FULL PROTOCOL TITLE

B Cell Targeted Treatment In Myasthenia Gravis: A Phase II Trial of Rituximab In Myasthenia Gravis

Protocol Version: V11.0

Protocol Date: (07/05/2017)

SHORT PROTOCOL TITLE

BeatMG: Rituximab in Myasthenia Gravis

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TABLE OF CONTENTS

INVESTIGATOR AGREEMENT

I have read the foregoing protocol V11.0 07/05/2017 and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information provided by the NeuroNEXT Network in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study documents provided by the NeuroNEXT Network will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

_____ _____

Investigator Signature **Date**

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Print Investigator's Name

SIGNATURE PAGE

Study Number:

NeuroNEXT Grant Award: 1U01NS084495-01A1
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LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

Ab	Antibody
AChR	Acetylcholine Receptor
AChR+	Acetylcholine Receptor Antibody Positive
AE	Adverse Event
AZA	Azathioprine
CCC	Clinical Coordination Center
CDE	Common Data Elements
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
CMSU	Clinical Materials Services Unit at the University of Rochester Medical Center
CRF	Case report form
CS	Clinically Significant
CSS PI	Clinical Study Site PI
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordination Center
DM	Data Management
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IMM	Independent Medical Monitor
IVIg	Intravenous Immunoglobulin
IST	Investigator Sponsored Trial
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis Activity of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MG-QOL	Myasthenia Gravis Quality of Life
MMF	Mycophenolate Mofetil
MS	Multiple Sclerosis
MuSK	Muscle Specific Kinase
MuSK+	Muscle Specific Kinase Antibody Positive
MTX	Methotrexate
NCI	National Cancer Institute
NHL	Non-Hodgkin’s Lymphoma
NIAID	National Institute of Allergy and Infectious Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NSAIDs	Non-steroidal anti-inflammatory drugs
PIS	Post-intervention Status
PLEX	Plasma Exchange
PML	Progressive Multifocal Leukoencephalopathy

PPI	Protocol Principal Investigator
PSC	Protocol Steering Committee
QMG	Quantitative Myasthenia Gravis
RA	Rheumatoid Arthritis
SAE	Serious adverse event
SLE	Systemic Lupus Erythematosus
SOA	Schedule of Activities
URMC	University of Rochester Medical Center

SYNOPSIS

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular transmission with an estimated annual incidence of about 1-2 per 100,000 and prevalence as high as 20-50 per 100,000.[1] Treatment consists of symptomatic therapy with acetylcholinesterase inhibitors and immunotherapy such as corticosteroids, azathioprine, cyclosporine, plasma exchange (PLEX) and intravenous immunoglobulin (IVIg).[1-3] Despite current therapies a subset of subjects remain medically refractory or have intolerable medication adverse effects. There is need for another agent in the management of MG as there are few effective drugs for these patients. Safe, well-tolerated, efficacious and steroid-sparing therapeutics are needed.

Several recent studies[4-6], including two performed by our group [7,8], have demonstrated the benefits of B cell depletion rituximab treatment in MG subjects. We completed a small retrospective study to evaluate B cell targeted therapy in medically refractory generalized MG [7,8]. In this analysis we showed that rituximab led to a sustained clinical improvement in parallel to a reduction or discontinuation of other immunotherapies.

We now plan on conducting a multicenter randomized, double-blind, placebo controlled Phase II clinical trial utilizing a futility design. The study would include acetylcholine receptor (AChR) antibody positive generalized MG subjects. This study also presents a unique opportunity to study both drug and disease mechanisms because unlike many other autoimmune diseases in which rituximab has been used, MG affords the investigation of antigen-specific components that participate in the immunopathology of the disease, namely autoantibodies, autoantibody-producing B cells, and antigen-specific T cells. This work will further our understanding of MG immunopathology and it represents the first step toward gaining a more complete understanding of the immune mechanisms underlying treatment of MG with rituximab leading to new ways to treat the disease.

The specific aim of this study is to determine whether rituximab is a safe and effective treatment for subjects with MG. Although not part of the current protocol, we believe that adding exploratory mechanistic studies to the protocol would be important in order to identify biomarkers that can potentially be used in future MG clinical trials as well as exploring whether B cell therapy is effective in MG. With this in mind, the investigators have received funding in full support of an exploratory mechanistic study with extended follow-up through the National Institute of Allergy and Infectious Diseases (NIAID). In addition, NINDS has awarded funding in support of the extended clinical follow-up visits.

Study Title

Full Title: **B** Cell Targeted Tr**eat**ment in **M**yasthenia **G**ravis: A Phase II Trial of Rituximab In Myasthenia Gravis

Short Title: BeatMG: Rituximab in Myasthenia Gravis

Objectives

The specific primary objective of this study is to determine whether rituximab is a safe and beneficial therapeutic for MG that warrants further study in a phase III efficacy trial. The primary clinical endpoint will be the steroid sparing effect of rituximab. Our retrospective study showed that rituximab treatment had a measurable and significant effect on conventional

immunosuppression, specifically demonstrating an unmistakable prednisone dose reduction[7]. Importantly, steroid-reduction was recently demonstrated to be a practical outcome measure in a MG trial by an independent group[9]. Also in 2012, the Task Force on MG Study Design of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America (MGFA) recommended steroid-sparing effect as a clinical outcome measure[10]. Our first primary outcome measure is the percent of subjects achieving ≥ 75% mean daily prednisone dose reduction in the 4 weeks prior to week 52 and with clinical improvement or no worsening of symptoms. Our second primary outcome is safety and will be assessed by examining the frequency of study-related adverse experiences between the treatment and placebo groups.

Design and Outcomes

We plan a multicenter randomized, double-blind, placebo controlled Phase II clinical trial evaluating the safety and steroid-sparing effect of rituximab in MG. The study will include 50 AChR antibody positive generalized MG subjects. We plan to enroll 25 subjects in a treatment group and 25 subjects in a control placebo group.

Primary Outcomes:

1. Steroid Sparing Effect: Percent of subjects that achieve a ≥ 75% reduction in mean daily prednisone dose in the 4 weeks prior to week 52 and with clinical improvement or no significant worsening of symptoms (≤ 2 point increase in MG composite score) as compared to the 4-week period prior to randomization and initiation of treatment.
2. Safety

Secondary Outcomes:

1. Evaluate whether there is a trend toward clinical benefit as measured by MG-specific clinical outcome scales used as endpoints in prior clinical trials. We will determine if rituximab can significantly improve the scores of the following MG-specific clinical outcome measures:
    a. Myasthenia Gravis Composite (MGC) score
    b. Quantitative Myasthenia Gravis (QMG) score

Interventions and Duration

Intervention (rituximab): The treatment group will receive a total of two cycles of rituximab separated by 6 months. Each cycle is defined as one infusion (375mg/m^2 IV) per week for four consecutive weeks. As such, cycle 1 will be administered weeks 0-3 and cycle 2 will be given weeks 24-27. The placebo group will receive a vehicle control infusion. A predetermined steroid taper schedule for both treatment (rituximab) and placebo groups will be utilized. In each subject, the prednisone dose will be gradually reduced based on the steroid taper schedule beginning at week 8. The dose will only be reduced after confirming clinical improvement or stable symptoms based on the MGC score (≤ 2 point increase).

Duration: We set a study period of 52 weeks based on the delayed benefits observed following rituximab treatment and in the setting of utilizing a two-cycle protocol. The extended time points are needed as normalization of B cell counts typically takes 12+ months following B cell depletion treatment. In order to assess safety in the B cell recovery period as well as assess the long-term durability of response, there are two additional optional observational off study-intervention time points (weeks 72 and 96). The subjects will be treated per medical standard of care during this period.

Evaluations: Subjects will have clinical evaluations at baseline and then every 4 weeks thereafter (week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52). Clinical evaluations will be completed by a blinded evaluator. The dose of prednisone will be recorded by each subject daily and collected at each scheduled assessment. Post-intervention status (PIS) will be assessed by measuring MGFA class, MGC, QMG, MG-ADL and MG-QOL scores. Adverse effects will be monitored to assess safety and tolerability in this subject population per the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. A limited clinical assessment per standard of care will be completed during the optional off study-intervention follow-up period at weeks 72 and 96.

Blinding

This is a double-blind clinical trial. All study subjects and Clinical Study Staff will be blinded to treatment assignment. The Clinical Study Site Investigator is responsible reviewing all adverse events and adjusting subjects' prednisone dose based on the Myasthenia Gravis Composite (MGC) score without knowing whether a subject has received drug or placebo. The clinical evaluators who determine the secondary outcome measures, Myasthenia Gravis Composite (MGC) and Quantitative Myasthenia Gravis (QMG), are blinded to treatment assignment and clinical adverse event information. Site Pharmacists will be the only staff who have access to treatment information.

Sample Size and Population

Sample Size: 50

Population: Generalized AChR Antibody Positive (AChR+) Myasthenia Gravis

Randomization will be performed through an interactive website, and will be stratified based on the steroid dose at baseline: moderate dose prednisone (15-35 mg/day) and high dose prednisone (>35 mg/day) as well as their treatment at baseline, prednisone only versus prednisone plus another immunosuppressive therapy (IST). Subjects will be assigned a study ID at the time of enrollment. The study ID includes the identification of the center and a unique subject ID. The DCC will generate a randomization table for each of the strata using a permuted block design with random block sizes.

Inclusion Criteria:

1. Subjects 21 to 90 years old
2. Subjects must have generalized MG, defined as MGFA clinical classification grades 2 (mild), 3 (moderate), or 4 (severe, but not intubated) at the time of screening/randomization.
3. Elevated AChR antibody titer
4. Subject's signs and symptoms should not be better explained by another disease process.
5. Subjects must be on a stable standard immunosuppressive regimen:
   a. *Prednisone only:* Prednisone dose must be at least 15mg/day (or the equivalent on alternate days), and the dose of prednisone must have been stable for at least 4 weeks (28 days) prior to the baseline visit.
   b. *Prednisone plus another immunosuppressive therapy (IST).* Immunosuppressive therapies other than prednisone, specifically azathioprine, mycophenolate

mofetil, cyclosporine, tacrolimus or methotrexate, are permitted, but the dose must have been stable for at least 6 months prior to the baseline visit.
(Note: The prednisone dose must be stable as defined in the prednisone only group. The IST dose must remain stable throughout the course of the study).

6. Subjects must be willing to complete the study and return for follow-up visits.
7. No history of thymoma, tumor, infection, or interstitial lung disease on chest CT, MRI, or chest x-ray. Note: Chest x-ray will be completed at screening to look of interstitial lung disease. A chest CT or MRI to evaluate for thymoma must be completed as part of prescreening.
8. Able and willing to give written informed consent and comply with the requirements of the study protocol.
9. Subjects must be able to give written informed consent before participating in this study. A copy of the signed consent must be kept in the subject's medical record.
10. Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for twelve months (1 year) after completion of treatment.

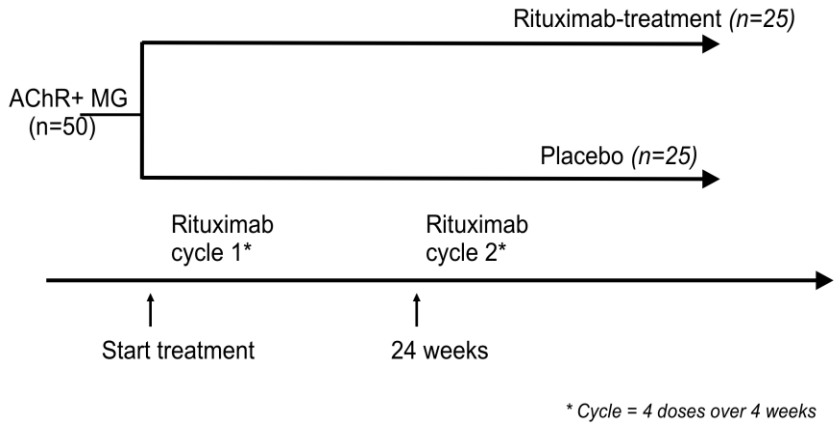
Exclusion Criteria:

1. A history of chronic degenerative, psychiatric, or neurologic disorder other than MG that can produce weakness or fatigue.
2. Other major chronic or debilitating illnesses within six months prior to study entry.
3. Female subjects who are premenopausal and are:
   (a) pregnant on the basis of a serum pregnancy test,
   (b) breast-feeding, or
   (c) not using an effective method of double barrier (1 hormonal plus 1 barrier method or 2 simultaneous barrier methods) or birth control (birth control pills, male condom, female condom, intrauterine device, Norplant, tubal ligation, or other sterilization procedures).
4. Altered levels of consciousness, dementia, or abnormal mental status.
5. Thymectomy in the previous six months.
6. Subjects who have been medicated with immunosuppressive drugs not listed in inclusion #5 within the last 8 weeks (56 days) prior to the baseline visit
7. Subjects who have been medicated with an immunosuppressive agent such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus or methotrexate, that is withdrawn within 8 weeks (56 days) of the Baseline Visit.
8. Subjects who have received IVIg or PLEX treatment within the last 4 weeks (28 days) prior to the baseline visit.
9. Unstable dose or a stable dose of > 480 mg/day of pyridostigmine in 2 weeks prior to screening visit.
10. Daily use of non-steroidal anti-inflammatory drugs (NSAIDs).
11. History of renal or hepatic insufficiency or elevated liver enzymes (AST or ALT >2.5 x Upper Limit of Normal).
12. History of bone marrow hypoplasia, leucopenia, thrombocytopenia, significant anemia, clinical or laboratory evidence of immunodeficiency syndromes, that are not transient events or side effects related to a clinical procedure (i.e. plasmapheresis) and within one year of screening.
13. Forced Vital Capacity (FVC) <50% of percent predicted.
14. ANC < 1.5 x 10^3 cells/microliter

15. Hemoglobin: < 8.0 gm/dL
16. Platelets: < 100,000/mm
17. Positive Hepatitis B or C serology (Hep B surface antigen and Hep C antibody)
18. History of positive HIV (HIV conducted during screening if applicable)
19. Treatment with any investigational agent within 4 weeks of screening or 5 half-lives of the investigational drug (whichever is longer)
20. Receipt of a live vaccine within 4 weeks prior to randomization
21. Previous treatment with rituximab (MabThera® / Rituxan®)
22. Previous treatment with natalizumab (Tysabri®)
23. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
24. History of recurrent significant infection or history of recurrent bacterial infections
25. Known active bacterial, viral fungal mycobacterial, or other infection (including tuberculosis or atypical mycobacterial disease, but excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening
26. Unstable steroid dose in the past 4 weeks (28 days)
27. Lack of peripheral venous access
28. History of drug, alcohol, or chemical abuse within 6 months prior to screening
29. Concomitant malignancies or previous malignancies, with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or prostate.
30. History of psychiatric disorder that would interfere with normal participation in this protocol
31. Significant cardiac or pulmonary disease (including obstructive pulmonary disease)
32. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications.
33. Subjects that do not record daily prednisone doses for at least 28 days before the Baseline visit, or subjects whose prednisone dose varies by ≥6mg/day on average.
34. Prednisone dose of more than 100 mg/day (or 200 mg over a two day period).

OVERVIEW STUDY SCHEMA

A randomized, double-blind, placebo controlled clinical trial schematic is shown below. A total of 50 AChR+ MG subjects will be enrolled (25 in a treatment arm and 25 in a placebo arm). The subjects will be evaluated every 4 weeks for 52 weeks after initial treatment along with two additional optional observational off study-intervention time points at weeks 72 and 96.



STUDY OBJECTIVES

1.1 Primary Objectives

Several recent studies [4-6], including two performed by our group [7,8], have demonstrated the benefits of B cell depletion rituximab treatment in MG subjects. We completed a small retrospective study to evaluate B cell targeted therapy in medically refractory generalized MG [7,8]. In this analysis we showed that rituximab led to a sustained clinical improvement in parallel to a reduction or discontinuation of corticosteroid therapy and plasma exchange treatments. We observed a prednisone dose reduction by a mean of 65%, 86% and 94% after one, two and three cycles of rituximab, respectively (**Figure 1**).

The specific primary aim of this study is to determine whether rituximab is a safe and beneficial therapeutic for MG that warrants further study in a phase III efficacy trial. The primary clinical endpoint will be the steroid sparing effect of rituximab (mean daily prednisone dose in the last 4 weeks of the study). Our retrospective study showed that rituximab treatment had a measurable and significant effect on conventional immunosuppression, specifically demonstrating an unmistakable prednisone dose reduction. Importantly, steroid-reduction was recently demonstrated to be a practical outcome measure in a MG trial by an independent group [9]. Also in 2012, the Task Force on MG Study Design of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America (MGFA) recommended steroid-sparing effect as a clinical outcome measure [10].

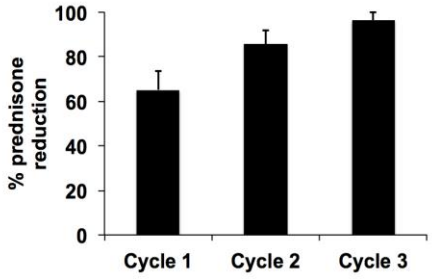


Figure 1. Effect of rituximab on conventional immunosuppression. Prednisone dose reduction following treatment with cycles 1 through 3 of rituximab. The mean dose reduction of the MG subject cohort (n=14) following each cycle of treatment was calculated as reduction of baseline dose given prior to treatment

Primary Outcome 1. Our first primary outcome measure is the percent of subjects that achieve a ≥ 75% reduction in mean daily prednisone dose in the 4 weeks prior to week 52 and with clinical improvement or no significant worsening of symptoms (≤ 2 point increase in MG Composite score)

as compared to the 4 week period prior to randomization and initiation of treatment. Statistical considerations, including futility design, will be further discussed in section 9.

Primary Outcome 2. Our second primary outcome is safety and will be assessed by examining the frequency of study-related adverse experiences in the two groups (treatment vs. placebo).

1.2 Secondary Objectives

The main secondary objective is to evaluate whether there is a trend toward clinical benefit as measured by MG-specific clinical outcome scales. If successful, measures studied would lay the groundwork toward optimizing the design of a subsequent phase III efficacy trial of rituximab in MG.

Secondary Outcomes. Our secondary outcomes will focus on whether there is a trend toward clinical benefit as measured by MG-specific clinical outcome scales used as endpoints in prior clinical trials. We will determine if rituximab can significantly improve the scores of the following MG-specific clinical outcome measures: (1) Myasthenia Gravis Composite score (MGC). (2) Quantitative Myasthenia Gravis score (QMG).[10] [11-13] These studied measures would lay the groundwork toward optimizing the design of a subsequent phase III efficacy trial of rituximab in MG.

Additional exploratory clinical outcomes will be investigated to monitor effectiveness as well as evaluate other endpoints that would be useful in optimizing future MG trial designs as well as a Phase III rituximab trial.

Clinical Exploratory Outcomes.
We will determine if rituximab can significantly improve the scores of the following outcome measures: (1) MG-Activities of Daily Living (MG-ADL).[14] (2) MG-Quality of Life (MG-QOL).[15]

Other previously used measures of steroid-sparing effect will be assessed: (1) Mean daily prednisone dose at each scheduled assessment (every 4 weeks). (2) A delayed start of the area under the dose-time curve (AUDTC), starting at week 8. (3) Percentage of subjects achieving a ≥ 50% mean daily prednisone dose reduction with maintenance of minimal or no symptoms in 4 weeks prior to week 52. (4) Body Mass Index (Screening Visit and weeks 24 and 52). (5) HbA1C (Screening Visit and week 52).

MG flare rate (failure of therapy) will be assessed by: (1) Number of rescue treatments (PLEX or IVIg). (2) Number of times prednisone dose needed to be increased. (3) Frequency of a ≥ 3-point increase in the MGC score.

Additionally, there will be two optional observational off study-intervention time points (weeks 72 and 96) The primary focus will be to assess B cell recovery/repopulation as a safety measure. Specifically, we will examine: (1) Percentage of subjects achieving normal B cell counts at week 72 and 96. (2) Percentage of achieving baseline B cell counts at week 72 and 96. (3) Percent B cell recovery to normal or baseline levels. In addition, the long-term durability of response will also be assessed. Specifically, we will examine: (1) Percentage of subjects achieving a sustained ≥ 75% mean daily prednisone dose reduction. (2) Percentage of subjects achieving a ≥ 50% mean daily prednisone dose reduction. (3) Prednisone AUDTC (if applicable). (4) Clinical status as

measured by MGFA Class, MGC, MG-QOL and MG-ADL scores. (5) Number of rescue treatments (PLEX or IVIg).

Biomarker/Mechanistic Exploratory Outcomes.
The biomarker or mechanistic studies are focused on identifying how treatment modifies the immunopathology of MG. We will study changes in the antigen specific components of the MG immune system. We have developed/adapted immunoassays so that we can examine autoantibodies, B cells and T cells. The principal mechanistic outcome will be the decrease in titer of circulating AChR autoantibodies within an individual. Other exploratory mechanism-based outcomes include determining how rituximab modifies antigen-specific B cell frequency, the B cell repertoire, B cell activating factor (BAFF) levels and whether rituximab modifies antigen-specific T cell frequency and phenotype. Measurements will be performed prior to and during B cell depletion and through repopulation of the B cell compartment, which will be of particular interest in terms of assessing the durability of the treatment. Blood will be collected for mechanistic studies at the Baseline Visit, and at weeks 24, 52, 72 and 96.

2 BACKGROUND

2.1 Rationale

Overview. Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular transmission with an estimated annual incidence of about 1-2 per 100,000 and prevalence as high as 20-50 per 100,000.[1, 16] Treatment consists of symptomatic therapy with acetylcholinesterase inhibitors and immunotherapy such as corticosteroids, azathioprine, cyclosporine, plasma exchange (PLEX) and intravenous immunoglobulin (IVIg).[1-3] Despite current therapies a subset of subjects remain medically refractory or have intolerable medication adverse effects.

