or rest for about 200 meters (650 ft.); disability severe enough to impair full daily activities (e.g., to work full day without special provisions). (Usual FS equivalents are one grade 5 alone (others 0 or 1); or combinations of lesser grades usually exceeding specifications for step 4.0.)
5.5	Ambulatory without aid or rest for about 100 meters (325 ft); disability severe enough to impair full daily activities. (Usual FS equivalents are one grade 5 alone (others 0 or 1); or combinations of lesser grades usually exceeding specifications for step 4.0.)
6.0	Intermittent or constant unilateral assistance (cane, crutch, or brace) required to walk about 100 meters (325 ft.) with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters (65 ft.). (Usual FS equivalents are combinations with more than two FS grade 3+.)
7.0	Unable to walk beyond about 5 meters (16 ft.) event with aid, essentially restricted to wheelchair, wheels self in standard wheelchair a full day and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfers, wheels self but cannot carry on in standard wheelchair a full day; may

	require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair; but may be out of bed much of the day; retains may self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)
8.5	Essentially restricted to bed for much of the day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)
9.0	Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4.)
9.5	Totally helpless bed patient; unable to communicate or effectively eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)
10	Death due to MS.