Project Rationale. Autoreactive B cells play an important role in the immunopathogenesis of MG and as such would seem to be appropriate for targeted drug therapy investigation.[17] Recent examples from other autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and multiple sclerosis (MS), which also frequently have poor response to current conventional therapy and frequent relapses or refractory disease, have suggested benefit with B cell directed therapies.[18-21] B cell depletion may therefore be a beneficial therapeutic goal in certain autoimmune diseases based on this experience[22] and may potentially translate into a new treatment strategy for MG, particularly in those subjects who have failed and are resistant to other medical therapies.

Rituximab is the only B cell directed biologic approved for use clinically. It is a chimeric monoclonal antibody that targets the CD20 antigen found on B lymphocytes and modulates B cell activation. CD20 is a 33-kDa protein expressed by all mature B cells, but not on pre-B or differentiated plasma cells. Rituximab has been used as part of the standard therapy for non-Hodgkin's lymphoma (NHL) as well as a number of autoimmune diseases.[18,23,24,] Interest in its use for MG began after Gajra and coworkers reported a subject with both lymphoma and MG who responded favorably to rituximab.[25] Since that time several groups, including our own, have observed the benefits of rituximab in autoimmune MG subjects.[4-8,26-33] It is, however, unclear what changes in the cellular and molecular immune system are associated with the clinical improvement.

The observed positive effect of rituximab in subjects with MG, based largely on anecdotal reports, is promising and suggests that further investigation of this agent in MG is warranted (refer to **Table 1**).[34] The rationale for the current proposal is to follow our pilot retrospective study with a prospective study to more carefully assess the safety, tolerability and identify biomarkers in this subject population as well as determine whether it is beneficial therapeutic, employing a futility trial design, that warrants further study in a phase 3 efficacy trial.[7,8,35] In addition, we will initiate an examination of the changes in the cellular immune system that are associated with the clinical improvement to further define the immune mechanisms associated with treatment by measuring immune components, which participate in the pathology of MG, prior to and after immunotherapy. This work is significant because it addresses an important and intractable immune-mediated problem involving the neuromuscular junction as well as helps further our understanding of the immunopathology of MG. It also represents, for the first time in MG, the application of targeted therapy. The study of immunologic biomarkers will help elucidate potentially important differences in subjects that are responders and non-responders to B cell directed therapy. This may give insight into further development of individual subject tailored therapies in the future.

Table 1: Key Reports of Rituximab in Myasthenia Gravis (adapted from Ibrahim et al.)[34]

Study	Year	Subject number	Controlled	Grade of Evidence	Dose of rituximab	Outcomes
Illa et al	2008	6	No	D	375 mg/m^2 every week for four consecutive weeks	Improvement of clinical and laboratory parameters, especially in the 3 MuSK+ cases
Lindberg et al	2010	5	No	D	375 mg/m^2 every week for four consecutive weeks, retreatment with 1000 mg weekly x2	Slow but remarkable reduction in MG symptoms.
Maddison et al	2010	12	No	C	375 mg/m^2 every week for four consecutive weeks	8 improved,4 subject did not have significant benefit
Tandan et al	2010	10	No	C	Ongoing pilot study	Ongoing pilot study
Stieglbauer et al	2009	3	No	D	Guided by the total count of peripheral B lymphocytes	Improved
Lebrun et al	2009	6	No	D	375 mg/m^2 every week for four weeks then 2-monthly dose of 375 mg/m^2	3 MuSK+, 1 AChR+ and 2 double seronegative improved
Nelson et al	2009	3	No	D	375 mg/m^2 every week for four consecutive weeks, one subject received only one dose	3 MG cases with thymoma responded with stabilization and reductions in immunosuppressive medications
Kundi et al	2010	3	No	D	1 gram (750mg/m^2) repeated twice	1 MuSK+, 1 AchR+ and 1 double seronegative improved
Nowak et al	2011	14	No	C	375 mg/m^2 every week for four, repeated every 6 mo	6 AChR+ and 8 MuSK+ subjects showed clinical

Study	Year	Subject number	Controlled	Grade of Evidence	Dose of rituximab	Outcomes
						improvement and significant steroid dose reduction
Blum et al	2011	14	No	C	1 gram in 2 divided doses	11 subjects clinically improved and 12 were able to reduce other immunotherapies
Diaz-Manera et al	2012	17	No	C	375 mg/m^2 every week for 4 weeks, then monthly x 2 months	6/6 MuSK+ subjects achieved remission or minimal manifestation status; 10/11 AChR+ subjects improved with 6/10 subjects needing reinfusion 6-34 mo after 1st dose.

There is a paucity of proven steroid-sparing agents in the management of MG. The most convincing steroid-sparing agent is azathioprine (AZA) with some recent evidence supporting methotrexate (MTX).[36,37] The current mycophenolate mofetil (MMF) and tacrolimus data are not very strong but are suggestive of some benefit.[9,38] There is need for another agent in the management of MG as there are few effective drugs, as well as a subset of subjects that are medically refractory or drug-resistant to standard therapies. Safe, well-tolerated, efficacious and steroid-sparing therapeutics are needed.

Protocol Rationale. A standard protocol for rituximab infusion in MG has not been established. Therefore, the non-Hodgkin's Lymphoma (NHL) treatment protocol was adopted which consists of weekly infusions at 375 mg/m^2. One cycle is defined as 1 infusion per week for 4 consecutive weeks. The interval between cycles is 6 months. We have based our decision to use a two-cycle regimen, instead of a single cycle approach, on the following evidence. A recently published European series evaluating the long-term effects of rituximab following one cycle did show clinical improvement [4]. While clinical improvement was achieved, an immunotherapy-free remission state was not. Fifteen of 17 subjects continued to remain on prednisone and/or additional immunotherapy. Six out 10 AChR+ subjects in this study needed to be retreated to maintain initial clinical benefits. We believe that an additional treatment cycle may be indicated to achieve a durable response in parallel to successful withdrawal/reduction of steroids and/or other chronic immunotherapy. Retrospective analysis of twenty MG subjects followed in our neuromuscular clinic has shown that only 5 of 20 subjects were immunotherapy-free after completing one cycle as compared to 12 of 20 following two cycles. Mean steroid dose was reduced by 65% and 86% following one and two cycles, respectively. This suggests that a two-cycle protocol may be more clinically advantageous in MG and serves as the basis for our approach. Retrospective analysis of our data with the DCC also revealed that 82% of subjects who received rituximab achieved at least a 75% reduction in their prednisone dose at 52 weeks (95% CI: 48%-98%). This statistical analysis is the basis for our primary endpoint.

2.2 Supporting Data

The first reports on the use of rituximab in MG were in subjects treated for lymphoma.[25,39] In three of these subjects, rituximab was administered at 375 mg/m^2 weekly for four weeks, and in one, the

dose was 260 mg/m^2 weekly for four weeks. Clinical symptoms of MG such as diplopia and muscle fatigability as well as pulmonary function tests showed improvement with a decrease in the serum AChR antibody levels.

This was followed by the publication of several small and one large uncontrolled case series. In 2008, Illa and co-workers reported treating six severe refractory MG subjects (three AChR+ and three MuSK+ (Muscle Specific Kinase Antibody Positive)) with rituximab at 375 mg/m^2 weekly for four weeks.[5] All six cases (five MGFA Grade IVb and one Grade V) dramatically improved clinically. There was a decline in serum antibody titers in both AChR+ and MuSK+ groups. There appeared to be a more sustained clinical improvement in the MuSK+ group. No severe adverse events were reported.

Investigators in the United Kingdom reported data obtained from a nationwide survey of physicians treating MG.[27] They identified ten subjects diagnosed with generalized MG (seven AChR+ and three MuSK+) and two with Lambert-Eaton myasthenic syndrome. Rituximab was administered in standard doses in eight cases, whereas the rest received one or two infusions at 375 mg/m^2. Over the 4 to 48 month follow-up period, three of seven AChR+ MG cases improved on their MGFA post-intervention status, whereas all MuSK+ cases improved. Both Lambert-Eaton myasthenic syndrome cases improved but did not achieve remission. Four subjects did not have significant benefit from rituximab, three of which received fewer than four infusions.

There are other small case series that have suggested similar efficacy of rituximab in generalized MG.[8,29,30] Lebrun and coworkers evaluated six bedridden MG cases; one was AChR+, three had MuSK+, and two were double-seronegative cases.[6] Rituximab was administered at 375 mg/m^2 on Days 1, 8, 15, and 21 during the first month and then one dose every 2 months. All subjects responded very well to rituximab with significant clinical improvement allowing for the tapering of prednisone and pyridostigmine bromide.

Our group has recently completed a retrospective study of fourteen subjects to evaluate B cell targeted therapy in medically refractory generalized MG, including both MuSK+ and AChR+ antibody subjects.[7] Rituximab was given at a standard dose of 375 mg/m^2 weekly. Each cycle was defined as one infusion per week for four consecutive weeks. Interval between cycles was set at 6 months. In this analysis, we showed that rituximab led to a sustained clinical improvement in parallel to a reduction or discontinuation of corticosteroid therapy and plasma exchange treatments. We observed a prednisone dose reduction by a mean of 85.7% and 93.8% after two and three cycles of rituximab, respectively. AChR antibody titers significantly decreased by a mean of 52.1% after the second cycle ($p = 0.005$).

A group in Europe recently published a report describing seventeen drug-resistant MG subjects treated with rituximab (six MuSK+ and eleven AChR+).[4] After a mean post-treatment period of 31 months, ten of the AChR+ subjects improved but six of them needed reinfusions. In contrast, all MuSK+ subjects achieved a remission or minimal manifestations status and no need for reinfusions. Consequently, in the MuSK+ group, prednisone doses were reduced (average dose before rituximab: 49 mg/day; at last visit: 6.5 mg/day) and other immunotherapies could be withdrawn. Clinical improvement was associated with a significant decrease in the antibody titers only in the MuSK+ subjects (mean reduction of 86.7%, $p = 0.002$). MuSK antibody levels were either negative or decreased at the last follow-up period. They concluded that rituximab has long-lasting benefits in MuSK+ subjects and recommend rituximab as an early therapeutic option in this group of subjects with MG if they do not respond to steroids. AChR+ subjects also responded to treatment but required repeat treatment.

To date, approximately seventy-five cases of MG treated with rituximab have been reported. The majority of subjects were observed to benefit from treatment. In the absence of a controlled, prospective clinical trial and reporter bias for positive studies, it is difficult to firmly conclude that rituximab is an efficacious therapeutic in MG. The evidence thus far warrants further investigation.

The safety of rituximab therapy is an important concern. The most common side effect reported is an infusion reaction consisting mainly of fever, rigors, nausea and hypotension. Progressive multifocal leukoencephalopathy (PML) is the most significant complication, however, the relative risk is thought to be low per a recent review[40]. Per this review, there have been a total of 57 PML cases following rituximab therapy in HIV-negative patients from 1997 to 2008. These numbers are based on cases reported to the Food and Drug Administration (FDA) as well as reported in the medical literature. Fifty-two of the cases were patients with B-cell lymphoproliferative disorders and the remaining 5 cases were patients with an autoimmune disorder (i.e., SLE, rheumatoid arthritis, autoimmune pancytopenia). There have been no cases of PML reported in MG subjects treated with rituximab. We plan to minimize concomitant immunosuppressive therapies in our subjects and plan to enroll subjects who are either only on prednisone or on prednisone plus only one other IST. Please refer to eligibility criteria for specific details. These regimens represent real world scenarios and are also consistent with the types of patients included in our pilot study[7]. We recommend this type of approach prior to initiating rituximab as combination treatments could pose a higher PML risk.

Please refer to the study drug package insert for additional details.

3 STUDY DESIGN

Clinical Trial Design. We propose a multicenter randomized, double-blind, placebo controlled clinical trial evaluating the safety and steroid-sparing effect of rituximab in MG. The study would enroll AChR antibody positive generalized MG subjects (**Figure 2**). Based on sample size calculations we propose a study of 50 total subjects. We expect to enroll 25 AChR+ subjects in a treatment group along with 25 subjects in a control placebo group.

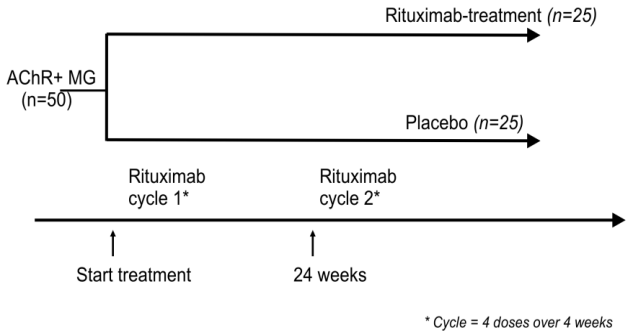


Figure 2. Schematic diagram outlining trial design. A randomized, double-blind, placebo controlled clinical trial is shown. A total of 50 AChR+ subjects would be enrolled (25 in a treatment arm and 25 in a placebo arm). The subjects will be evaluated every 4 weeks for 52 weeks after initial treatment. There are two additional optional time points at weeks 72 and 96 in order to follow B cell recovery and long-term durability of response.

Subjects. Subjects who are on standard of care treatment regimens for MG may enroll. Each previously diagnosed generalized MG subject at time of enrollment will be expected to be on a stable fixed dose of prednisone (minimum dose of 15 mg/day) for at least 4 weeks (28 days) with stable symptoms. Prednisone dose variation would be limited to less than 6 mg/day on average in the 4 weeks (28 days) prior to the start of the study or randomization. There will be two groups of standard of care treatment regimens and are defined as:

- *Prednisone only.*

- *Prednisone plus another IST.* The prednisone dose must be as defined above and the subject must be on a stable dose for at least 6 months prior to baseline on one of the following IST: azathioprine, mycophenolate mofetile, cyclosporine, tacrolimus or methotrexate.

Study Duration. We set a study period of 52 weeks based on the delayed benefits observed following rituximab treatment and in the setting of utilizing a two-cycle protocol.

In order to assess the long-term durability of response, there are two additional optional observational off study-intervention time points (weeks 72 and 96). The subjects will be treated per medical standard of care during this period. The extended time points are also needed as normalization of B cell counts typically takes 12+ months following B cell depletion treatment.

Randomization. Randomization will be performed through an interactive website, and will be stratified based on the steroid dose at baseline: moderate dose prednisone (15-35 mg/day) and high dose prednisone (>35 mg/day) as well as standard of care treatment regimen at the baseline visit (prednisone only vs. prednisone plus another IST). Subjects will be assigned a study ID at the time of enrollment. The study ID includes the identification of the center and a unique subject ID. The DCC will generate a randomization table for each of the strata using a permuted block design with random block sizes.

Blinding. This is a double-blind clinical trial. All study subjects and Clinical Study Staff will be blinded to treatment assignment. The Clinical Study Site Investigator is responsible reviewing all adverse events and adjusting subjects' prednisone dose based on the Myasthenia Gravis Composite (MGC) score without knowing whether a subject has received drug or placebo. The clinical evaluators who determine the secondary outcome measures, Myasthenia Gravis Composite (MGC) and Quantitative Myasthenia Gravis (QMG), are blinded to treatment assignment and clinical adverse event information. Site Pharmacists will be the only staff who have access to treatment information.

Rituximab. Treatment group will receive a total of two cycles of rituximab (375mg/m^2) separated by 6 months. Each cycle is defined as one infusion per week for four consecutive weeks. As such, cycle 1 will be administered weeks 0-3 and cycle 2 will be given weeks 24-27. The placebo group will receive an infusion that contains only the vehicle components of the rituximab solution.

Prednisone. A predetermined steroid taper schedule for both treatment (rituximab) and placebo groups will be utilized. In each subject, the prednisone dose will be gradually reduced based on the steroid taper schedule beginning at week 8. The dose will only be reduced after confirming clinical improvement or stable symptoms based on the MGC score (≤ 2 point increase) as compared to the Baseline Visit or prior study visit MGC score. If the MGC score change is ≥ 3 points, the prednisone dose would be increased until symptoms resolved or at least stabilized to baseline status (baseline visit MGC score). After symptom stabilization, prednisone taper can again be resumed at next scheduled assessment. Subjects would continue in the study even if they could not taper off higher doses of steroids (40-60 mg/day) as long as their symptoms were controlled on that dose as this would be considered standard-of-care.

Rescue Therapy. If subject symptoms significantly worsen during the course of the trial and are not controlled by increased steroid doses (high dose prednisone), the subject can receive PLEX or IVIg as a rescue therapy. PLEX and IVIg treated subjects would remain in the study and be

included in data analysis. The rationale for this is that these subjects would have already been up titrated to a high prednisone dose but failed to adequately respond. Subjects that could not be managed with steroids, IVIg, or PLEX and required additional immunotherapy (e.g., pulse IV steroids, azathioprine, etc.) would be considered treatment failures and potentially drop out of the study.

Pyridostigmine. Subjects on pyridostigmine must be on a stable dose of ≤480 mg/day for a minimum of 2 weeks prior to the Screening Visit. Subject must remain on a stable fixed dose for the duration of the study. The dose cannot be changed after study entry.

Note: Subjects on pyridostigmine should be instructed to hold their medication for a minimum of 12 hours prior to the Baseline Visit and all subsequent Clinical Study Visits.

Assessments. Subjects will have clinical evaluations at baseline and then every 4 weeks thereafter (week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52) completed by a blinded evaluator (refer to SOA). Evaluations must be completed within +/- 3 days of scheduled assessment. The dose of prednisone will be recorded by each subject daily and collected at each scheduled evaluation. Post-intervention status will be assessed by measuring MGFA, MGC, QMG, MG-ADL and MG-QOL scores. Blood will be collected for safety, specialized and other studies at scheduled time points (refer to SOA table). Adverse effects will be monitored at each visit to assess safety and tolerability in this subject population per Genentech and DAIT's guidelines. Please see SOA and Section 6.4.5 for details pertaining to assessments done at the optional off-intervention follow-up visits at Weeks 72 and 96.

Outcome Measures. We will assess both the safety and steroid-sparing effect of rituximab in MG. The primary clinical endpoint, steroid sparing effect, will be measured by determining the percentage of subjects achieving a ≥ 75% mean daily prednisone dose reduction and with clinical improvement or no significant worsening of symptoms in the last 4 weeks of the study (weeks 49-52).

MGC, QMG, MG-ADL and MG-QOL scales will be completed at each clinic visit and determine changes.

Laboratory Assessments, Safety monitoring, serology testing, and specialized blood work will be obtained at the Screening Visit, Baseline Visit, Week 24 Visit, Week 52 visit and any Unscheduled Visits. All these labs will be centrally analyzed. These include:

- Standard bloods: comprehensive metabolic panel, uric acid, LDH and CBC with platelets and differential (Screening, Week 52 and Unscheduled).
- HbA1C will be measured (Screening and Week 52).
- Serology testing: HBV, HCV, HIV (Screening).
- Specialized bloods: AChR antibody titer, Total IgG, IgA and IgM levels, Flow cytometry to assess B cell count (Baseline, Week 24, Week 52 and Unscheduled).
  NOTE – Specialized bloods should be drawn prior to daily prednisone dose.
- Mechanistic Bloods (Baseline, Week 24, Week 52 and Unscheduled).

Note Specialized and Mechanistic Biomarker blood work will also be done at the optional off-intervention follow-up visits at Weeks 72 and 96. For more details, please refer to section 6.4.7.

Infusion Labs (complete metabolic panel, uric acid, LDH and CBC with platelets and differential) will be collected at each infusion visit and analyzed at each institution's local laboratory prior to study drug infusion.

A complete listing of Laboratory Assessments is included in Section 6.3.6

Optional off-intervention follow-up. A limited clinical assessment will be completed during the optional observational off-study intervention period at weeks 72 and 96. Evaluations for these visits, if the subject is willing to participate, must be completed within /+/-30 days of scheduled assessment. Procedures include physical exam, outcomes assessments and blood collection. For more details regarding what is required to be done and collected, please refer to the SOA and section 6.4.5.

Note As the primary focus of the two additional optional observational time points is to assess B cell recovery/repopulation as a safety measure, subjects who have received treatment with rituximab, or have been involved with other interventions that result in Bcell depletion since completion of the trial (i.e. Week 52) will be excluded from the optional off-intervention follow-up visits.

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

Subject selection will be based on a diagnosis of MG and the following specific criteria:

1. Subjects 21 to 90 years old
2. Subjects must have generalized MG, defined as MGFA clinical classification grades 2 (mild), 3 (moderate), or 4 (severe, but not intubated) at the time of screening/randomization.
3. Elevated AChR antibody titer
4. Subject's signs and symptoms should not be better explained by another disease process.
5. Subjects must be on a stable standard immunosuppressive regimen:
   a. *Prednisone only:* Prednisone dose must be at least 15mg/day (or the equivalent on alternate days), and the dose of prednisone must have been stable for at least 4 weeks (28 days) prior to the baseline visit.
   b. *Prednisone plus another immunosuppressive therapy (IST).* Immunosuppressive therapies other than prednisone, such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus or methotrexate, are permitted, but the dose must have been stable for at least 6 months prior to the baseline visit.
   (Note: The prednisone dose must be stable as defined in the prednisone only group. The IST dose must remain stable throughout the course of the study).
6. Subjects must be willing to complete the study and return for follow-up visits.
7. No history of thymoma, tumor, infection, or interstitial lung disease on chest CT, MRI, or chest x-ray. Note: Chest x-ray will be completed at screening to look of interstitial lung disease. A chest CT or MRI to evaluate for thymoma must have been completed as part of prescreening.
8. Able and willing to give written informed consent and comply with the requirements of the study protocol.

9. Subjects must to able to give written informed consent before participating in this study. A copy of the signed consent must be kept in the subject's medical record.
10. Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for twelve months (1 year) after completion of treatment.

4.2 Exclusion Criteria

Disease Specific Exclusion Criteria

1. A history of chronic degenerative, psychiatric, or neurologic disorder other than MG that can produce weakness or fatigue.
2. Other major chronic or debilitating illnesses within six months prior to study entry.
3. Female subjects who are premenopausal and are:
   (a) pregnant on the basis of a serum pregnancy test,
   (b) breast-feeding, or
   (c) not using an effective method of double barrier (1 hormonal plus 1 barrier method or 2 simultaneous barrier methods) or birth control (birth control pills, male condom, female condom, intrauterine device, Norplant, tubal ligation, or other sterilization procedures).
4. Altered levels of consciousness, dementia, or abnormal mental status.
5. Thymectomy in the previous six months.
6. Subjects who have been medicated with immunosuppressive drugs not listed in inclusion #5 within the last 8 weeks (56 days) prior to the baseline visit.
7. Subjects who have been medicated with an immunosuppressive agent such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus or methotrexate, that is withdrawn within 8 weeks (56 days) of the Baseline Visit.
8. Subjects who have received IVIg or PLEX treatment within the last 4 weeks (28 days) prior to the baseline visit.
9. Unstable dose or a stable dose of > 480 mg/day of pyridostigmine in 2 weeks prior to screening visit
10. Daily use of non-steroidal anti-inflammatory drugs (NSAIDs).
11. History of renal or hepatic insufficiency or elevated liver enzymes (AST or ALT >2.5 x Upper Limit of Normal).
12. History of bone marrow hypoplasia, leucopenia, thrombocytopenia, significant anemia, clinical or laboratory evidence of immunodeficiency syndromes, that are not transient events or side effects related to a clinical procedure (i.e. plasmapheresis) and within one year of screening.
13. Forced Vital Capacity (FVC) <50% of percent predicted.

General Safety & Laboratory Exclusion Criteria

14. ANC < 1.5 x 10^3 cells/microliter
15. Hemoglobin: < 8.0 gm/dL
16. Platelets: < 100,000/mm
17. Positive Hepatitis B or C serology (Hep B surface antigen and Hep C antibody)
18. History of positive HIV (HIV conducted during screening if applicable)
19. Treatment with any investigational agent within 4 weeks of screening or 5 half-lives of the investigational drug (whichever is longer)

20. Receipt of a live vaccine within 4 weeks prior to randomization
21. Previous treatment with rituximab (MabThera® / Rituxan®)
22. Previous treatment with natalizumab (Tysabri®)
23. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
24. History of recurrent significant infection or history of recurrent bacterial infections
25. Known active bacterial, viral fungal mycobacterial, or other infection (including tuberculosis or atypical mycobacterial disease, but excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening
26. Unstable steroid dose in the past 4 weeks (28 days)
27. Lack of peripheral venous access
28. History of drug, alcohol, or chemical abuse within 6 months prior to screening
29. Concomitant malignancies or previous malignancies, with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or prostate.
30. History of psychiatric disorder that would interfere with normal participation in this protocol
31. Significant cardiac or pulmonary disease (including obstructive pulmonary disease)
32. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications
33. Subjects that do not record daily prednisone doses for at least 28 days before the Baseline Visit, or subjects whose prednisone dose varies by ≥6mg/day on average.
34. Prednisone dose of more than 100 mg/day (or 200 mg over a two day period).

4.3 Subject Withdrawal Criteria

If subject symptoms significantly worsen during the course of the trial and are not controlled by increased steroid doses (high dose prednisone), the subject can receive PLEX or IVIg as a rescue therapy. PLEX and IVIg treated subjects would remain in the study and be included in data analysis. The rationale for this is that these subjects would have already been up titrated to a high prednisone dose but failed to adequately respond. Subjects that could not be managed with steroids, IVIg, or PLEX and required additional immunotherapy (e.g., pulse IV steroids, azathioprine, etc.) would be considered treatment failures and likely withdrawn from the study.

Sample size has been determined to include a 20% subject withdrawal rate and will not replace subjects.

Subjects that exhibit serious adverse effects will be reviewed by the safety monitoring board to determine if removal from the study is necessary.

4.4 Study Enrollment Procedures

The informed consent will be obtained by study team member at the Screening Visit or up to 1 week (7 days) prior.

4.4.1 Subject Recruitment and Retention

Participants will be recruited from clinics at participating NeuroNEXT Network sites. Postings will be placed on www.neuronext.org, www.myasthenia.org, www.mda.org, www.ninds.nih.gov/disorders/clinical_trials,and other disease specific websites. Flyers about the study will be sent to community neurologists at NeuroNEXT clinical sites. Webinars will be conducted for participant recruitment as needed. Interested participants will be contacted by the investigators or their staff and invited to participate. These recruitment strategies will include a mechanism by which the subjects can provide their contact information. We will use the NeuroNEXT Recruitment and Retention Committee to identify recruitment strategies. If recruitment is slower than expected and specific enrollment targets are not reached, we plan to activate additional NeuroNEXT sites.

4.4.2 Screening Logs

Screening logs to document reasons for ineligibility and reasons for nonparticipation of eligible subjects will be stored centrally at the NeuroNEXT Data Coordination Center.

Sites will be instructed to complete EDC based pre-screening logs for all pre-screened patients that meet the following criteria: generalized AChR positive MG AND on prednisone.

4.4.3 Informed Consent

Written informed consent will be obtained from each study participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form approved by the NeuroNEXT Central Institutional Review Board (CIRB), which will be signed by the participant with the date of that signature indicated. The site will keep the original consent forms and a copy will be given to the participant. It will also be explained to the participant that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

Written informed consent will also be obtained from each study participant prior to proceeding with and performing all procedures at the optional Week 72 and Week 96 Visits. A separate consent form will be provided by the study team, which will be used to document the subject's willingness to participate in the off study-intervention follow-up visits. All the requirements outlined above also apply to this secondary consent form and consent process. Subjects may be consented prior to Week 52 or at Week 72 prior to any study-related procedures being performed. If the Week 72 window has passed for any given subject, but they are willing to coming for Week 96, they can be consented at Week 96 prior to any procedures being performed.

4.4.4 Subject Prednisone Diary

Subjects will be provided a daily prednisone diary at the Screening Visit. Subjects will be instructed how to fill out the diaries for accurate recording of dosage for prednisone. These will be collected, reviewed and information recorded at each scheduled visit, including the baseline visit. Compliance with prednisone diary completion will be monitored at each visit.

Prednisone Diaries do not need to be collected at the extended follow-up visits at Weeks 72 and 96.

4.4.5 Randomization/Treatment Assignment

Randomization will be performed through an interactive website, and will be stratified based on the steroid dose at baseline, moderate dose prednisone (15-35 mg/day) and high dose prednisone (>35 mg/day), as well as standard of care treatment regimen at the baseline visit. Subjects will be assigned a study ID at the time of enrollment. The study ID includes the identification of the center and a unique subject ID. The DCC will generate a randomization table for each of the strata using a permuted block design with random block sizes.

5 STUDY INTERVENTIONS/STUDY MEDICATION/STUDY DRUG OR DEVICE

5.1 Study Medications/Interventions, Administration, and Duration

Genentech, Inc. will provide rituximab (Rituxan®) and matching placebo labeled for investigational use. The NeuroNEXT central pharmacy, the Clinical Materials Services Unit (CMSU) at the University of Rochester Medical Center (URMC) will create active and placebo study drug kits with unique identifiers not associated with the randomization ID. Each kit will contain 12 of the 100mg/10ml vials of the Rituxan® or matching placebo and four (4) of the 500mg/50ml vials of the Rituxan® or matching placebo. Each kit is good for 1 full cycle of dosing (4 infusions over the course of 4 weeks) of study drug assuming a maximum dose of 800mg/weekly dose. Each subject will receive a total of 2 full kits to allow for 2 full cycles of dosing. The CMSU will provide each approved site with an appropriate number of active and placebo kits to support subjects enrolled at the site. CMSU will prepare and dispense both study drug and placebo control. The Protocol PI will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with Title 21 Code of Federal Regulations (C.F.R.), Part 312.57 and 312.62 and Genentech requirements.

Rituximab is a highly purified, 1328–amino acid antibody with an approximate molecular mass of 145 kD. The chimeric mouse/human anti-CD20 antibody is a glycosylated IgG1 κ immunoglobulin containing murine light and heavy chain variable regions and human γ_1 heavy chain and κ light chain constant regions.

Rituximab will be administered intravenously (IV) at 375mg/m^2 weekly consecutively for four weeks and then repeated at six months. To prevent infusion-associated reactions, each subject will be administered premedication with 1000 mg oral acetaminophen and 50 mg oral diphenhydramine within 30 to 60 minutes prior to each rituximab infusion. If subject has an infusion related reaction, the subject will receive 100 mg methylprednisolone IV 30 minutes prior to the next infusion. If the subject tolerates this infusion than methylprednisolone premedication would not be offered at next infusion. Subjects will be administered rituximab by staff and at an infusion center experienced with this medication. Refer to section 5.2 for additional specific details.

The most common side effects are infusion-related symptoms, particularly with the first rituximab infusion. These symptoms include flu-like symptoms, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, and hypotension. Since hypotension may occur during

Rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout the rituximab infusion. The decision to hold antihypertensive medications will be based on the discretion of local site investigator. Angina pectoris or cardiac arrhythmias, such as atrial flutter or fibrillation, have occurred in subjects treated with rituximab. Therefore, cardiac monitoring will be performed during and after all infusions (immediate post-infusion period) for subjects with a history of cardiac disease. In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular reactions was 1.7% and 1.3% in the rituximab and placebo treatment groups, respectively. In rare instances, severe and fatal infusion-related reactions have occurred.

Progressive multifocal leukoencephalopathy (PML) is the most significant potential complication, however, the relative risk is thought to be low in HIV negative subjects based on a recent review.[40] The incidence is < 1 per every 10,000 patients treated with rituximab. It is reassuring that no cases of PML have been reported in the rituximab MG population. We plan to minimize concomitant immunosuppressive therapies in our subjects and enroll subjects who are only receiving standard of care MG treatment regimens. We have defined these groups as subjects receiving either only prednisone or prednisone plus only one IST. Please refer to eligibility criteria for specific details. These regimens represent real world scenarios and are also consistent with the types of patients included in our pilot study where no significant safety concerns were observed[7]. We recommend careful review of immunotherapy regimen for every subject prior to initiating rituximab and to limit use of rituximab treatment to the groups as defined above as combined treatments could pose a higher PML risk. Refer to the manufacture Investigator's Brochure for additional details. Subjects who are on prednisone plus one other IST, will continue to have routine safety monitoring as per standard of care practices specific to that IST. This monitoring will be conducted by treating the physician.

5.2 Handling of Study Medications/Interventions

Overview. Rituximab is formulated for IV administration as a sterile product in 9.0 mg/mL sodium chloride, 0.7 mg/mL polysorbate 80, 7.35 mg/mL sodium citrate dihydrate, and Sterile Water for Injection (pH 6.5). Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials and will be reconstituted for infusion by the site's investigational drug pharmacy in 0.9%NaCl or D5W. Local pharmacists should refer to the Study Drug Package Insert provided to obtain guidance on the dilution of Rituximab, and follow the institutional policies for the specific dilution ratio.

Placebo will be provided by Genentech and is a sterile product in 9.0 mg/mL sodium chloride, 0.7 mg/mL polysorbate 80, 7.35 mg/mL sodium citrate dihydrate, and Sterile Water for Injection (pH 6.5). Placebo will be reconstituted for infusion by the site's investigational drug pharmacy or appropriately trained designee for IV administration as a sterile product of 0.9%NaCl or D5W.

To prevent infusion-associated reactions, each subject will be administered premedication with 1000 mg oral acetaminophen and 50 mg oral diphenhydramine within 30 to 60 minutes prior to each rituximab infusion. If subject has an infusion related reaction, subject will receive 100 mg methylprednisolone IV 30 minutes prior to the next infusion. If subject tolerates this infusion than methylprednisolone premedication would not be offered at next infusion. Premedications will be stored at each local pharmacy and prepared by the local pharmacist.

Storage and Stability. No preservative is used in rituximab; therefore, the vials are intended for single use only. Rituximab is biologically and chemically stable at 2°C–8°C (36°F–46°F). Do not use rituximab vials beyond the expiration date stamped on the drug packaging and protect the drug from direct sunlight. Rituximab solutions for infusion, once diluted, may be stored at 2°C–8°C (36°F–46°F) for 24 hours and at room temperature (23°C) for an additional 24 hours. However, since Rituximab solutions do not contain preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between rituximab and polyvinyl chloride or polyethylene bags have been observed. A temperature monitoring log is to be maintained at all sites to record temperature on an at least daily basis.

5.2.1 Preparation of Rituximab for Administration

The dose of Rituximab should be based on the subject's Body Surface Area (BSA), calculated per local institution procedures, and the amount to be infused should be calculated for a dose of 375 mg/m^2 for each infusion. For more details, please refer to the NN103 Drug Dispensing System Users Manual and Site Pharmacy Manual.

Note: The weight recorded at Baseline Visit should be used for the first Infusion Cycle (Infusions1-4) and the weight recorded at Week 24 Visit should be used for the second Infusion Cycle (Infusions 5-8).

Rituximab should be given as a slow intravenous infusion. It should not be administered as an intravenous push or bolus. Premedication as noted in Section 5.1 is required before each infusion. Although rituximab may be administered on an outpatient basis, subjects may be hospitalized for observation at the discretion of the investigator. Irrespective, rituximab should be administered in a hospital environment where full resuscitation facilities are immediately available and under close supervision of the investigator or Safety assessor. Caution should be exercised when administering rituximab to subjects with a history of asthma. Rituximab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

Since hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications approximately 12 hours prior to and throughout the rituximab infusion. This will be completed at the discretion of local site investigator.

First Infusion (Infusion 1 only): Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Subsequent Infusions (Infusions 2-8): Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion rate should be reduced to half that rate, i.e. from 100 mg/h to 50 mg/h. Subjects who experience a moderate to severe infusion related reaction (fever, chills, or hypotension) should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. The

infusion should not be restarted before all the symptoms have disappeared and then the infusion can continue at one-half the previous rate.

Immediate infusion related reactions can occur with either placebo or rituximab treatment.

After the end of infusion, the intravenous line should remain in situ for at least 1 hour in order to be able to administer drugs intravenously if necessary. If there are no adverse events during this period of time, the intravenous line may be removed.

For further details, including further management of infusion reactions, see the Investigator Brochure and the Rituxan® Package Insert.

5.2.2 Vital Sign Collection and Infusion Monitoring

Vital signs and monitoring for infusions reactions will be performed per standard practices of the local infusion center. For purposes of this study, vital signs will be measured and recorded at a minimum of every 15 minutes for the first hour, then every 30 minutes until completion of the rituximab infusion. Pulse oximetry will be obtained at baseline and as needed for symptoms of dyspnea.

Cardiac monitoring will be performed during and after all infusions of rituximab for subjects who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

5.2.3 Local Labs Prior to Infusion

Lab panels will be drawn and analyzed locally up to 1 day prior to initiation of study drug infusion. Lab panels will include complete metabolic panels (including LFT and GFR calculation), uric acid, LDH and CBC with differential (including ANC). These labs will be reviewed by the site investigator to ensure that there are no contraindications to infusion.

5.3 Study Drug Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount received from the central pharmacy, and the amount destroyed upon completion of the study. Each site investigator is responsible for ensuring product accountability records are maintained throughout the course of the study. The designated unblinded pharmacist will keep drug inventory and accountability logs. The inventory will include details of rituximab received and dispensed to subjects, batch, and ID numbers. All unused vials must be kept until reconciliation of delivery records with accountability logs by the monitor. After the monitor has performed accountability, the site will be instructed by the CCC or designee to either destroy the remaining study medication/device or return it to the Central Pharmacy or manufacturer. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of rituximab received and dispensed drug must be reconciled.

5.4 Concomitant Interventions

Subjects will be on either prednisone only or prednisone plus another IST at time of enrollment. Subjects who are on prednisone plus one other IST, will continue to have routine safety monitoring as per standard of care practices specific to that IST. This monitoring will be conducted by the treating physician. The dose of IST must remain stable throughout the course of the study (i.e. through week 52). Subjects who are on pyridostigmine (≤ 480 mg/day) at the time of enrollment must remain on a stable dose throughout the course of the study,and cannot be changed.

These requirements are not applicable to the optional off-intervention follow-up visits. During this time subjects will be treated per best medical practice (standard of care) for their MG at the discretion of the treating physician. However, as the primary focus of the two additional optional observational time points is to assess B cell recovery/repopulation as a safety measure, subjects who have received treatment with rituximab, or have been involved with other interventions that result in b cell depletion since completion of the trial (i.e. Week 52) will be excluded from the optional off-intervention follow-up visits.

For more details please refer to section 6.4.5.

5.5 Subject compliance

Subject compliance with study intervention (rituximab) will be directly monitored at the infusion center. Subjects will complete a daily prednisone dose log that will be collected and reviewed every 4 weeks to monitor steroid compliance during the study.

6 CLINICAL AND LABORATORY EVALUATIONS/STUDY PROCEDURES

6.1 Schedule of Activities (SOA) – on-intervention period (Screening – Week 52)

Visit Windows +/- 3 days for Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Cycle 1 Infusion Visits will take place weekly beginning at Week 0 through Week 3. Cycle 2 Infusion Visits will take place beginning at Week 24 through Week 27 (See Section 6.3.3 for timing of visits)

	Screening Visit	Day 0	Week 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 24	Wk 25	Wk 26	Wk 27	Wk 28	Wk 32	Wk 36	Wk 40	WK 44	Wk 48	Wk 52	Unscheduled
	(-4 - 6 wk)	Baseline	Infusion 1	Infusion 2	Infusion 3	Infusion 4							Infusion 5	Infusion 6	Infusion 7	Infusion 8								
Informed Consent	X																							
Randomization		X																						
Demographics	X																							
Medical History	X																							
Physical Exam	X	X					X	X	X	X	X	X					X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X					X	X	X	X	X	X					X	X	X	X	X	X	X	X
Pregnancy Testing[a]	X	X	X	X	X	X							X	X	X	X								
Standardized Bloods[b]	X																						X	X
HbA1C	X																						X	
Serology Testing (HBV,HCV, HIV)	X																							
Rituximab Infusions[c]			X	X	X	X							X	X	X	X								
Infusion Labs[c]			X	X	X	X							X	X	X	X								
Specialized Bloods [d]		X										X											X	X
Mechanistic Bloods		X										X											X	X
MGC Score	X	X					X	X	X	X	X	X					X	X	X	X	X	X	X	X
QMG Score		X					X	X	X	X	X	X					X	X	X	X	X	X	X	
MG-ADL Score	X	X					X	X	X	X	X	X					X	X	X	X	X	X	X	
MG-QOL Score	X	X					X	X	X	X	X	X					X	X	X	X	X	X	X	
Prednisone Dose Adjustments							X[e]	X	X	X	X	X					X	X	X	X	X	X	X	X[g]
Daily Steroid Diary Information	X[f]	X					X	X	X	X	X	X					X	X	X	X	X	X	X	X
AE Review/ Safety Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG	X																							
Chest X-ray	X																							

[a] – Serum pregnancy test at screening; urine pregnancy tests thereafter

[b] – Standard bloods: Comprehensive metabolic panel, LDH, uric acid, CBC with platelets and differential

[c] – Rituximab dose: 375mg/m^2 IV (cycle 1: week1-4; cycle 2: week 24-27). Infusion visit labs (comprehensive metabolic panel, LDH, uric acid, CBC with platelets and differential) performed locally

[d] – Specialized Bloods: 1. AChR antibody titer (Mayo Medical Laboratory, Rochester, MN). 2. Total IgG, IgA and IgM levels. 3. IgG subclasses (1,2,3, 4) . 4. Flow Cytometry to assess B cell counts. NOTE – Specialized bloods should be drawn prior to daily prednisone dose.

[e] – Prednisone dose may be increased at this visit per Site Investigator judgment in cases of clinical worsening. Forced taper begins at Week 8 based on steroid taper protocol.

[f] – Subjects will be instructed on how to fill out the diaries for accurate recording of dosage for prednisone only. Subjects will record their daily prednisone dose on a Daily Prednisone Diary beginning the day after the Screening Visit. The diary will be recorded in the EDC starting at the Baseline Visit and every visit thereafter.

[g] – Prednisone dose may be evaluated and increased at the Unscheduled Visit per Site Investigator judgment in cases of clinical worsening. Prednisone tapering should not occur at Unscheduled Visits that occur after Week 8. If the Site Investigator feels that it is clinically necessary to taper at the visit, the study team must be consulted and provide approval for doing so.

6.2 Schedule of Activities (SOA) – optional off-intervention period (Weeks 72 and 96)

Visit Windows +/-30 days for Weeks 72 and 96

	Wk 72	Wk 96
Informed Consent[a]	X	
Randomization		
Demographics		
Medical History[b]	X	X
Physical Exam	X	X
Concomitant Medication[c]	X	X
Vital Signs	X	X
Pregnancy Testing		
Standardized Bloods		
HbA1C		
Serology Testing (HBV,HCV, HIV)		
Rituximab Infusions		
Infusion Labs		
Specialized Bloods[d]	X	X
Mechanistic Bloods	X	X
MGC Score	X	X
QMG Score		
MG-ADL Score	X	X
MG-QOL Score	X	X
Prednisone Dose Adjustments		
Daily Steroid Diary Information		
AE Review/ Safety Monitoring[e]	X	X
EKG		
Chest X-ray		

Note Subjects who have received treatment with rituximab, or have been involved with other interventions that result in B cell depletion since completion of the trial (i.e. Week 52) will be excluded from the optional off-intervention follow-up visits. If there's a plan or interest by the treating physician to utilize rituximab clinically as part of the disease management strategy for a given subject prior to the Week 72 or 96 Visits, the study team should be notified and all efforts should be made to bring the subject in prior to receipt of rituximab in order to capture long-term follow-up data.

[a] – Written informed consent will also be obtained from each study participant prior to proceeding with and performing all procedures at the optional Week 72 and Week 96 Visits. Subjects may be consented prior to Week 52 or at Week 72 prior to any study-related procedures being performed.
[b] – Medical History will be updated at these two visits to record only any autoimmune disease(s) that the subject has been diagnosed with since the previous visit.
[c] – MG-related medication, including prednisone dose and/or any changes if applicable will be recorded. Additionally, any immunosuppressive therapies and steroids taken for other diseases will also be recorded.

[d] – Specialized Bloods: 1. AChR antibody titer (Mayo Medical Laboratory, Rochester, MN). 2. Total IgG, IgA and IgM levels. 3. IgG subclasses (1,2,3, 4) . 4. Flow Cytometry to assess B cell counts. NOTE – Specialized bloods should be drawn prior to daily prednisone dose.
[e] – At the Week 72 and 96 Visits, only those adverse events, serious and non-serious, that in the opinion of the Investigator are deemed ***related*** to study procedures will be reported, given that the subject has consented to the optional off-intervention follow-up visits. Additionally, any MG relapses requiring rescue therapy that have occurred since the last visit will also be recorded.

6.3 Study Staffing

A blinded Clinical Evaluator will be required to perform the outcome assessments (QMG, MGC, MG-QOL, and MG-ADL) and attend the Investigator's Meeting for training. The Clinical Evaluator may be a MD, RN, PA, PT, NP, or other health professional. This individual may not be directly involved in reviewing adverse events.

The principal investigator or a co-investigator (considered “treating physicians”) will perform the following procedures:

- Medical history
- Physical examination including assigning a MGFA MG grade.
- Prednisone dose adjustment beginning at week 8.
- Determination of worsening of MG symptoms.
- Review of adverse events and concomitant medications

The study coordinator will perform the following:

- Explain in detail how subjects will fill out the diaries for accurate recording of dosage for prednisone
- Collect and review daily prednisone dose diaries
- Vital signs including weight
- Pregnancy test for women of childbearing potential

6.4 Timing of Study Activities

6.4.1 Screening Evaluations and Procedures

Subjects identified as a potential candidate will be appropriately consented prior to the initiation of any study related procedures. The signing of consent constitutes the start of the study for a given subject.

The following will be performed during the screening visit:

- Subjects will undergo a complete physical and neurological examination
- Vital signs will be measured
- Phlebotomy will be performed in order to analyze the following:

- Serum Pregnancy
- Standard Labs: Comprehensive metabolic panel, uric acid, LDH and CBC with differential
- HbA1C
- Serology Testing: HBV, HCV, and HIV

- Subjects will be provided with information about the HIV and Hepatitis testing prior to the blood draw. Subjects will be referred for HIV and hepatitis post-test counseling and medical care at each institution if necessary.

- A 2-view chest x-ray (posterioranterior and lateral), and EKG will be obtained to document baseline status. Chest x-rays will be read by a local radiologist, and EKGs will be read locally by an internist/cardiologist or any qualified physician. If a cardiologist/internist is not available to do the read, it is recommended for the EKG to be remotely read, if possible based on the site's current setup.

  Note: If the subject has had a chest x-ray done within 60 days prior to the Screening Visit, a repeat will not be required at Screening, provided that the results from the previous chest x-ray are available and unrevealing. The previous chest x-ray source document will be required.

- Immunization status or need for the following vaccinations in advance of randomization will be completed: tetanus, diphtheria, influenza, pneumococcus polysaccharide, *Varicella*, measles, mumps, rubella (MMR) and hepatitis B vaccines.

  Note: Any required vaccination/booster for a subject must be given at least 28 days (4 weeks) prior to the baseline/randomization visit. Required immunizations should be determined based on a subject's age and comorbidities and are per best medical practice standard.

- MGC, MG-ADL and MG-QOL assessments will be completed. (Note: MG-QOL should be administered prior to other outcomes evaluations.)

- Women of child bearing potential will be instructed to take proper precautions to avoid pregnancy.

- When inclusion/exclusion criteria are met, protocol eligibility and admission information consisting of demographic data including age, sex, past medical history, concomitant medications including prednisone dose, prior AChR antibody titer history, confirmation of no history of thymoma on each subject will be documented. Subjects will be instructed not to take pyridostigmine for at least 12 hours prior to the Baseline Visit and each follow-up visit.

  Note: It is recommended that a chest CT or MRI source document (i.e. radiology report) be obtained to evaluate for thymoma during the prescreening process to determine eligibility.

- Subjects will be instructed to complete prednisone diaries for accurate recording of dosage. These will be collected, reviewed and information recorded at the Baseline Visit and each scheduled visit thereafter.

- Concomitant medications will be recorded.

6.4.2 Baseline Visit Evaluations and Procedures

All screening evaluations to determine eligibility will be completed within 4 to 6 weeks of screening visit (refer to SOA for details). All successfully screened subjects will be randomized into the study within 6 weeks.

The following will be performed during the baseline visit:

- Prednisone diaries will be reviewed to ensure that subjects have maintained a stable prednisone dose during the 28 days before the Baseline Visit. A stable dose is defined as a dose that does not vary by ≥ 6mg per day on average.
- All Eligibility Criteria will be reviewed and verified by the site investigator. The site investigator will sign off on the eligibility confirmation form prior to the randomization of any subject.
- Subjects will undergo a complete physical examination
- Vital signs will be measured
- Urine Pregnancy Test
- Phlebotomy will be performed in order to analyze the following (Note: Subjects will be asked to hold their usual prednisone dose on the day of the visit.):
    - Specialized bloods: AChR antibody titer, Total IgG, IgA and IgM levels, IgG subclasses (1,2,3, 4), and Flow Cytometry to assess B cell counts
        - NOTE – Specialized bloods should be drawn prior to daily prednisone dose.
    - Mechanistic bloods (immune cell analyses)

- Outcome Assessments: MGC, QMG, MG-ADL and MG-QOL will be completed. (Note: MG-QOL should be administered prior to other outcomes evaluations.)
- Adverse Events will be reviewed and recorded
- Concomitant medications will be recorded.

6.4.3 Infusion Visits

Cycle 1 Infusion Visits will take place weekly beginning at Week 0 through Week 3. Cycle 2 Infusion Visits will take place beginning at Week 24 through Week 27.

Ideally, the timing of Infusions 2-4 would be anchored to Infusion Visit 1, such that:

- Infusion 2 is 7 (+/- 1) days from Infusion 1
- Infusion 3 is 14 (+/- 1) days from Infusion 1
- Infusion 4 is 21 (+/- 1) days from Infusion 1

Ideally, the timing of Infusions 6-8 would be anchored to Infusion Visit 5, such that:

- Infusion 6 is 7 (+/- 1) days from Infusion 5
- Infusion 7 is 14 (+/- 1) days from Infusion 5
- Infusion 8 is 21 (+/- 1) days from Infusion 5

Please refer to the Manual of Operations, Section X (Study Medication and Central Pharmacy) and the Visit Windows Report available in the EDC once the Baseline Visit is complete.

Infusion 1 may take place the same day as the Baseline Visit and must take place within 3 days following the Baseline Visit.

Infusion 5 may take place the same day as the Week 24 Visit and must take place within 3 days of the Week 24 Visit.

If, for any reason, an infusion is held during either of the two cycles, it can be postponed up to one week (7 days) after the original scheduled date.

- If the delayed infusion is administered within that one week, the subsequent infusion should take place within the original time window in order to resume the initial infusion schedule. For example, if Infusion 2 is delayed but administered < 7 days after the scheduled date, Infusion 3 should be administered as originally planned and not delayed as well.

  ***Note** Two separate Infusions should not be scheduled on consecutive days. There should be a minimum of one day in between infusions.*

- If an Infusion is delayed by one week (7 days), then all subsequent infusions should be delayed by that same amount. For example if Infusion 2 takes place 14 days after Infusion 1, then Infusion 3 will take place 21 days after Infusion 1, and Infusion 4 will take place 28 days after Infusion 1.

  ***Note** If the Infusion cycles are delayed, the 4th infusion must take place prior to the Week 4 Visit, and the 8th Infusion must take place prior to the Week 28 Visit. The visits may take place on the same day,*

- If an infusion is held and cannot be administered within one week (7 days) of the original scheduled date, then that Infusion will be skipped altogether (this will be designated as "missed"), and efforts should be made to administer all subsequent infusions as scheduled.

- If the 1st infusion of either cycle (Infusion 1 or 5) cannot be administered as scheduled, it can be delayed up to one week after the original date. Subsequent infusions will be anchored on the **new** date of the first infusion and will follow the weekly window described above. If the first infusion of the cycle cannot be administered within one week of the original date, then that Infusion will be skipped altogether (this will be designated as "missed"), The schedule will then resume with second infusion of that cycle (i.e. the second infusion and all subsequent infusions will be anchored to the original date of the first infusion).

The study team must be notified, consulted and provide approval, should the site PI feel that an Infusion be held or postponed.

The following will be performed during the infusion visits:

- Urine Pregnancy Test
- Infusion Labs: Complete metabolic panel, uric acid, LDH and CBC with differential (analyzed locally up to 1 day prior to each infusion)
- Adverse Events will be reviewed and recorded
- Concomitant medications will be recorded.
- Study drug infusions (detailed in section 5.2)

6.4.4 Clinical Study Visits

Study Intervention Follow-up Visits:

The allowable time window for study visits is plus or minus 3 days for Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 visits.

The following will be performed during each study visit:

- Prednisone diaries will be collected and reviewed
  - Prednisone dose will be reviewed and adjusted at Week 4 and each visit thereafter. The forced prednisone taper will begin at Week 8 as per steroid taper protocol.
- Subjects will undergo a complete physical examination
- Vital signs will be measured
- Phlebotomy will be performed at week 24 and 52.
- Outcome Assessments: MGC, QMG, MG-ADL and MG-QOL will be completed. (Note: MG-QOL should be administered prior to other outcomes evaluations.)
- Adverse Events will be reviewed and recorded
- Concomitant medications will be recorded.

A Participation Survey will also be given to each subject at the Week 52 or last Study Visit. This will be a brief survey consisting of five questions. The purpose of the questionnaire will be to determine why the subject decided to participate in the study. The questions will ask how the subject initially heard of the study, why they chose to participate, and what motivated them to stay in the trial. This information will help to determine which recruitment and retention efforts were the most effective.

For procedures done at Unscheduled Visits, see section 6.3.11.

6.4.5 Optional Observational Off-Intervention Follow-up Visits:

Weeks 72 and 96 Visits:

The allowable time window for study visits is 60days for Week 72 and 96 visits (+/-30 days). These two additional optional time points at weeks 72 and 96 will be done to follow B cell recovery and long-term durability of response.

Subjects will be consented prior to the initiation of any study related procedures at these optional visits. Subjects will also be instructed not to take pyridostigmine for at least 12 hours prior to the Baseline Visit and each follow-up visit.

The following will be performed during each study visit:

- Subjects will undergo a complete physical examination
- Vital signs will be measured
- Phlebotomy will be performed at week 72 and 96 (please refer to the SOA and section 6.4.7).
- Outcome Assessments: MGC, MG-ADL and MG-QOL will be completed. (Note: MG-QOL should be administered prior to other outcomes evaluations.)
- Medical history will be updated at these two visits to record only any autoimmune disease(s) that the subject has been diagnosed with since the previous visit.
- MG-related medication, including prednisone dose and/or any changes if applicable will be recorded. Additionally, any immunosuppressive therapies and steroids taken for other diseases will also be recorded.
- MG relapse requiring rescue therapy will be recorded
- Adverse Events, serious and non-serious, related to study procedures per site investigator, will be reviewed and recorded.

Note Subjects who have received treatment with rituximab, or have been involved with other interventions that result in B cell depletion since completion of the trial (i.e. Week 52) will be excluded from the optional off-intervention follow-up visits. If there's a plan or interest by the treating physician to utilize rituximab clinically as part of the disease management strategy for a given subject prior to the Week 72 or 96 Visits, the study team should be notified and all efforts should be made to bring the subject in prior to receipt of rituximab in order to capture long-term follow-up data.

6.4.6 Outcome Evaluations

A blinded evaluator will be required to perform the outcome assessments (QMG, MGC, MG-QOL, and MG-ADL) and attend the Investigator's Meeting for training. The Clinical Evaluator may be a MD, RN, PA, PT, NP, or other health professional. This individual may not be directly involved in reviewing adverse events.

Myasthenia Gravis Composite (MGC).
The MGC is a new end-point that has been developed for MG. Specific components of the QMG, MG-ADL, and muscle testing are combined to obtain the MGC score. This is a brief assessment that takes approximately 10 minutes to complete.

Quantitative Myasthenia Gravis (QMG).
The QMG is a validated 13-item test that objectively measures ocular, bulbar, extremity fatigue/strength, and respiratory function (forced vital capacity). A battery of quantitative

functional tests is completed from which a QMG score is calculated. This assessment takes 30-40 minutes to administer.

MG-Activities of Daily Living score (MG-ADL)
This 8 point scale assesses the subject's ability to perform daily activities and can be performed in approximately 5 minutes.

MG-Quality of Life (MG-QOL) score.
The subject completes the 15-question MG-QOL questionnaire and reports the effect of MG on their quality of life. The MG-QOL should be administered prior to other outcomes evaluations at each visit.

6.4.7 Laboratory Testing

Safety labs will be drawn and analyzed locally the day before or at each infusion visit. All other labs will be analyzed centrally and sent to CMSU with the exception of the mechanistic labs which will be sent to Yale University.

Subjects will be instructed not to take pyridostigmine for at least 12 hours prior to the Baseline Visit and each follow-up visit.

Subjects are asked not to take their usual prednisone dose on the day of the Baseline Visit, Week 24 Visit, and Week 52 Visit as well as any Unscheduled Visit

Screening Visit:
- Serum Pregnancy
- Standard Labs: Comprehensive metabolic panel, uric acid, LDH and CBC with differential
- HbA1C
- Serology Testing: HBV, HCV, and HIV

Baseline:
- Urine Pregnancy (analyzed on site)
- Specialized bloods: AChR antibody titer, Total IgG, IgA and IgM levels, IgG subclasses (1,2,3, 4), and Flow Cytometry to assess B cell counts
- Mechanistic bloods (immune cell analyses)

Note: Please remind subjects to hold their usual prednisone dose the day of the visit.

Infusion 1-4
- Urine Pregnancy (analyzed on site)
- Infusion Labs: Comprehensive metabolic panel, uric acid, LDH and CBC with differential (analyzed locally up to 1 day prior to each infusion)

Week 24
- Specialized bloods: AChR antibody titer, Total IgG, IgA and IgM levels, IgG subclasses (1,2,3, 4), and Flow Cytometry to assess B cell counts
- Mechanistic bloods (immune cell analyses)

Note: Please remind subjects to hold their usual prednisone dose the day of the visit.

Infusion 5-8

- Urine Pregnancy (analyzed on site)
- Infusion Labs: Comprehensive metabolic panel, uric acid, LDH and CBC with differential (analyzed locally up to 1 day prior to each infusion)

Week 52

- Specialized bloods: AChR antibody titer, Total IgG, IgA and IgM levels, IgG subclasses (1,2,3, 4), and Flow Cytometry to assess B cell counts
- Standard Labs: Comprehensive metabolic panel, uric acid, LDH and CBC with differential
- HbA1C
- Mechanistic bloods (immune cell analyses)

Note: Please remind subjects to hold their usual prednisone dose the day of the visit.

Unscheduled Visit (if applicable)

- Specialized bloods: AChR antibody titer, Total IgG, IgA and IgM levels, IgG subclasses (1,2,3, 4), and Flow Cytometry to assess B cell counts
- Standard Labs: Comprehensive metabolic panel, uric acid, LDH and CBC with differential
- Mechanistic bloods (immune cell analyses)

Note: Please remind subjects to hold their usual prednisone dose the day of the visit.

Optional Observation Off-Intervention Follow-up Visits (weeks 72 and 96):

- Specialized bloods: AChR antibody titer, Total IgG, IgA and IgM levels, IgG subclasses (1,2,3, 4), and Flow Cytometry to assess B cell counts
- Mechanistic bloods (immune cell analyses)

Note: Please remind subjects to hold their usual prednisone dose the day of the visit.

6.4.8 Prednisone Dose Adjustments

Subjects will be treated with a minimum oral prednisone dose of 15 mg/day or equivalent every other day until week 8. Each subject's prednisone dose will be evaluated at the Week 4 Visit.

The prednisone dose **cannot** be tapered at the Week 4 Visit. It should be maintained at enrollment dose and only increased in cases of clinical worsening (as determined by the MGC Score) only, per the site investigator's discretion.

Forced Prednisone Taper

A forced prednisone steroid taper will begin at the Week 8 Visit. Dose adjustments are based on changes from the subject's baseline MGC score and prior study visit. The MGC score will be calculated, confirmed and available during the study visit in order to make steroid dose adjustment. Prednisone dose will be lowered at every 4-week assessment beginning at the Week

8 Visit following confirmation of clinical improvement or stable symptoms based on MGC score (current MGC score is not more than 2 points above the Baseline Visit or prior study visit MGC score).

Prednisone will be tapered:

- If the MGC score is no more than 2 points higher than the Baseline Visit score **AND**
- MGC score is no more than 2 points above the Prior Study Visit score

For subjects taking prednisone daily, the every 4 week taper schedule will be:

Daily Prednisone Dose (mg)	Taper to Dose (mg):
100	90
90	80
80	70
70	60
60	50
50	40
40	30
30	20
20	15
15	10
10	7.5
7.5	5
5	3
3	2
2	1
1	0

For subjects taking prednisone every other day, the every 4 week taper schedule will be:

Every Other Day Prednisone Dose (mg)	Taper to Dose (mg):
200	180
180	160
160	140
140	120
120	100
100	80
80	60
60	40
40	30
30	20
20	15
15	10
10	7.5
7.5	5

Every Other Day Prednisone Dose (mg)	Taper to Dose (mg):
5	2.5
2.5	0

Note: While typical maximum daily doses of prednisone will be 60 mg per day (or equivalent on alternating days), the above table details a taper schedule with rows shaded in grey if subjects enter the study on a higher dose. The absolute maximum allowable prednisone dose at study entry is 100 mg per day (or equivalent on alternating days).

As subjects may be on a dose that is slightly different than the above (i.e., 45 mg/day, alternating doses), the tapered dose will begin at the closest lower dose on the table and then follow tapering as per protocol. Subjects taking more than 100 mg/day or 200 mg over a two day period will be excluded from the study.

It is recommended that the Prednisone Dose Adjustment at Week 52 be done in the same manner as the other clinical study visits (i.e. tapered, maintained, or increased based on the subject's MGC score). However, if the site PI feels that it is in the best interest of the subject to deviate from the dose adjustment protocol (i.e., for safety related reasons for instance), this will be allowed. If the decision is to not adjust the prednisone dose per protocol at Week 52, please notify the study team prior to proceeding.

Prednisone Dose Adjustments in Cases of Clinical Worsening

If the MGC score is 3 or more points higher than the Baseline Visit score:

❖ The taper will be stopped and prednisone will be increased per the guidelines below.

If the MGC score is less than or no more than 2 points higher than the Baseline Visit score, but has increased 3 or more points than the MGC score at the previous Study Visit:

❖ The taper will be stopped and prednisone dose may be either held or increased per study prednisone schedule. The decision to hold or increase the prednisone dose in this case is at the discretion of the Site Investigator.

Note: The prednisone dose will be increased until symptoms are resolved or at least stabilized to baseline status (MGC score is the same or less than the Baseline Visit score).

The following schedule will be followed for subjects with clinical worsening and who require the prednisone dose to be increased:

- For subjects on > 15 mg daily or the equivalent for every other day dosing, it is recommended that the prednisone daily dose be initially increased by 20 mg.
- For subjects on ≤ 15 mg daily or the equivalent for every other day dosing, prednisone may be increased by 10 or 20 mg, at the physician's discretion.
- If the prednisone dose is up titrated, the maximum dose would be 60 mg/day even if the subject was on a higher dose at study entry.

Once symptoms stabilize (MGC score is the same or less than the Baseline Visit score and not more than 2 points above the prior study visit), the prednisone taper can again be resumed per the above protocol at the next scheduled visit/assessment.

This is a forced steroid taper that is based on MGC score. If the site investigator (treating physician) did not taper per protocol, this will be recorded as a protocol deviation and will be corrected immediately. As this is linked with primary outcome we wanted to make the decision on lowering the dose as objective as possible. A mechanism will be put in place to double check the MGC score calculation made at the visit and whether or not prednisone adjustment decision was made correctly.

6.4.9 Physical Exam

A physical exam will be completed at the Screening Visit, Baseline Visit, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 Visits, as well as the optional weeks 72 and 96 Visits.

The physical exam will include assigning a MGFA clinical classification grade. The grades are as follows:

Class I- Any ocular muscle weakness, may have weakness of eye closure, all other muscle strength is normal.

Class II – Mild weakness affecting other than ocular muscles, may also have ocular muscle weakness of any severity.

Class III – Moderate weakness affecting other than ocular muscles, may also have ocular muscle weakness of any severity.

IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV – Severe weakness affecting other than ocular muscles, may also have ocular muscle weakness of any severity.

IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V – Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management.

6.4.10 Study Medication/Intervention Discontinuation Evaluations/Procedures

Subjects will be monitored through regular physical examinations, vital signs, laboratory tests, and incidence and severity of adverse events. Infections will be treated symptomatically. Cardiovascular risk factors will be assessed prospectively by recording risk factors (e.g., family history, smoking history, and status). The safety evaluations will be conducted on conventional safety variables, such as serious adverse events, laboratory tests, and vital sign changes. In particular, B cell counts, immunoglobulin levels, infusion-related reactions, and thromboses, infections will be carefully examined.

Adverse events will be reviewed and recorded at each study visit and infusion visit. An adverse event is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, laboratory or physiologic observations occurring in study participants. Information on adverse effects of medication and on inter-current events will be determined at each visit by direct

questioning of the subjects, clinical examination, and laboratory tests. Tolerability will be determined by the ability to complete the study on the assigned experimental medication.

Study Hold Rules (Safety).

Individual study subjects may be withdrawn from the study medication but continue to be followed for safety if subjects develop a grade 3 or more suspected toxicity as graded by the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 or a Serious Adverse Event (SAE) related to study medication as determined by the Independent Medical Monitor (IMM). Grade 3 adverse events are severe or medically significant but not immediately life-threatening and may cause hospitalization or prolongation of hospitalization indicated. Descriptions of CTCAE grading criteria are included in the Manual of Operations and SAEs are specifically defined in Section 10.4.1.2. Subjects will be allowed to resume participation in the study if their suspected toxicity or adverse event (AE) resolves completely and if the judgment of the investigator and IMM it is safe for the subject to continue.

Please see Section 8 for additional details regarding Criteria For Intervention Discontinuation.

Please also see Package Insert and Investigator Brochure for additional safety information. Additional safety monitoring visits will be at the discretion of the investigator or as directed by the IRB and/or other regulatory authorities.

Study Stopping Rules (Safety).

The study will be permanently stopped and no further administration of rituximab will be given if the investigator, the IRB and/or DSMB and/or any other institutional or regulatory body deems it inappropriate for the study to resume due to the following:

A significant number of enrolled subjects develop safety concerns that cannot otherwise be attributed to MG, infections, disease relapse or pre-existent comorbidities as deemed by theIMM.

Please also see SOA for additional safety monitoring information. Additional safety monitoring visits will be at the discretion of the investigator or as directed by the IRB and/or other regulatory authorities.

6.4.11 Off-Intervention Evaluations

In the event that a subject is unable to tolerate study drug infusions resulting in the study medication being withdrawn but has completed at least one infusion, and is otherwise able to comply with study procedures, the subject will be asked to attend all study visits per protocol.

If the subject is withdrawn from the study, either for being unable to tolerate the study drug (i.e. unable to complete any infusions) or being unable to comply with the remaining study procedures, they will go on reduced follow-up. For more information regarding the reduced follow- up, please see Section 8 – Criteria for Intervention Discontinuation.

There are two additional off study-intervention time points (week 72 and 96) to assess durability of response as well as monitor B cell count normalization. Subjects will have similar clinical evaluations as during the on-study drug intervention period. Subjects will be treated per medical standard of care. For more details regarding these visits, please refer to the SOA and Section 6.4.5.

6.4.12 Unscheduled Visits

Subjects will be clinically evaluated at an Unscheduled Visit at the discretion of the treating physician for any concern of disease relapse and/or significant worsening of symptoms as well concern for adverse event related to study. A standard physical exam and the MGC score assessments will be performed during this visit. Prednisone diary will also be reviewed. Blood work will also be performed as per SOA and primary study team recommendations.

The following are recommended to be performed during Unscheduled Visits:

- Prednisone diaries will be collected and reviewed
  - Prednisone dose may be evaluated and increased at the Unscheduled Visit per Site Investigator judgment in cases of clinical worsening. Prednisone tapering should not occur at Unscheduled Visits that occur after Week 8. If the Site Investigator feels that it is clinically necessary to taper at the visit, the study team must be consulted and provide approval for doing so.
- Subjects will undergo a complete physical examination
- Vital signs will be measured
- Phlebotomy will be performed. For a complete list of recommended lab tests, please see Section 6.3.6.
- Outcome Assessments: MGC will be completed.
- Adverse Events will be reviewed and recorded
- Concomitant medications will be recorded.

6.4.13 Final On-Study Evaluations

Final on-study visit (week 52) includes: physical exam, vital signs, blood draws, safety assessments and specific myasthenia gravis clinical assessments as described above.

***NOTE** All subjects will have the option to return for two additional off-intervention follow-up visits (weeks 72 and 96) in order to monitor B cell counts along with MG clinical status. This portion of the trial will only include subjects that have not received rituximab or other B cell depleting treatments after study completion (i.e. Week 52). B cell levels typically return to normal levels approximately 12+ months following B cell depletion therapy.*

6.4.14 Pregnancy

Pregnancy is an exclusion criterion. Routine testing as described above at screening visit and prior to each rituximab infusion will be performed in all women of child-bearing age. Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for twelve months (1 year) after completion of treatment.

If a subject becomes pregnant within the course of the study, site staff will be asked to follow the subject by telephone to determine the outcome of the pregnancy.

6.5 SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

6.5.1 Informed Consent

The Clinical Study Site PI (CSS PI) and all IRB approved Licensed Physician Sub-Investigators personnel will be able to obtain informed consent from the participant.

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are performed and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, approved by the NeuroNEXT CIRB, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants. HIPAA guidelines for confidentiality and the principles of medical ethics will be adhered to during the study.

***NOTE** The above statement applies to the secondary consent form for the Weeks 72 and 96 Visits as well. Subjects may be consented prior to Week 52 or at Week 72 prior to any study-related procedures being performed. If the Week 72 window has passed for any given subject, but they are willing to coming for Week 96, they can be consented at Week 96 prior to any procedures being performed.*

6.5.2 Protocol Violations

Deviations from the written protocol will be considered a protocol violation and reported to the medical monitor and the safety monitoring board.

6.5.3 Documentation of Myasthenia Gravis

Autoimmune myasthenia gravis will be defined as a person who has the following:

1. Positive serum acetylcholine receptor (AChR) binding antibodies* in conjunction with
2. Positive decremental response on repetitive nerve stimulation at 3 Hz, **OR** a clinical examination consistent with generalized myasthenia gravis.

   *Positive acetylcholine receptor binding antibodies as defined by a certified commercial laboratory. The following are some common labs.
   - Mayo Medical Laboratories: Muscle AChR Binding Antibody >0.02 nmol/L
   - Quest Diagnostics: AChR Binding Antibody ≥0.50 nmol/L
   - LabCorp: AChR Binding Antibodies >0.40 nmol/L

6.5.4 Medical History

A routine medical history will be obtained during the screening phase of the trial. Subjects will be asked about adverse events at each subsequent visit. Medical history will be updated at the

optional off-intervention follow-up visits to record only any autoimmune disease(s) that the subject has been diagnosed with between weeks 52 and 72 and weeks 72 and 96.

6.5.5 Treatment History

All prior treatments from the time of diagnosis (a minimum of one year's history prior to screening) with immune therapies (prednisone, azathioprine, mycophenolate mofetil, monoclonal antibodies, etc.) will be obtained from the subject source documents. Treatment history between weeks 52 and 72 and weeks 72 and 96 will be documented at the optional off-intervention follow-up visits. MG-related medication, including prednisone dose and/or any changes if applicable will be recorded.

6.5.6 Concomitant Medications/Treatments

All immune therapies and treatments that modulate or suppress the immune system will be obtained from source documents. MG-related medication (including prednisone dose and/or any changes if applicable) taken between weeks 52 and 72 and weeks 72 and 96 will be documented at the optional off-intervention follow-up visits. Any immunosuppressive therapies and steroids taken for other diseases will be recorded as well during these visits.

Note Subjects who have received treatment with rituximab, or have been involved with other interventions that result in B cell depletion since completion of the trial (i.e. Week 52) will be excluded from the optional off-intervention follow-up visits.

6.5.7 Immunization during B Cell Depletion

The efficacy and safety of immunization during periods of B cell depletion have not been adequately studied. Subject's vaccination record and the need for immunization will be carefully evaluated prior to receiving study drug. For those who are likely to require immunization in the foreseeable future, such as subjects planning to travel to countries where specific immunization is required or subjects requiring vaccination/booster for their professional activity, any required vaccination/booster must be given at least 4 weeks prior to the baseline/randomization visit. Review of the subject's immunization status or need for the following vaccinations in advance of randomization (as noted previously) will be completed: tetanus, diphtheria, influenza, pneumococcus polysaccharide, varicella, measles, mumps, rubella (MMR) and hepatitis B, vaccines. Required immunizations should be determined based on a subject's age and comorbidities and are per best medical practice standard.

The safety and efficacy of immunization with a live or attenuated live vaccine in B cell depleted subjects are not known. For this reason, the use of live or attenuated vaccines (e.g., measles, mumps, rubella, oral polio vaccine, Bacillus Calmette-Guérin [BCG], typhoid, yellow fever, vaccinia, varicella-zoster virus (VZV) or any other vaccines not yet licensed but belonging to this category) is specifically excluded 28 days prior to screening through the end of the 52 week follow-up period or until return of B cells to within normal limits or baseline.

Vaccines that do not contain live organisms (e.g., influenza, Pneumovax®, tetanus) are not prohibited; however, vaccinations during B cell depletion may be ineffective.

6.5.8 Protocol Amendments and Study Termination

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the CIRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the CIRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

The Sponsor and NeuroNEXT Network reserve the right to discontinue the study at a clinical study site(s) for safety or administrative reasons at any time. Should the study be terminated and/or the clinical study site closed for any reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

6.5.9 Clinical Assessments

Subjects will have clinical evaluations at the Baseline Visit and then every 4 weeks thereafter (week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52). Post-intervention status will be assessed by measuring the MGFA clinical classification grade, MGC, QMG, MG-ADL and MG-QOL scores. Most of these clinical evaluations will also be completed at unscheduled visits (MGC only) as well as at weeks 72 and 96 (all except QMG). The dose of prednisone will be recorded by each subject daily and collected at each scheduled evaluation. These will be recorded on the CRFs.

All appropriate MG-specific common data elements as determined by the protocol steering committee will be collected and recorded on CRFs.

Adverse effects will be monitored to assess safety and tolerability in this subject population per Genentech and DAIT's guidelines.

6.5.10 Laboratory Evaluations

The Investigator will review, sign and date all lab reports. The investigator will indicate if out of range lab value is Clinically Significant "CS" or Not Clinically Significant "NCS" on the lab report. CTCAE version 3.0 will be used for grading events.

Safety labs will be drawn and analyzed locally up to 1 day prior to each infusion visit. All other labs will be analyzed centrally and sent to CMSU.

Subjects will be instructed not to take pyridostigmine for at least 12 hours prior to the Baseline Visit and each follow-up visit, including the optional Week 72 and Week 96 Visits.

Subjects are asked not to take their usual prednisone dose on the day of the Baseline Visit, Week 24 Visit, Week 52 Visit, as well as the optional Week 72 and Week 96 Visits.

- *Pregnancy Testing.* All women of childbearing potential will have a serum pregnancy test at Screening and urine pregnancy test at Baseline and all Infusion Visits (infusion visit 1, 2, 3, 4, 5, 6, 7 and 8). The serum pregnancy test will be analyzed centrally. The urine pregnancy tests will be locally read.

- *Standard Bloods.* All subjects will have standard safety blood work completed at the Screening Visit and week 52. These include: comprehensive metabolic panel, uric acid,

LDH and CBC with platelets and differential. These labs will be shipped to CMSU to be analyzed centrally.

- *HbA1C* will be checked at the Screening and Week 52 Visits. These labs will be shipped to CMSU to be analyzed centrally.

- *Infusion Labs*. Complete metabolic panel, uric acid, LDH and CBC with differential will be analyzed locally up to 1 day prior to each infusion. Site Investigators will review the lab results prior to the infusion. Site Investigators may hold the rituximab infusion if the lab results indicate that the subject is not medically able to tolerate the infusion.

- *Serology Testing.* All subjects will have hepatitis panel and HIV testing completed at the Screening Visit. These labs will be shipped to CMSU to be analyzed centrally. Subjects will be referred to pre-test and post-test counseling and provided with an information sheet.

- *Specialized Bloods.* All subjects will have specialized blood work completed at the Baseline Visit, Week 24, Week 52, and optional Week 72 and Week 96 Visits. These include: 1. AChR antibody titer (Mayo Medical Laboratory, Rochester, MN). 2. Total IgG, IgA and IgM levels. 3. IgG subclasses (1, 2, 3 and 4). 4. Flow Cytometry to assess B cell count. These labs will be shipped to CMSU to be analyzed centrally.

- *Biomarker/Mechanistic Blood*. The biomarker or mechanistic studies are focused on identifying how treatment modifies the immunopathology of MG. These blood draws will be completed at the Baseline Visit, Week 24, Week 52, and optional Week 72 and Week 96 Visits. Samples will be kept at room temperature and shipped priority overnight to Dr. Kevin O'Connor's Laboratory at Yale University for processing and immunologic studies. Deliveries must arrive within 24 hours of collection.

  Shipping Address:

Refer to SOA and section 6.3.6 for additional details.

6.5.11 Pharmacokinetic Studies

Pharmacodynamics will specifically be followed by monitoring B cell depletion and repopulation.

6.5.12 Subject Adherence Assessments

Daily prednisone dose will be recorded in a diary by each subject and reviewed at each scheduled clinic evaluation (every 4 weeks). Adherence to taking prednisone as well as taking correct dose of prednisone will be monitored.

6.5.13 Biomarker/Mechanistic Studies

The biomarker or mechanistic studies are focused on identifying how treatment modifies the immunopathology of MG. We will study changes in the antigen specific components of the MG immune system. We have developed/adapted immunoassays so that we can examine autoantibodies, B cells and T cells. The principal mechanistic outcome will be the decrease in titer of circulating AChR autoantibodies within an individual. Other exploratory mechanism-based outcomes include determining how rituximab modifies antigen-specific B cell frequency, the B cell repertoire, B cell activating factor (BAFF) levels and whether rituximab modifies antigen-specific T cell frequency and phenotype. Measurements will be performed prior to and during B cell depletion and through repopulation of the B cell compartment, which will be of particular interest in terms of assessing the durability of the treatment. Blood will be collected for mechanistic studies at the Baseline Visit, Week 24, Week 52 Visits, as well as the optional Week 72 and Week 96 Visits.

7 MANAGEMENT OF ADVERSE EVENTS

The most common side effects are infusion-related symptoms, particularly with the first rituximab infusion. These symptoms include flu-like symptoms, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, and hypotension. Since hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout rituximab infusion. The decision to hold antihypertensive medications will be based on the discretion of local site investigator. Angina pectoris or cardiac arrhythmias, such as atrial flutter and fibrillation, have occurred in subjects treated with rituximab. Therefore, subjects with a history of cardiac disease should be monitored closely. In rare instances, severe and fatal infusion-related reactions have occurred.

If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion rate should be reduced to half that rate, i.e. from 100 mg/h to 50 mg/h. Subjects who experience a moderate to severe infusion related reaction (fever, chills, or hypotension) should have their infusion interrupted immediately and should receive aggressive symptomatic treatment per local institutional policy or protocol. The infusion should not be restarted before all the symptoms have disappeared and then the infusion can continue at one-half the previous rate. If hypersensitivity reaction should occur, subject will receive 100 mg methylprednisolone IV 30 minutes prior to the next infusion.

The infusion should be interrupted for severe reactions, and supportive care measures should be instituted as medically indicated (e.g., IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). The infusion should not be restarted until all the symptoms have disappeared.

Pregnancy:
Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies that occur during paternal or maternal exposure to study drug (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and

documented even after the subject has been withdrawn from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the data safety monitor.

Disease-Related Events (DREs):
Given that variations in symptoms are an inherent part of the natural history of MG, all recorded information regarding MG status will be captured as outcomes data. While disease relapse or treatment failure is not considered an AE in our study, the DSMB will monitor the percentage of treatment failures in the two groups. If the treatment failure rate reaches a level of concern, the DSMB has the ability to stop the trial at any point. In the setting of a forced steroid taper, we expect to possibly observe an increased frequency of disease relapse, particularly in the placebo group. As the forced steroid taper is guided by the MGC score, we do not expect for this to be a significant concern. Relapses will be managed by increasing the prednisone dose and possibly offering PLEX or IVIg (rescue therapies) depending on severity. These are standard of care practices. For the purpose of this study, variation in MG symptoms will not be considered an AE unless the MG relapse requires hospitalization for rescue therapy. If a subject is hospitalized for an MG relapse, it will be reported as an SAE.

8 CRITERIA FOR INTERVENTION DISCONTINUATION

See section 6.2.9

Subjects that are withdrawn from the study or intervention discontinued due to an SAE will have reduced follow-up. This will include being followed monthly via telephone or in person for a minimum of 90 days or until SAE resolution, whichever comes first, after which a Termination Visit will be conducted. The Termination Visit will mirror the Week 52 Visit.

- If the SAE is resolved within 90 days, the Termination Visit can occur earlier.
- If the SAE is not resolved within 90 days, the SAE will be Resolved with Sequelae, and the Termination Visit occur.

During the 90 day (or less) SAE follow-up period, no new AEs will be recorded. Existing AEs would be followed until resolution, or the Termination Visit, whichever comes first.

Subjects that are withdrawn from the study or intervention discontinued due to reasons other than an SAE, will complete a Termination Visit only – no follow-up will be required.

9 STATISTICAL CONSIDERATIONS

The NeuroNEXT Data Coordinating Center has developed a statistical analysis plan, in collaboration with the PPI, co-PPI, co-investigators and protocol steering committee.

9.1 General Design Issues

9.1.1. Summary of Study Design

A previous study conducted at Yale demonstrated that 82% of subjects who received rituximab achieved at least a 75% reduction in their prednisone dose at 52 weeks (95% CI: 48%-98%). The

objective of the proposed study is to determine whether the large benefit observed in the prior Yale study can be refuted, or looks promising enough to justify a future phase III trial. This objective will be accomplished using a futility design, which tests the hypothesis that subjects treated with rituximab will achieve at least an absolute 30% increase in the frequency of favorable responses.[60,61] If "futility" is declared, then the results would imply that it is not cost effective to conduct a future phase III trial with this agent. If "futility" is not declared, then the study would suggest that there could be a potentially clinically meaningful effect of rituximab which should be explored in a larger follow-up study.

The proposed study will involve a randomized, double-blind, placebo-controlled multicenter futility study with 50 subjects randomized in a 1:1 manner to receive either rituximab or placebo (25 per group). The primary objective of the study is to test whether rituximab is a beneficial steroid sparing therapeutic for myasthenia gravis subjects. A predetermined steroid taper schedule will be utilized. At the time of enrollment, each subject will be expected to be on a stable fixed dose of prednisone for at least 28 days (4 weeks). Subjects assigned to the rituximab group will receive a total of two cycles of rituximab separated by six months. Each cycle is defined as one infusion (375 mg/m2) per week for four consecutive weeks. As such, cycle 1 will be administered at weeks 0-3 and cycle 2 will be given during weeks 24-27. Subjects assigned to the placebo group will receive similar cycles of placebo.

MGFA clinical classification grade along with quantitative testing (i.e., MG-ADL score, QMG score, MG Composite, MG-QOL) will be assessed every four weeks. The proposed study duration is 52 weeks. In each subject, the prednisone dose will be gradually reduced based on the steroid taper schedule beginning at week 8 (8 weeks after starting cycle 1 of rituximab). The dose will only be reduced after confirming improvement or minimal stable symptoms based on judgment of the examining physician and MG Composite Score. If symptoms worsen, the prednisone dose would immediately be increased until the symptoms improved and/or resolved. In addition, subjects who worsen can receive PLEX or IVIg if the investigator decides it is warranted, and these subjects can remain in the study. Prednisone taper would again be resumed four weeks after the subjects have improved. The dose of prednisone will be recorded by each subject daily and collected at each evaluation.

The primary endpoint will be a binary indicator of whether a subject achieved at least a 75% reduction of prednisone dose from baseline. The endpoint will be computed by comparing the mean daily prednisone dose during the four-week period prior to randomization versus the four week period at the end of the study (weeks 49-52). Secondary endpoints will include the MGC and QMG. Other exploratory clinical endpoints will include MG-ADL, other clinical measures, immune markers, and safety evaluations. There will be a treating investigator who does the dose adjustments and a blinded investigator who performs the blinded assessments.

9.1.2. Randomization

Randomization will be performed through an interactive website, and will be stratified based on the steroid dose at baseline [moderate (15-35 mg/day) vs. high (>35 mg/day)] and baseline therapy (prednisone only vs. prednisone plus another IST). Subjects will be assigned a study ID at the time of enrollment. The study ID includes the identification of the center and a unique subject ID. The DCC will generate a randomization table for each of the strata using a permuted block design with random block sizes. At the time of randomization, the study coordinator logs into the study website and enters the potential subject's baseline prednisone dose as well as other

eligibility criteria. The subject will then be randomized to one of the two treatments. The study ID is added to all subsequent CRF's and on the dispensed study medication.

9.2 Outcomes

9.2.1 Primary Outcome (including definition)

The specific primary aim of this study is to determine whether rituximab is a safe and shows sufficient promise as a steroid sparing therapeutic for MG to warrant further study in a phase III efficacy trial. Refer to Section 9.5 for statistical analysis plan.

Steroid Sparing Effect. The primary endpoint is the percent of subjects that achieve a ≥ 75% reduction in mean daily prednisone in the four weeks prior to week 52 (week 49-52) along with clinical improvement or no significant worsening of symptoms (≤2 point increase in MG composite score) as compared to the four week period prior to randomization.

Safety. Safety will be assessed by examining the frequency of study-related adverse experiences in the two groups.

9.2.2 Secondary Outcome(s)

Our secondary objective is to evaluate whether there is a trend toward clinical benefit as measured by MG-specific clinical outcome scales used as endpoints in prior clinical trials. We will determine if rituximab can significantly improve the scores of the following MG-specific clinical outcome measures: (1) Myasthenia Gravis Composite (MGC). (2) Quantitative Myasthenia Gravis (QMG). These studied measures would lay the groundwork toward optimizing the design of a subsequent phase III efficacy trial of rituximab in MG.

Myasthenia Gravis Composite (MGC). The MGC is a new end-point that has been developed for MG. Specific components of the QMG, MG-ADL, and manual muscle testing scales are combined to obtain the MGC score.

Quantitative Myasthenia Gravis (QMG). The QMG is a validated 13-item test that objectively measures ocular, bulbar, extremity fatigue/strength, and respiratory function. A battery of quantitative functional tests are completed from which a QMG score is calculated.

9.2.3 Exploratory Outcomes

9.2.3.1 Clinical Exploratory Outcomes

Determine if rituximab can significantly improve the scores of the following other previously validated MG-specific outcome measures: (1) MG-Activities of Daily Living score (MG-ADL). (2) MG-Quality of Life (MG-QOL) score.

Other previously used measures of steroid-sparing effect will be assessed: (1) Mean daily prednisone dose at each scheduled assessment (every 4 weeks). (2) A delayed start of the area under the dose-time curve (AUDTC), starting at week 8. (3) Percentage of subjects achieving a ≥ 50% mean daily prednisone dose reduction with maintenance of minimal or no symptoms in 4 weeks prior to week 52. (4) Body mass index (Screening Visit and weeks 24 and 52). (5) HbA1C (Screening Visit and week 52).

MG flare rate (failure of therapy) will be assessed by: (1) Number of rescue treatments (PLEX or IVIg). (2) Number of times prednisone dose needed to be increased. (3) Frequency of a ≥ 3-point increase in the MGC score.

The primary focus of the two observational off study-intervention time points (weeks 72 and 96) will be to assess B cell recovery/repopulation as a safety measure. Specifically, we will examine: (1) Percentage of subjects achieving normal B cell counts at week 72 and 96. (2) Percentage of achieving baseline B cell counts at week 72 and 96. (3) Percent B cell recovery to normal or baseline levels. In addition, the long-term durability of response will also be assessed. Specifically, we will examine: (1) Percentage of subjects achieving a sustained ≥ 75% mean daily prednisone dose reduction. (2) Percentage of subjects achieving a ≥ 50% mean daily prednisone dose reduction. (3) Prednisone AUDTC (if applicable). (4) Clinical status as measured by MGFA Class, MGC, MG-QOL and MG-ADL scores. (5) Number of rescue treatments (PLEX or IVIg).

9.2.3.2 Biomarker/Mechanistic Exploratory Outcomes

The biomarker or mechanistic studies are focused on identifying how treatment modifies the immunopathology of MG. We will study changes in the antigen specific components of the MG immune system. We have developed/adapted immunoassays so that we can examine autoantibodies, B cells and T cells. The principal mechanistic outcome will be the decrease in titer of circulating AChR autoantibodies within an individual. Other exploratory mechanism-based outcomes include determining how rituximab modifies antigen-specific B cell frequency, the B cell repertoire, B cell activating factor (BAFF) levels and whether rituximab modifies antigen-specific T cell frequency and phenotype. Measurements will be performed prior to and during B cell depletion and through repopulation of the B cell compartment, which will be of particular interest in terms of assessing the durability of the treatment. Blood will be collected for mechanistic studies at the Baseline Visit, Week 24. Week 52 Visits, as well as the optional Week 72 and Week 96 Visits.

9.3 Sample Size and Accrual

Below, we introduce some key notation that we use to describe the analysis plan for the proposed trial:

- Let p_P represent the true (unknown) percentage of subjects treated with placebo who will achieve success on the primary endpoint
- Let p_R represent the true (unknown) percentage of subjects treated with rituximab who will achieve success on the primary endpoint

Based on a prior study completed by Sanders and coworkers in 2008 on MMF in AChR+ MG, 38.6% of placebo treated case achieved a treatment response.[38] The placebo start point was 34.1 mg prednisone; hence, 38.6% of placebo recipients had a reduction of prednisone dose by at least 78%. Also the MMF start point was 30.7 mg prednisone; therefore, 44.3% of MMF recipients had a reduction of prednisone dose by at least 76%. Based on this information, we assume that 40% of placebo recipients will achieve a 75% or greater prednisone dose reduction ($p_P = 0.40$).

The design of this trial was somewhat restricted due to the fact that the company that produces rituximab has only agreed to provide 25 doses to the investigators. As a consequence, this study requires more of a sample size justification (for the sample size fixed by external factors) as opposed to a standard sample size calculation that determines the required sample size for a

fixed target power. Using the notation above, the one-sided futility hypothesis that the treatment achieved the desired clinically meaningful level of interest may be stated as:

$$H_{0,F}: p_R - p_P \geq 0.30 \quad vs. \quad H_{A,F}: p_R - p_P < 0.30.$$

Therefore, rejecting the null hypothesis suggests 'futility' in the sense that it appears unlikely that conducting a future phase III clinical trial would lead to a significant effect with a magnitude at least as large as the specified clinically meaningful effect of interest. If we don't reject the null hypothesis, this would provide one of the "go" conditions for conducting a future phase III study.

The table below shows the power computed across a range of assumed values for the true response rate in the rituximab subjects. The calculations assume a type I error rate of 10%, p_P = 0.40, and a conservative assumption of up to 20% missing data. The table below demonstrates the benefits of using the futility design. When the true success rate for rituximab is near or below the true success rate for placebo, the study will declare "futility" with high probability. Likewise, when the true success rate for rituximab is well above the true success rate for placebo, the study has a very low chance of incorrectly declaring "futility". Given the sample size limitations mentioned above, we feel that this provides a reasonable chance of having a successful study – where "success" is defined as answering the main question of interest regarding whether there is clear evidence to rule out an effect of rituximab in this population, or to provide enough evidence to justify a larger trial in the future.

Rituximab Rate (p_R)	**30%**	**35%**	**40%**	**45%**	**50%**	**55%**	**60%**	**65%**	**70%**	**75%**	**80%**	**85%**	**90%**
Pr(Futility)	92%	84%	74%	63%	50%	37%	25%	16%	10%	4%	2%	1%	<1%

9.4 Data Monitoring

All aspects of the study will be monitored by qualified individuals designated by the sponsor. Monitoring will be conducted according to Good Clinical Practice and applicable government regulations. The investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and to the clinical files of the study subjects, and, if requested, agrees to assist the monitors.

Safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include contemporaneous assessment of serious adverse events.

The monitoring of subject safety and data quality will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. A Data and Safety Monitoring Board (DSMB) appointed by the NIH/NINDS will meet at six-month intervals (or as determined by the NINDS) to review partially unblinded study data provided by the study statistician. This committee will monitor rates of adverse events and endpoints in the trial and will monitor the performance of the trial. The frequency and format of DSMB meetings, reports, and guidelines for interim analysis will be agreed upon prior to study subject enrollment.

The Protocol PI will appoint an Independent Medical Monitor (IMM) to review all adverse events, in a blinded fashion, on a periodic basis. In addition, the IMM will review all events that meet the regulatory definition of a Serious Adverse Event, upon receipt of notification via the Electronic Data Capture (EDC) system.

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device. FDA, Office of Human Research Protection (OHRP), and NeuroNEXT CIRB requirements for reporting AEs will be followed. Subjects will be monitored for AEs from the time they sign consent until the Week 52 Visit. If a new AE is discovered at the Week 52 Visit, it will be followed until resolution or for a minimum of 30 days, whichever comes first. The IMM/DSMB will review cumulative AEs; the frequency of this review will be determined by the IMM/DSMB in conjunction with the Protocol PI.

All SAEs must be followed until resolution, or until the Week 52 Visit, whichever comes first. If the SAE is still ongoing at Week 52, it will be Resolved with Sequelae.

- SAEs that are discovered less the 90 days prior to the Week 52 Visit will be followed until resolution or for a minimum of 90 days, whichever comes first, even if it is past the Week 52 Visit. A repeat Termination Visit does not need to occur.
- If a new SAE is discovered at the Week 52 Visit, it must be followed until resolution, or for a minimum of 90 days, whichever comes first.
- For SAEs that result in study treatment discontinuation and a limited follow-up period, please refer to Section 8 – Criteria for Intervention Discontinuation.

At the Week 72 and 96 Visits, only those adverse events, serious and non-serious, that in the opinion of the Investigator are deemed ***related*** to study procedures will be reported, given that the subject has consented to the optional off-intervention follow-up visits. Additionally, any MG relapses requiring rescue therapy that have occurred since the last visit will also be recorded.

Each Clinical Study Site Investigator and research team (co-Investigators, research nurse, clinical trial coordinator) are responsible for identifying and reporting AEs and determining the relationship of the event to the study drug/study procedures. Aggregate reports blinded by treatment group, detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures, will be available from the DCC for review by the IMM. A separate report detailing protocol compliance will also be available monthly from the DCC for review by the Protocol PI, who will provide feedback to individual sites as needed. The Protocol Steering Committee (PSC) will advise the Protocol PI as to whether the protocol or informed consent document requires revision based on these reports.

9.5 Statistical Analysis Plan

9.5.1. Primary Hypotheses

Primary Futility Hypothesis: *Subjects treated with rituximab will have at least a 30% absolute increase in the frequency of achieving at least a 75% reduction in mean daily prednisone dose with maintenance of minimal or no symptoms.*

The primary futility hypothesis being tested in this trial is that subjects treated with rituximab will achieve at least an absolute 30% increase in the frequency of favorable responses. Assuming a placebo response rate of 40% (as in the original sample size calculations), this corresponds to an odds ratio of 3.5. Therefore, the primary futility hypothesis will be assessed using a logistic regression model, adjusted for the two stratification variables, to estimate the log-odds of primary endpoint success in each group. The logistic regression model used for these purposes is stated here:

$$logit(Y_i) = \beta_0 + \beta_1 X_{dose} + \beta_2 X_{IST,i} + \beta_3 X_{RMB,i}$$

where

- Y_i represents the binary variable indicating whether or not the i[th] subject met the primary outcome requirement of a 75% or greater reduction in prednisone dose
- $X_{dose,i}$ is an indicator variable for prednisone dose at baseline (=0 if moderate, =1 if high)
- $X_{IST,i}$ is an indicator variable for whether the subject was receiving prednisone plus IST at baseline (=0 if prednisone alone, =1 if prednisone plus IST)
- $X_{RMB,i}$ is an indicator variable for whether the i[th] subject was randomized to the Rituximab group

Correspondingly, the primary futility hypothesis of interest can be assessed by performing the following hypothesis test:

$$H_{0,F}: \log(\beta_3) \geq 3.5 \quad vs. \quad H_{A,F}: \log(\beta_3) < 3.5.$$

Therefore, rejecting the null hypothesis suggests 'futility' in the sense that it appears unlikely that conducting a future phase III clinical trial would lead to a significant effect with a magnitude at least as large as the specified clinically meaningful effect of interest. If we don't reject the null hypothesis, this would provide justification for proceeding to examine the superiority hypothesis. Due to randomization, it is unlikely that important covariates will be imbalanced in this study. However, given the small sample size, this cannot be dismissed. We will assess for important baseline imbalances, and if any imbalances exist, we will adjust for these additional covariates in the logistic regression model.

Primary Safety Hypothesis: ***There will be no increase in adverse experiences for the rituximab-treated vs. placebo subjects.***
The second primary hypothesis will involve a comparison of the safety profiles of rituximab vs. placebo. As described elsewhere, general assessments of safety will occur throughout the trial in conjunction with the medical safety monitor. This specific hypothesis will be assessed in two ways. First, the percentage of subjects who experience a study-related AE, overall and by body system, will be compared across the two groups using standard chi-square tests. Then, the rates of study-related AE's across the two groups will be compared using a Poisson regression model.

9.5.2. Secondary Hypotheses

Secondary Hypothesis #1: ***Rituximab-treated subjects will have clinically significant improvement in their Myasthenia Gravis Composite (MGC) scores at the end of the 52 week treatment period.***

The first secondary hypothesis assesses the change in Myasthenia Gravis Composite (MGC) scores at the end of the 52 week study period. The outcome will be defined as the change from baseline to week 52 in the MGC. This hypothesis will be assessed using a linear regression model, adjusted for baseline MGC score. For example, the following model will be fit to these data:

$$Y_i = \beta_0 + \beta_1 X_{dose} + \beta_2 X_{IST,i} + \beta_3 X_{MGC,i} + \beta_3 X_{RMB,i}$$

where

- Y_i represents the change from baseline in the MGC score for the i[th] subject
- $X_{dose,i}$ is an indicator variable for prednisone dose at baseline (=0 if moderate, =1 if high)

- $X_{IST,i}$ is an indicator variable for whether the subject was receiving prednisone plus IST at baseline (=0 if prednisone alone, =1 if prednisone plus IST)
- $X_{MGC,i}$ is the baseline MGC score for the i^{th} subject
- $X_{RMB,i}$ is an indicator variable for whether the i^{th} subject was randomized to the Rituximab group

Correspondingly, the secondary hypothesis of interest can be assessed by performing a test of:

$$H_0: \beta_4 = 0 \text{ vs. } H_A: \beta_4 \neq 0.$$

As above, should important treatment imbalances occur across treatment groups with respect to covariates of interest, the model will be adjusted to control for these additional covariates.

Secondary Hypothesis #2: ***Rituximab-treated subjects will have clinically significant improvement in their Quantitative Myasthenia Gravis (QMG) scores at the end of the 52 week treatment period.***

The second secondary hypothesis assesses the change in Quantitative Myasthenia Gravis (QMG) scores over the course of the 52 week study period. Because the only difference between this and the first secondary hypothesis is the choice of outcome, the analysis will proceed in the same manner described above for the first secondary hypothesis.

Secondary Hypothesis #3: Rituximab subjects will have complete B-cell recovery by the end of the 96 week assessment period.

The third secondary hypothesis will assess the rate of B-cell recovery among subjects treated with rituximab during the study. The rate of B-cell recovery will be assessed by quantifying the percentage of subjects who: 1) return to their individual baseline level of B-cells, and 2) return to either the individual baseline level of B-cells or the lower limit of 'normal' based on the central lab (whichever is lower). Point estimates, and 95% confidence intervals, will be computed for the rate of B-cell recovery at both 72 & 96 weeks. If rates are high, as expected, exact methods for the computation of confidence intervals will be utilized. We expect the upper limit of the confidence intervals to include the value 100% - which would support a high rate of B-cell recovery in this population. Any subject who receives open-label rituximab treatment after Week 52 would be excluded from this analysis as well as from the extended follow-up study.

9.5.3. Exploratory Analyses

Additional exploratory clinical outcomes will be investigated to monitor effectiveness as well as evaluate other endpoints that would be useful in optimizing future MG trial designs as well as a Phase III rituximab trial. We will assess whether rituximab can improve the scores on the MG-Activities of Daily Living (MG-ADL) and MG-Quality of Life (MG-QOL) scales. We will also assess other measures of steroid-sparing effect: 1. Mean daily prednisone dose in the 4 weeks prior to week 52. 2. Mean daily prednisone dose in the 8 weeks prior to week 52. 3. Percentage of subjects achieving a ≥ 50% mean daily prednisone dose reduction with maintenance of minimal or no symptoms in 4 weeks prior to week 52. 4. Mean daily prednisone dose at each scheduled assessment (every 4 weeks). 5. A delayed start of the area under the dose-time curve (AUDTC), started at week 8. Failure of therapy (or MG flare rate) will be assessed by examining the number of rescue treatments (PLEX or IVIg), number of times prednisone dose needed to be increased, and the frequency of a ≥ 3 point increase in the MGC score. In addition we will review the following predictable steroid related effects between the two groups: 1)

HbA1C (screening and week 52); 2) BMI (screening, week 24 and week 52). A formal statistical analysis plan for these outcomes will be prepared and approved prior to final data lock by the protocol steering committee. Finally, we assess B cell recovery/repopulation as a safety measure at the optional observational off study-intervention time points (weeks 72 and 96) along with MG clinical status during off study-intervention. A formal statistical analysis plan for these outcomes will be prepared and approved prior to final data lock by the protocol steering committee. Refer to Section 9.2.3.1.

9.5.4. Impact of Missing Data

The primary analysis will follow the intent-to-treat (ITT) paradigm. All enrolled subjects must be included in the primary ITT analysis, and will be analyzed in the treatment group to which they were initially randomized. As such, it will be critically important to minimize the occurrence of missing data. Obviously, the optimal strategy for dealing with missing data is to make every effort to obtain complete data during the conduct of the study. Our team of data managers and protocol coordinators will work diligently and use a variety of methods in order to minimize the percentage of missing data in this trial. Nevertheless, there is likely to be a small percentage of missing data. For the primary analysis, we will take a conservative approach. If the mean prednisone dose is not known during weeks 49-52, then that subject will be considered to not have achieved a 75% dose reduction (i.e., they will be counted as a failure). In order to further assess the potential dependence of the results of the primary analysis of these missing values, a series of sensitivity analyses will be conducted, including:

- A Multiple Imputation Approach: This multiple imputation approach will be implemented using a model based on the prednisone dose at baseline and all observed time points for subjects throughout the study. We will use five separate implementations of this approach, and will average the parameters across the five imputations for the final analysis.
- Using Only Observed Data (No Imputation)
- Using a Last Observation Carried Forward Approach
- Worst-case scenario: Assume all missing subjects in the rituximab group did not achieve a dose reduction and all missing subjects in the placebo group did achieve a dose reduction
- Best-case scenario: Assume all missing subjects in the rituximab group did achieve a dose reduction and all missing subjects in the placebo group did not achieve a dose reduction.

10 DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

10.1 Data Management

Site personnel will collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The DCC will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices. The DCC is responsible for developing, testing, and managing clinical data management activities, as required, at the study sites, the CCC, and at the DCC.

The general NINDS Common Data Elements (CDE) will be used to construct data collection forms. All study data will be collected via systems created in collaboration with the DCC and will comply with all applicable guidelines regarding subject confidentiality and data integrity.

10.1.1 Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical study site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. NeuroNEXT CIRB approval for the protocol must be on file at the DCC before accrual can occur from the clinical study site.

The DCC will use a system of coded identifiers to protect participant confidentiality. When the participant is registered to participate in the study using the DCC-provided web-based registration, the system will assign a participant ID number. The unique ID code will include a protocol ID, a site ID, and a unique participant ID. To confirm the correct participant ID, the data entry system will require a second entry of the unique participant ID and compare for consistency. In this fashion, no personal identifiers would be accessible to the DCC and the data will be collected on the correctly identified subject.

10.1.2 Data Entry

Data entry will occur at the enrolling clinical study sites. Data quality assurance and analyses will be performed by the DCC. The DCC, located at the University of Iowa, will coordinate all data and statistical services for the study, as well as on-site monitoring for all participating clinical study sites.

Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, online forms will be developed that contain the requisite data fields.

10.2 Role of Data Management

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with NeuroNEXT policies, and applicable Sponsor and regulatory requirements. The DCC will instruct site personnel to collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The DCC will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices. The DCC is responsible for developing, testing, and managing clinical data management activities, as required, at the clinical study sites (CSS), the CCC, and at the DCC.

The DCC is responsible for all aspects of clinical data management, and for properly instructing key study personnel (including the CCC, the CSS, and DCC staff) on how to collect, transcribe, correct and transmit the data onto CRFs or other data collection forms and logs.

The DCC is responsible for establishing procedures to ensure that clinical data management activities occur as required at the CCC, the CSS, and at the DCC.

10.3 Quality Assurance

By signing this protocol, the Sponsor and Investigator agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.3.1 Development of Monitoring Plan

Onsite monitoring visits will be conducted by DCC monitors according to a pre-defined Monitoring Plan. The monitoring plan will detail the frequency of on-site visits, the study data to be monitored, the review of any regulatory files, drug and supplies accountability (if applicable), documentation of the on-site visit, and the resolution process for data errors that are discovered during the visits. All participating clinical study sites will be monitored at least once after a study initiation visit and all sites will have a close-out visit for each protocol. One on-site monitoring visit is anticipated for each clinical study site per year. All subjects will be monitored for inclusion and exclusion criteria, informed consent procedures, and adverse events. A certain percentage of data is also monitored/ source data verified against the data entered into the study database. The monitoring plan will include flexibility to revise the frequency of visits or data monitored depending on clinical study site or study related issues.

10.3.2 Site Monitoring Visits

On-site monitoring visits will be conducted by DCC monitors according to a pre-defined monitoring plan for each protocol. The goal of on-site monitoring is to analyze (review) the data as it is collected, to check the validity and integrity of the data, to verify source documentation, to ensure protection of human subjects, and to ensure protocol compliance with federal regulations. During the monitoring visit, the monitor assesses the overall status of the study, staff, and facilities to determine whether the study is being conducted per protocol and in compliance with regulatory requirements. The monitor also conducts a CRF review that includes checks of all adverse event documentation, verifies the presence of all critical correspondence and records related to investigational products and clinical supplies (if applicable), and determines if protocol violations have occurred and are documented properly. After the monitoring visit, the monitor documents the results of the monitoring visit and completes a post-visit monitoring letter that conveys any issues discovered during the visit and the need for data corrections, if appropriate. Drug and supplies accountability may also be monitored during the site visit. The DCC will work closely with the CCC to monitor and document drug distribution from the manufacturers to the clinical study sites (CSS). Each CSS will be provided with a drug accountability log which will be reviewed by the DCC monitors and reconciled with distribution logs. At the study closeout visit, the monitors confirm that appropriate data have been reviewed, source documentation has been verified, and all required documents are present in the Study Regulatory File.

10.3.3 Laboratory Data Flow

Specialized bloods. The DCC will provide laboratories with online forms and/or electronic data exchange mechanisms - depending on their capabilities and needs - to enter, update and obtain relevant data. When biologic sample has been obtained, the clinical study site study coordinator will send the sample (participant ID, site ID, and protocol ID numbers will be used) to the University of Rochester central laboratory). Results will be sent via a secure system to University of Rochester laboratory with no individual-identifying information on the report. The laboratory will electronically communicate the test results to the respective clinical study sites in a secure manner. The laboratory will also transfer test results electronically to the DCC.

Safety Monitoring Labs. The safety monitoring labs will be performed at specific visits as part of routine care. The DCC will provide online forms and/or electronic data exchange mechanisms - depending on their capabilities and needs - to enter, update and obtain the results from these tests. Results that meet criteria for adverse experience reporting, including study drug discontinuation will be reported in accordance with guidelines noted below.

Biomarker/Mechanistic Blood. When biologic sample has been obtained, the clinical study site study coordinator will send the sample (participant ID, site ID, and protocol ID numbers will be used) to Dr. Kevin O'Connor's Laboratory at Yale University. Samples will be kept at room temperature and shipped priority overnight for processing and immunologic studies. Deliveries must arrive within 24 hours of collection.

10.4 Adverse Event Reporting

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States FDA regulations and International Conference on Harmonization (ICH) guidelines. The Site Investigator will carefully monitor each subject throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

All SAEs must be followed until resolution, or until the Week 52 Visit, whichever comes first. If the SAE is still ongoing at Week 52, it will be Resolved with Sequelae.

- SAEs that are discovered less the 90 days prior to the Week 52 Visit will be followed until resolution or for a minimum of 90 days, whichever comes first, even if it is past the Week 52 Visit. A repeat Termination Visit does not need to occur.
- If a new SAE is discovered at the Week 52 Visit, it must be followed until resolution, or for a minimum of 90 days, whichever comes first.
- For SAEs that result in study treatment discontinuation and a limited follow-up period, please refer to Section 8 – Criteria for Intervention Discontinuation.

At the Week 72 and 96 Visits, only those adverse events, serious and non-serious, that in the opinion of the Investigator are deemed *related* to study procedures will be reported, given that the subject has consented to the optional off-intervention follow-up visits. Additionally any MG relapses requiring rescue therapy that have occurred since the last visit will also be recorded.

Each clinical study site's Principal Investigator and research team are responsible for identifying adverse events and reporting them through the DCC Online Adverse Event Reporting System.

Investigators are also responsible for complying with NeuroNEXT CIRB's reporting requirements for all safety reports. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

On-line Adverse Event Reporting System

Upon entry of a serious adverse event by a site investigator, the DCC Online Adverse Event Reporting System will immediately notify the Independent Medical Monitor (IMM).

- Within **24 hours** (of learning of the event), investigators must report any Serious Adverse Event (SAE). Investigators must report all other AEs within **5 working days/7 calendar days** (of learning of the event).

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will review the SAE report. The IMM may request further information if necessary. The Online Adverse Event Reporting System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study. The IMM may determine that the Serious Adverse Event requires expedited reporting to the FDA. The DCC will prepare a Medwatch safety report for submission to the FDA and to Genentech. If warranted, the IMM will notify the DSMB chair. The DSMB may suggest changes to the protocol or consent form to the Study Chair as a consequence of adverse events.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his or her research team will be submitted to the DCC in a timely fashion (within 5 working days/7 calendar days). The events will be presented in tabular form and given to the IMM on a quarterly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

For the purposes of this study, *before randomization*, only those adverse events, serious and non-serious, that in the opinion of the Investigator are deemed *related* to study procedures will be reported. After randomization, all adverse events will be reported.

The DCC will prepare aggregate reports of all adverse events (serious/not serious, expected/unexpected and relationship to study drug) for the IMM and the DSMB on a quarterly basis or as requested. In addition, all adverse events will be coded using the MedDRA system. A separate report detailing protocol compliance will also be available from the DCC for DSMB and/or site review monthly or as requested. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator would be required within 60 days of the anniversary date that the IND went into effect to submit a brief report of the progress of the investigation. This study has Exempt IND status and as such there are no required annual IND reports to the FDA. The section below details additional reporting requirements.

Safety Reporting Requirements for IND Exempt Studies

For Investigator Sponsored IND Exempt Studies, there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

Postmarketing 15-Day "Alert Report":

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of Rituximab. An unexpected adverse event is one that is not already described in the Investigator Brochure.

10.4.1 Definitions of Adverse Events, Suspected Adverse Drug Reactions & Serious Adverse Events

10.4.1.1 Adverse Event and Suspected Adverse Drug Reactions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc),

or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

Clinical → symptoms reported by the subject or signs detected on examination.
Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures: the results of which are not being captured as AEs).

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the Site Investigator.

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current Investigators Brochure or package insert or described in the protocol. An unexpected, suspected adverse drug reaction is any unexpected adverse event that, in the opinion of the Site Investigator or Sponsor, there is a reasonable possibility that the investigational product caused the event.

10.4.1.2 Serious Adverse Events

A SAE is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study subject, in the view of the Site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled “procedure” or a “treatment” is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the “disability” caused by the reported AE results in a substantial disruption of the subject’s ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an *adverse* experience, and will therefore, not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the Site Investigator or Sponsor, suggests a reasonable possibility that the investigational product caused the event.

The Site Investigator is responsible for classifying adverse events as serious or non-serious.

10.4.1.3 Pregnancy

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

10.4.1.4 AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product

The Rituxan Events of Special Interest are: NONE

10.4.2 Assessment and Recording of Adverse Events

This study will utilize the CTCAE version 4.0 coding system for adverse event recording. Adverse events reported using CTCAE will be recoded into MedDRA terms by the DCC.

Assessment of Adverse Events

At each visit (including telephone interviews), the subject will be asked “Have you had any problems or symptoms since your last visit?” in order to determine the occurrence of adverse events. If the subject reports an adverse event, the Investigator will determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease

6. Action taken regarding investigational product
7. Outcome

Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the Site Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (suspected ADR)
4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (suspected ADR)
5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (suspected ADR)

Recording of Adverse Events

All clinical adverse events are recorded in the AE Log in the subject's study binder. The site should fill out the AE Log and enter the AE information into the online Adverse Event Reporting System within 5 working days/7 calendar days of the site learning of a new AE or receiving an update on an existing AE.

Please Note: SAEs must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site learning of the SAE.

All SAEs must be followed until resolution, or until the Week 52 Visit, whichever comes first. If the SAE is still ongoing at Week 52, it will be Resolved with Sequelae.

- SAEs that are discovered less the 90 days prior to the Week 52 Visit will be followed until resolution or for a minimum of 90 days, whichever comes first, even if it is past the Week 52 Visit. A repeat Termination Visit does not need to occur.
- If a new SAE is discovered at the Week 52 Visit, it must be followed until resolution, or for a minimum of 90 days, whichever comes first.
- For SAEs that result in study treatment discontinuation and a limited follow-up period, please refer to Section 8 – Criteria for Intervention Discontinuation.

Entries on the AE Log (and into the online Adverse Event Reporting System) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

Adverse Events and Serious Adverse Events - Reportable Events

The following are considered reportable events and must be reported to the NeuroNEXT Data Coordinating Center within 24 hours of the site being notified of the event.

- All events that meet the above criteria for Serious Adverse Events (SAEs)

All occurrences of SAEs must be reported within 24 hours of discovery of the event. All other AEs must be reported within 5 working days/7 calendar days of discovery of the event.

Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event by a clinical site, the DCC Online Adverse Event Reporting System will immediately notify the IMM. If warranted, the IMM will notify the DSMB chair.

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will review the SAE report. The IMM may request further information if necessary. The DSMB may suggest changes to the protocol or consent form to the Project PI as a consequence of adverse events. The Online Adverse Event Reporting System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DCC within 5 working days/7 calendar days. The events will be presented in tabular form and given to the IMM on a monthly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DCC will prepare aggregate reports of all adverse events (serious/not serious and expected, unexpected) for the DSMB.

10.4.2.1 Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

10.4.2.2 Study Close Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to

Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

[redacted]

11 HUMAN SUBJECTS

Documented approval from the NeuroNEXT CIRB will be obtained for all participating centers prior to clinical trial start, according to ICH GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the CIRB approval must be obtained.

Evidence of training in responsible conduct of research shall be on file for each CSS PI and co-investigator.

11.1 Central Institutional Review Board (CIRB) Review and Informed Consent

This protocol and the informed consent document (Appendix A) and any subsequent modifications will be reviewed and approved by the NeuroNEXT CIRB responsible for oversight of the study. A signed consent form, approved by the NeuroNEXT CIRB, will be obtained from the subject. For subjects who cannot provide consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the clinical study site will be identified only by the study specific Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by CIRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the CIRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies of the NeuroNEXT Network and procedures developed by the NeuroNEXT Data Sharing and Publication Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NINDS prior to submission. A copy of proposed publications or presentations should be submitted to Genentech a minimum of 2 months in advance.

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Appendix 1

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SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

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

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]
Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

NN103

Statistical Analysis Plan

B Cell Targeted Treatment in Myasthenia Gravis: A Phase II Trial of Rituximab in Myasthenia Gravis

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VERSION 1.0
November 17, 2017

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

NN103

[BEAT MG: B Cell Targeted Treatment in Myasthenia Gravis: A Phase II Trial of Rituximab in Myasthenia Gravis]

Principal Investigator Approval

Signature: _____ **Date:** 17Nov2017
Name: Richard J. Nowak, MD, MS

NeuroNEXT Clinical Coordinating Center Approval

Signature: _____ **Date:** 17NOV2017
Name: Merit Cudkowicz, MD

NeuroNEXT Data Coordinating Center Approval

Signature: _____ **Date:** 11/17/2017
Name: Christopher S. Coffey, PhD

PREFACE

This Statistical Analysis Plan (SAP) describes the planned analyses for the NeuroNEXT NN103 (BEAT MG) study [National Institute of Neurological Disorders and Stroke (NINDS) grant # U01NS084495]. The planned analyses identified in this SAP are intended to support the completion of the Final Study Report (FSR) and will be included in regulatory submissions and/or future manuscripts. All final, planned analyses identified in this SAP will be performed only after the last randomized subject has completed the full 52 week study period. Once all week 52 data have been cleaned and verified, a "locked" version of the data will be used for reporting the final study results. Key statistics and study results will be made available to the Protocol Principal Investigator (PPI) following database lock and prior to completion of the final FSR. It is important to recognize that this SAP only applies to the primary 52 week study. Additional exploratory analyses added to the protocol as part of the extended follow-up study will be reported separately.

1. STUDY DESIGN

A previous study conducted at Yale demonstrated that 82% of subjects who received rituximab achieved at least a 75% reduction in their prednisone dose at 52 weeks (95% CI: 48%-98%). This study follows up on that finding with a multicenter randomized, double-blind, placebo controlled phase II clinical trial evaluating the safety and steroid-sparing effect of rituximab in MG utilizing a futility design. The specific primary objective of this study is to determine whether rituximab is a safe and beneficial therapeutic for MG that warrants further study in a phase III efficacy trial. The primary clinical endpoint will be the steroid sparing effect of rituximab, and the primary objective will be accomplished using a futility design which tests the hypothesis that subjects treated with rituximab will achieve at least an absolute 30% increase in the frequency of favorable responses (Levin, 2012). If "futility" is declared, then the results would imply that it is not cost effective to conduct a future phase III trial with this agent. If "futility" is not declared, then the study would suggest that there could be a potentially clinically meaningful effect of rituximab which should be explored in a larger, phase III follow-up study.

The study will enroll 50 AChR antibody positive generalized MG subjects, with subjects randomized in a 1:1 manner to receive either rituximab or placebo (25 per group). Each previously diagnosed generalized MG subject will be expected to be on a stable dose of prednisone (minimum dose of 15 mg/day) for at least 4 weeks (28 days) with stable symptoms at the time of enrollment. There will be two groups of standard of care treatment regimens allowed into the study:

- Prednisone Only
- Prednisone + Another IST: The subject must be on a stable dose for at least 6 months prior to baseline on one of the following IST: azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, or methotrexate

Subjects on pyridostigmine must be on a stable dose of ≤ 480 mg/day for a minimum of 2 weeks prior to the Screening Visit. Subjects must remain on a stable fixed dose for the duration of the study. The dose cannot be changed after study entry.

For the main study, subjects will be followed for 52 weeks. The study period of 52 weeks was chosen based on the delayed benefits observed following rituximab treatment, and in the setting of utilizing a two-cycle protocol. In order to assess safety in the B cell recovery period, as well as assess the long-term durability of response, there are two additional optional observational off study-intervention time points (weeks 72 & 96 – extended study follow-up).

The treatment group will receive a total of two cycles of rituximab (375mg/m^2 IV) separated by 6 months. Each cycle is defined as one infusion per week for four consecutive weeks. As such, cycle 1

will be administered weeks 0-3 and cycle 2 will be given at weeks 24-27. The placebo group will receive an infusion that contains only the vehicle components of the rituximab solution.

A predetermined, forced steroid taper schedule for both treatment (rituximab) and placebo groups will begin at the week 8 visit. At every 4-week assessment thereafter, the MGC score will be calculated, confirmed, and available during the study visit in order to make the steroid dose adjustment. Prednisone dose will be lowered following confirmation of clinical improvement or stable symptoms based on the MGS score (current MGC score is ≤ 2 points above the baseline visit or MGC score at the prior study visit). If the MGC score change is ≥ 3 points above the baseline visit score, the taper will be stopped the prednisone dose increased until symptoms resolve or are at least are stabilized to baseline status (baseline visit MGC score). If the MGC score is ≤ 2 points above the baseline visit score, but has increased ≥ 3 points from the MGC score at the previous study visit, the taper will be stopped and prednisone dose will either be held or increased (at the discretion of the Site Investigator). Once symptoms stabilize (MGC score is the same or less than the baseline visit score and ≤ 2 points above the prior study visit), the prednisone taper can again be resumed at the next scheduled assessment. If the Site Investigator does not taper per protocol, this will be recorded as a protocol deviation and will be corrected immediately. As this is linked with primary outcome, we wanted to make the decision on lowering the dose as objective as possible. A mechanism will be put in place to double check the MGC score calculation made at the visit, and whether or not the prednisone adjustment was made correctly. The dose of prednisone taken will be record by each subject daily and collected at each evaluation.

Subjects will have clinical evaluations at baseline and then every 4 weeks thereafter (week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52). Clinical evaluations will be completed by a blinded evaluator. The dose of prednisone will be recorded by each subject daily and collected at each scheduled assessment. Post-intervention status will be assessed by measuring MGFA class, Myasthenia Gravis Composite (MGC), Quantitative Myasthenia Gravis (QMG), MG-Activities of Daily Living (MG-ADL), and MG-Quality of Life (MG-QOL) scores. Blood will be collected for safety, specialized and other studies at scheduled time points. Adverse effects will be monitored at each visit to assess safety and tolerability in this subject population per the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials and Genentech guidelines.

If subject symptoms significantly worsen during the course of the trial and are not controlled by increased steroid doses (high dose prednisone), the subject can receive PLEX or IVIg as a rescue therapy. Subjects that could not be managed with steroids, IVIg, or PLEX and required additional immunotherapy (e.g. pulse IV steroids, azathioprine, etc.) would be considered treatment failures and likely withdrawn from the study.

1.1. Primary Outcomes

Primary Objective 1 – Steroid Sparing Effect: *Percent of subjects that achieve a ≥75% reduction in mean daily prednisone dose in the 4 weeks prior to week 52 and with clinical improvement or no significant worsening of symptoms (≤ 2 point increase in MG composite score) as compared to the 4-week period prior to randomization and initiation of treatment.*

Primary Objective 2 - Safety: *Percentage of subjects with treatment-related adverse events.*

1.2. Major Secondary Objective

The main secondary objective is to evaluate whether there is a trend towards clinical benefit at the end of the 52 week treatment period, as measured by MG-specific clinical outcome scales used as endpoints in prior clinical trials:

(1) Myasthenia Gravis Composite (MGC) Score

(2) Quantitative Myasthenia Gravis (QMG) Score

The clinical evaluators who determine the MGC & QMG will be blinded to treatment assignment. If successful, measures studied would lay the groundwork toward optimizing the design of a subsequent phase III efficacy trial of rituximab in MG.

2. PRIMARY ENDPOINTS

2.1. Prednisone Reduction

The first primary outcome measure for this study is the percent of subjects achieving a ≥ 75% mean daily prednisone reduction in the four weeks prior to week 52 (week 49-52) along with clinical improvement or no significant worsening of symptoms (≤2 point increase in MG composite score), as compared to the four week period prior to randomization. The primary endpoint will be a binary indicator of whether the subject achieved the definition above. The prednisone-sparing aspect of the endpoint will be computed by comparing the mean daily prednisone dose (per the protocol defined taper) during the four week period prior to randomization versus the four week period at the end of the study (weeks 49-52). For subjects that had their prednisone dose changed after the week 48 visit, or who missed their week 48 visit, the primary endpoint will be determined by comparing the prednisone dose reported at baseline to the last prednisone dose recorded prior to the week 52 visit. The MGC aspect of the endpoint will be computed by comparing the MGC obtained at baseline to the MGC obtained at the week 52 visit. For the primary analysis, we will take a conservative approach and impute an outcome of “failure” for any subject that either terminates the study early, for whom the prednisone dose in the last 4 weeks is unknown, or for whom the week 52 MGC score is missing.

2.2. Safety

The second primary outcome will assess the safety profiles of rituximab vs. placebo. Primary interest involves an examination:

- Treatment-related adverse events (AEs)
- Treatment-related serious adverse events (SAEs)

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Examples of AEs include new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc), or clinically significant abnormal test results (i.e. lab values or vital signs). Stable chronic conditions (i.e. diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered AEs. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as AEs.

AEs are generally detected in two ways:

- Clinical → Symptoms reported by the subject or signs detected on examination
- Ancillary Tests → Abnormalities of vital signs, laboratory tests, and other diagnostic procedures

All AEs should be reported within 5 working days / 7 calendar days of the site learning of a new AE. Similar timelines apply for reporting upon receipt of any updates for previously reported AEs. If discernible at the time of reporting, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded as an AE. However, if an observed or reported sign, symptom, or clinically specific disease or syndrome, then it should be recorded as a separate AE. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified by the Site Investigator.

The study will utilize the CTCAE version 4.0 coding system for AE recording. AEs reported using CTCAE will be recoded into MedDRA terms by the DCC.

For the purposes of this study, a treatment-related AE (also referred to as an Adverse Drug Reaction) is defined as any noxious or unintended response to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as treatment related if there is thought to be a causal relationship to Rituximab. At the time of reporting, the relationship of the AE to the investigational product should be specified by the Site Investigator using the following definitions:

- Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure (suspected treatment related AE or ADR)
- Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state (suspected treatment related AE or ADR)
- Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject (suspected treatment related AE or ADR)
- Unlikely to be Related: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists
- Not Related: Concomitant illness, accident, or event with no reasonable association with treatment

As this is a double-blind study, the causality assessment should be made under the assumption that the subject is receiving active study medication. If considering unblinding, this assessment should be made prior to unblinding to avoid bias.

An AE is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening (i.e., poses an immediate risk of death as the event occurred)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female)
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to the body structure
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical AE may meet criteria for “seriousness” but is not an adverse experience, and will therefore not be considered an SAE. An example of this would include a social admission (subject admitted for reasons other than medical, e.g. lives far from the hospital, has no place to sleep). The Site Investigator is responsible for initially classifying AEs as serious or non-serious. SAEs must be reported using the OEARS within 24 hours of the site learning of the SAE.

Dr. Michael Shy will serve as the Medical Safety Monitor (MSM) for this trial. Dr. Shy will work closely with the DCC, and will use the online AE reporting system to review all SAEs in near real time and evaluate them to identify the need for timely intervention. For any reported SAEs, an automatic email will be sent to Dr. Shy to prompt a review of the event for determination of whether the event meets the criteria for an SAE and, if so, whether the SAE is unanticipated and/or related to study drug. An unexpected SAE is any SAE for which the specificity or severity is not consistent with the current Investigators Brochure or package insert described in the protocol. An unexpected and treatment-related SAE is an unexpected SAE that, in the opinion of the MSM, has a reasonable possibility that the investigational product caused the event. With the assistance of the coordinators at the DCC, Dr. Shy has the option of requesting additional information about any SAE. He will complete a form for each review, and this information will be entered into the online data entry system.

Thus, in summary, the determination of whether an AE or SAE is treatment-related (at least possibly related to treatment) differs. Because the MSM only reviews SAEs in real-time, the determination of whether or not a non-serious AE is considered treatment-related will be made at the site level. However, for SAEs, the MSM determination of whether or not an SAE is treatment-related will take precedent over the classification at the site level.

3. MAJOR SECONDARY ENDPOINTS

3.1. Myasthenia Gravis Composite Score (MGC)

The Myasthenia Gravis Composite (MGC) score is a validated, patient- and physician-reported 10-item assessment tool for evaluating the symptoms and signs of MG. Physician assessment includes evaluation for ptosis (upward gaze), double vision on lateral gaze, eye closure, neck flexion or extension, should abduction, and hip flexion. Patient assessment includes self-report of impact (normal, mild, moderate, or severe) and is additionally weighted for clinical significance. Total score ranges from 0 to 50, with higher scores indicating a greater impact of MG on functional activities. A three point change is considered clinical meaningful. This brief assessment takes approximately 10 minutes to complete (Burns et al, 2008; Burns et al, 2010; Burns, 2012; Sadjadi et al, 2012).

3.2. Quantitative Myasthenia Gravis Score (QMG)

The QMG score is a validated, physician-reported 13-item disease-severity assessment tool. It evaluates muscle strength based on quantitative testing of sentinel muscle groups: ocular (two items), facial (one item), bulbar (two items), gross motor (six items), axial (one item), and respiratory (one item). Each item is graded on a scale of 0 to 3, with 3 being the most severe. Total score ranges from 0 to 39, with higher scores representing greater disease burden. A 3-point improvement in total score considered a clinically meaningful improvement. This assessment takes 30-40 minutes to complete, and is the most widely used tool in MG trials (Barohn et al, 1998).

4. ENROLLMENT & RANDOMIZATION

Subjects who meet the eligibility criteria and have given their consent will be randomized to one of the 2 treatment arms. Randomization will be performed through an interactive website, and will be stratified based on the steroid dose at baseline [moderate dose prednisone (15-35 mg/day) vs. high dose prednisone (>35 mg/day)] and treatment regimen at the baseline visit [prednisone only vs.

prednisone plus another immunosuppressive therapy (IST)]. Subjects will be assigned a study ID at the time of enrollment. The study ID includes the identification of the clinical study site and a unique subject ID. The DCC will generate a randomization table for each of the strata using a permuted block design with random block sizes.

5. PRELIMINARY TABLULATIONS

All subjects who provide informed consent will be accounted for in this study. Regularly generated enrollment reports will describe:

- Number of subjects consented, eligible, and randomized by site
- Ongoing study status of all randomized subjects
- Reasons for ineligibility
- Protocol deviations
- Early study terminations

The data set will also be summarized by treatment group with respect to important confounders. The distributions of categorical variables will be tabulated by treatment group and overall. Continuous variables will be summarized as mean, median, standard deviation, minimum, and maximum by treatment group and overall. Variables to be collected will include:

- Gender
- Race
- Ethnicity
- Age
- Baseline Prednisone Dose (mg/day)
- Baseline Myasthenia Gravis Composite Score (MGC)
- Baseline Quantitative Myasthenia Gravis Score (QMG)
- Baseline MG-Activities of Daily Living Score
- Baseline MG-Quality of Life Score (MG-QOL)
- Baseline MGFA Clinical Classification Grade
- Hand Preference
- Thymectomy Results

6. ANALYSIS POPULATIONS

Due to the exploratory nature of this study, all analyses to address the primary and major secondary objectives will be conducted at the 0.10 significance level. All analyses will be implemented using an intent-to-treat approach. Any subject who received a random treatment assignment will be included in all analyses.

7. PRIMARY EFFICACY ANALYSES

7.1 Primary Futility Hypothesis: *Subjects treated with rituximab will have at least a 30% absolute increase in the frequency of achieving at least a 75% reduction in mean daily prednisone dose with maintenance of minimal or no symptoms.*

The primary futility hypothesis being tested in this trial is that subjects treated with rituximab will achieve at least an absolute 30% increase in the frequency of favorable responses. Assuming a placebo response rate of 40% (as in the original sample size calculations – see section 9), this corresponds to

an odds ratio of 3.5. Therefore, the primary futility hypothesis will be assessed using a logistic regression model, adjusted for the two stratification variables, to estimate the log-odds of primary endpoint success in each group. The logistic regression model used for these purposes is stated here:

$$\text{logit}(Y_i) = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}$$

where

- Y_i represents the binary variable indicating whether or not the i^{th} subject met the primary outcome requirement of a 75% or greater reduction in prednisone dose, with no significant worsening of symptoms (≤2 point increase in MG composite score at baseline)
- X_{1i} is an indicator variable for prednisone dose at baseline (=0 if moderate, =1 if high)
- X_{2i} is an indicator variable for treatment status at baseline (=0 if prednisone alone, =1 if prednisone plus IST)
- X_{3i} is an indicator variable for whether the i^{th} subject was randomized to the Rituximab group (=0 if placebo, =1 if rituximab)

Correspondingly, the primary futility hypothesis of interest can be assessed by performing the following hypothesis test:

$$H_0: \exp(\beta_3) \geq 3.5 \textit{ vs. } H_A: \exp(\beta_3) < 3.5$$

Results will be summarized in the following tables (number and percent of primary endpoint success are displayed in Table 7.1; Odds ratios and confidence intervals are displayed in Table 6.2).

Table 7.1: Number and Percent of Primary Endpoint Success

Treatment Group	Number in each group	Number and Percent of Success	Number and Percent of Failure	Number missing
Rituximab	xx	xx (xx%)	xx (xx%)	xx
Placebo	xx	xx (xx%)	xx (xx%)	xx

Table 7.2: Odds-ratios of Primary Endpoint Success

Comparison	Odds-ratio (1-sided 90% CI)	p-value
Rituximab vs. Placebo	xx.x (xx.x, xx.x)	x.xx

Rejecting the null hypothesis suggests 'futility' in the sense that it appears unlikely that conducting a future phase III clinical trial would lead to a significant effect with a magnitude at least as large as the specified clinically meaningful effect of interest. If we don't reject the null hypothesis, this would provide justification for proceeding to examine the superiority hypothesis, with the magnitude of the estimate and confidence intervals surrounding β_3 providing information helpful for planning the future phase III trial.

Due to randomization, it is unlikely that important covariates will be imbalanced in this study. However, given the small sample size, this cannot be dismissed. We will assess for important baseline imbalances, and if any imbalances exist, we will conduct sensitivity analyses to examine the impact on the results when the relevant covariate(s) are added to the logistic regression model.

7.2 Primary Safety Hypothesis: *There will be no increase in adverse experiences for the rituximab-treated vs. placebo subjects.*

As described elsewhere, general assessments of safety will occur throughout the trial in conjunction with the medical safety monitor. The primary assessment of safety will compare the percentage of subjects in each group with:

- Treatment-related adverse events (AEs)
- Treatment-related serious adverse events (SAEs)

This hypothesis will be assessed in two ways. First, the percentage of subjects who experience any treatment-related AE or SAE (overall and by MedDRA system organ class) in each group will be compared using a Fisher's exact test. If the null hypothesis is rejected, with a greater frequency observed in the rituximab group, we will conclude that rituximab was associated with a significantly greater frequency of treatment-related AEs. If the hypothesis is not rejected, we will conclude that the study does not provide sufficient evidence to conclude that rituximab was associated with a significantly greater frequency of treatment-related AEs. If there are significant differences between groups within any specific SOC, then additional tests will compare differences across groups for specific MedDRA preferred terms in order to further explore the cause of observed differences.

In addition to the comparison of percentages in the manner described above, the rates of treatment-related AEs in each group will be compared using the following Poisson regression model:

$$\log\left(\frac{Y_i}{T_i}\right) = \beta_0 + \beta_1 x_{1i} + \epsilon_i$$

where

- Y_i represents the number of treatment related AEs experienced by the i^{th} subject.
- T_i represents the number of days between the date of randomization and the date of last follow-up for the i^{th} subject.
- x_{1i} = 1 if i^{th} subject was randomized to rituximab, and 0 if the subject was randomized to placebo group
- ϵ_i is random error for the i^{th} subject

To determine if the rate of treatment related AEs differ across treatment group we will test the following hypothesis:

$$H_o: \beta_1 = 0 \text{ vs. } H_A: \beta_1 \neq 0$$

If the null hypothesis is rejected, the direction of β_1 will indicate the direction of the observed effect. Values of $\beta_1 > 0$ indicate an increased rate of treatment-related AEs associated with the rituximab group, while values of $\beta_1 < 0$ indicate a decreased rate of treatment-related AEs associated with the rituximab group.

Treatment-related SAEs will be analyzed in the same manner described above. Additional safety analyses will assess all treatment-emergent AEs, treatment-emergent SAEs, unanticipated SAEs, and treatment-related & unanticipated SAEs in a similar manner.

8. IMPACT OF MISSING DATA

The primary analysis will follow the intent-to-treat (ITT) paradigm. All enrolled subjects must be included in the primary ITT analysis, and will be analyzed in the treatment group to which they were initially randomized. As such, it will be critically important to minimize the occurrence of missing data. Obviously, the optimal strategy for dealing with missing data is to make every effort to obtain complete data during the conduct of the study. Our team of data managers and protocol coordinators will work diligently and use a variety of methods in order to minimize the percentage of missing data in this trial. Nevertheless, there is likely to be a small percentage of missing data. As specified above, we will take a conservative approach for the primary analysis and impute an outcome of "failure" for any subject that either terminates the study early, for whom the prednisone dose in the last 4 weeks is unknown, or for whom the week 52 MGC score is missing. We then propose a series of sensitivity

analyses to further assess the potential dependence of the results of the primary analysis on these missing values. This sensitivity analysis will employ multiple methods:

- **Using Only Observed Data:** Use only subjects who completed the study, for whom the prednisone dose in the last 4 weeks was known, and for whom the week 52 MGC score is known.
- **Tolerability/Imputation:** For all additional sensitivity analyses, all subjects who terminated from the study due to an AE or had clinical worsening (an MGC score >2 above baseline) at the time of termination will be considered "failures". For remaining subjects with missing data due to other reasons (lost to follow-up, discontinuation for reasons other than AE, etc.), outcomes will be imputed using a variety of methods
    - **Last Observation Carried Forward:** Last known prednisone dose status at the time of termination will be carried forward and used for the endpoint determination for these subjects
    - **Multiple Imputation**: For simplicity, we assume subjects requiring imputation will not have had clinical worsening had they stayed in the study. Thus, the imputation is focused solely on the missing prednisone dose information. To implement this multiple imputation model, we will impute week 52 prednisone dose data using a multiple imputation model based on the prednisone dose strata and treatment status at baseline, as well as prednisone dose data computed at each intermediate time point for all subjects with observed data. Imputed values will be derived using the MCMC method with multiple chains, adequate burn-in iterations, and a non-informative prior distribution. Once the imputed prednisone dose data have been obtained, the binary outcome variable will be generated for all subjects and fit using the same model described in section 6.1. We will conduct five separate iterations, and the mean of the parameter estimates from the five imputed data sets will be used as the estimate for the final analysis. Variances for the primary parameter estimate will be estimated using standard formulas as a function of within imputation and between imputation variable (Little & Rubin, 2002).
    - **Best-case scenario**: Assume all subjects missing prednisone dose information during the last 4 weeks, or missing a week 52 MGC score, in the rituximab group are "successes" (did achieve ≥ 75% dose reduction); Assume all subjects missing prednisone dose information during the least 4 weeks, or missing a week 52 MGC score, in the placebo group are "failures" (did not achieve ≥ 75% dose reduction).
    - **Worst-case scenario**: Assume all subjects missing prednisone dose information during the last 4 weeks, or missing a week 52 MGC score, in the rituximab group are "failures" (did not achieve ≥ 75% dose reduction); Assume all subjects missing prednisone dose information during the last 4 weeks, or missing a week 52 MGC score, in the placebo group are "successes" (did achieve ≥ 75% dose reduction)

Results will be reported from both the primary analysis and all sensitivity analyses in order to inform how robust the overall trend observed in the study is to the missing data. For example, if the final analysis suggests a non-futile study, future researchers might be more comfortable proceeding to a phase III study if that finding of non-futility is also supported by the majority of the sensitivity analyses. On other hand, if a primary finding of non-futility is not supported by the sensitivity analyses, further exploration of the data might be needed prior to embarking on a future phase III trial. These results will be displayed in the following table:

Table 8.1: Number and Percent of Subjects Meeting Primary Endpoint w/ Odds Ratios & One-Sided 90% CIs

Imputation Method	Reduction in mean daily prednisone dose ≥ 75%		Odds Ratios (1-Sided 90% CI) Rituximab vs. Placebo
	Rituximab N (%)	Placebo N (%)	
Primary	xx (xx.x%)	xx (xx.x%)	x.xx (x.xx, x.xx)
Observed	xx (xx.x%)	xx (xx.x%)	x.xx (x.xx, x.xx)
Last Observation Carried Forward	xx (xx.x%)	xx (xx.x%)	x.xx (x.xx, x.xx)
Multiple Imputation	xx (xx.x%)	xx (xx.x%)	x.xx (x.xx, x.xx)
Best Case	xx (xx.x%)	xx (xx.x%)	x.xx (x.xx, x.xx)
Worst Case	xx (xx.x%)	xx (xx.x%)	x.xx (x.xx, x.xx)

9. MAJOR SECONDARY ANALYSES

The secondary objective of the study is to evaluate whether there is a trend towards clinical benefit as measured by MG-specific clinical outcome scales used as endpoints in prior clinical trials. Specifically, we will determine if rituximab can significantly improve the scores of the following MG-specific clinical outcome measures: 1) Myasthenia Gravis Composite (MGC), and 2) Quantitative Myasthenia Gravis (QMG). These studies measures would lay the groundwork towards optimizing the design of a subsequent phase III efficacy trial of rituximab in MG.

9.1. Major Secondary Objective #1 – Myasthenia Gravis Composite: *Rituximab-treated subjects will have clinically significant improvement in their Myasthenia Gravis Composite (MGC) scores at the end of the 52 week treatment period.*

The first secondary hypothesis assesses the change in MGC scores at the end of the 52 week study period. This objective will be assessed longitudinally comparing the final score at the end of the study to the score obtained at baseline. The outcome will be defined as the change from baseline to week 52 in the MGC. This hypothesis will be assessed using a linear regression model, adjusted for baseline MGC score. For example, the following model will be fit to these data:

$$Y_i = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i} + \beta_4 X_{4i}$$

where

- Y_i represents the change from baseline in the MGC score for the i^{th} subject
- X_{1i} is an indicator variable for prednisone dose at baseline (=0 if moderate, =1 if high)
- X_{2i} is an indicator variable for baseline treatment (=0 if prednisone alone, =1 if prednisone plus IST)
- X_{3i} is the baseline MGC score for the i^{th} subject
- X_{4i} is an indicator variable for whether the i^{th} subject was randomized to the Rituximab group (=0 if placebo, =1 if rituximab)

Correspondingly, the secondary hypothesis of interest can be assessed by performing the following test:

$$H0: \beta_4 = 0 \text{ vs. } HA: \beta_4 \neq 0.$$

The results will be displayed in the following table

Table 9.1: Change in MGC Scores from Baseline to 52 Weeks

MGC Score	Rituximab	Placebo	Model Adjusted Difference (90% CI)
(52 week – baseline) **Mean (SD)** **Min. – Max** **Missing**	 xx (xx) xx – xx xx	 xx (xx) xx – xx xx	 xx.x (xx.x, xx.x)

9.2. Major Secondary Objective #2 – Quantitative Myasthenia Gravis: *Rituximab-treated subjects will have clinically significant improvement in their Quantitative Myasthenia Gravis (QMG) scores at the end of the 52 week treatment period.*

The second secondary hypothesis assesses the change in QMG scores over the course of the 52 week study period. Because the only difference between this and the first secondary hypothesis is the choice of outcome, the analysis will proceed in the same manner described above for the first secondary hypothesis.

9.3. Exploratory Analyses

A number of additional exploratory analyses are also planned to monitor effectiveness as well as evaluate other endpoints that may be useful in optimizing future MG trial designs, but will not be included as part of the FSR. These additional analyses may include, but are not limited to:

- Other Previously Validated MG-specific outcome measures
    - MG-Activities of Daily Living (MG-ADL) – This 8 point scale assesses the subject's ability to perform daily activities (Wolfe et al, 1999).
    - MG-Quality of Life (MG-QOL) – The subject completes a 15-question questionnaire and reports the effect of MG on their quality of life (Burns et al, 2008).
- Other Previously Used Measures of Steroid-Sparing Effect:
    - Mean daily prednisone dose at each scheduled assessment (every 4 weeks)
    - A delayed start of the area under the dose-time curve (AUDTC), starting at week 8
    - Percentage of subjects achieving a ≥ 50% mean daily prednisone reduction with maintenance of minimal or no symptoms in 4 weeks prior to week 52
    - Body mass index (screening visit and weeks 24 & 52)
    - HbA1C (screening visit and week 52)
- MG Flare Rate (Failure of Therapy)
    - Percentage of subjects requiring rescue treatments (PLEX or IVIg)
    - Percentage of subjects requiring prednisone dose increase
    - Rate of subjects requiring prednisone dose increase
    - Percentage of subjects with a ≥ 3 point increase in the MGC score

Additional exploratory analyses will be conducted as part of the extended follow-up study. The primary focus of the two observational off study-intervention time points (weeks 72 & 96) will be to assess B cell recovery/repopulation as a safety measure. Specifically, we will examine: (1) Percentage of subjects achieving normal B cell counts at weeks 72 & 96; and (2) Percentage of subjects returning to at least baseline (pre-treatment) B cell counts at weeks 72 & 96.

10. SAMPLE SIZE JUSTIFICATION

Below, we introduce some key notation that we use to describe the analysis plan for the proposed trial:

- Let p_P represent the true (unknown) percentage of subjects treated with placebo who will achieve success on the primary endpoint
- Let p_R represent the true (unknown) percentage of subjects treated with rituximab who will achieve success on the primary endpoint

Based on a prior study completed by Sanders et al (2008) on MMF in AChR+ MG, 38.6% of placebo treated case achieved a treatment response. The placebo start point was 34.1 mg prednisone; hence, 38.6% of placebo recipients had a reduction of prednisone dose by at least 78%. Also the MMF start point was 30.7 mg prednisone; therefore, 44.3% of MMF recipients had a reduction of prednisone dose by at least 76%. Based on this information, we assume that 40% of placebo recipients will achieve a 75% or greater prednisone dose reduction ($p_P = 0.40$).

The design of this trial was somewhat restricted due to the fact that the company that produces rituximab only agreed to provide 25 doses to the investigators. As a consequence, this study required more of a sample size justification (for the sample size fixed by external factors) as opposed to a standard sample size calculation that determines the required sample size for a fixed target power. Using the notation above, the one-sided futility hypothesis that the treatment achieved the desired clinically meaningful level of interest may be stated as:

$$H_0: p_R - p_P \geq 0.30 \textit{ vs. } H_A: p_R - p_P < 0.30$$

Therefore, rejecting the null hypothesis suggests 'futility' in the sense that it appears unlikely that conducting a future phase III clinical trial would lead to a significant effect with a magnitude at least as large as the specified clinically meaningful effect of interest. If we don't reject the null hypothesis, this would provide one of the "go" conditions for conducting a future phase III study.

The table below shows the power computed across a range of assumed values for the true response rate in the rituximab subjects. The calculations assume a type I error rate of 10%, $p_P = 0.40$, and a conservative assumption of up to 20% missing data. The table below demonstrates the benefits of using the futility design. When the true success rate for rituximab is near or below the true success rate for placebo, the study will declare "futility" with high probability. Likewise, when the true success rate for rituximab is well above the true success rate for placebo, the study has a very low chance of incorrectly declaring "futility". Given the sample size limitations mentioned above, we feel that this provides a reasonable chance of having a successful study – where "success" is defined as answering the main question of interest regarding whether there is clear evidence to rule out an effect of rituximab in this population, or to provide enough evidence to justify a larger trial in the future.

Table 10.1: Power of Futility Test as a Function of True Rituximab Rate

Rituximab Rate (p_R)	**30%**	**35%**	**40%**	**45%**	**50%**	**55%**	**60%**	**65%**	**70%**	**75%**	**80%**	**85%**	**90%**
Pr (Futility)	92%	84%	74%	63%	50%	37%	25%	16%	10%	4%	2%	1%	<1%

11. SAFETY MONITORING

The monitoring of subject safety and data quality will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. Subjects will be monitored through regular physical examinations, vital signs, laboratory tests, and incidence and severity of adverse events. Infections will be treated symptomatically. Cardiovascular risk factors will be assessed prospectively by recording risk factors (e.g. family history, smoking history, and status). Additional safety evaluations will be conducted on conventional safety variables, such as adverse events, laboratory tests, and vital sign changes. In

addition, B cell counts, immunoglobulin levels, infusion-related reactions, and thromboses infections will be carefully examined. Tolerability will be determined by the ability to complete the study on the assigned experimental medication.

11.1. Adverse Experience Reporting

The adverse event (AE) definitions and reporting procedures for this study comply with all applicable United States FDA regulations and International Conference on Harmonization (ICH) guidelines. Adverse events will be reviewed and recorded at each study visit and infusion visit. Information on AEs of medication and on inter-current events will be determined at each visit by direct questioning of the subjects, clinical examination, and laboratory tests. The Site Investigator will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Subjects will be monitored for AEs from the time they sign consent until the Week 52 visit. All SAEs must be followed until resolution, or until the Week 52 Visit, whichever comes first. If the SAE is still ongoing at Week 52, it will be Resolved with Sequelae.

- SAEs that are discovered less the 90 days prior to the Week 52 Visit will be followed until resolution or for a minimum of 90 days, whichever comes first, even if it is past the Week 52 Visit. A repeat Termination Visit does not need to occur.
- If a new SAE is discovered at the Week 52 Visit, it must be followed until resolution, or for a minimum of 90 days, whichever comes first.
- Subjects that are withdrawn from the study or have intervention discontinued due to an SAE will have reduced follow-up. This will include being followed monthly via telephone or in person for a minimum of 90 days or until SAE resolution, whichever comes first, after which a Termination Visit will be conducted. The Termination visit will mirror the Week 52 Visit.
    - If the SAE is resolved within 90 days, the Termination Visit can occur earlier.
    - If the SAE is not resolved within 90 days, the SAE will be Resolved with Sequelae, and the Termination Visit will occur

  During the 90 day (or less) SAE follow-up period, no new AEs will be recorded. Existing AEs will be followed until resolution, or the Termination Visit, whichever comes first.

During the optional week 72 & 96 visits, only those AEs that in the opinion of the investigator are deemed related to study procedures will be reported.

Each Clinical Study Site Investigator and research team (co-investigators, research nurse, clinical trial coordinator) are responsible for identifying AEs, reporting them through the DCC Online Adverse Event Reporting System (OEARS), and determining the relationship of the AE to the study drug/study procedures (as described in section 2.2). Investigators are also responsible for complying with the NeuroNEXT Central IRB (CIRB) reporting requirements for all safety reports. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

For the purposes of this study, before randomization only those AEs (serious and non-serious) that, in the opinion of the investigator, are deemed related to study procedures will be reported. Non-serious adverse events that are reported to or observed by the investigator or a member of their research team will be submitted to the DCC in a timely fashion (within 5 working days / 7 calendar days). Investigators must report any SAE within 24 hours of learning of the event. Upon entry of an SAE by a site investigator, the DCC Online Adverse Event Reporting System (OEARS) will immediately notify the Medical Safety Monitor (MSM). The MSM will review the SAE report, and may request further information if necessary. The OEARS maintains audit trails and stores data and communication related to the review of any AE reported in the study. The MSM may determine that the SAE requires

expedited reporting to the FDA. For example, the Sponsor-Investigator are required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the MSM to be at least possibly related to the use of Rituximab. If expedited reporting is required, the DCC will prepare a MedWatch safety report for submission to the FDA and Genentech. If warranted, the MSM will notify the DSMB chair. The DSMB may suggest changes to the protocol or consent form to the PPI as a consequence of SAEs.

11.2 Medical Safety Monitor

As previously indicated, Dr. Michael Shy will serve as the MSM for this trial. In addition to performing real-time reviews of all SAEs (as described in section 2.2), Dr. Shy will also receive quarterly tabulations, by blinded treatment group, of all AEs/SAEs for the purpose of determining if any safety trends exist that may raise concerns. Aggregate reports, blinded by treatment group, will be provided by severity, attribution (anticipated or unanticipated), and relationship to study treatment. The percentage of subjects who experience any AE will be compared by body system across the two groups. The additional questions related to whether the AE/SAE is related to treatment and/or unanticipated will be used to subset these into a series of additional tables. The quarterly review will identify any disconcerting discrepancy in the frequency of any AE/SAE between the two groups.

11.3 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB), appointed by the NIH/NINDS, will meet at approximately six-month intervals (or as determined by the NINDS) to review partially unblinded study data provided by the study statistician. The DSMB will periodically review and evaluate the accumulated data for participant safety, adverse events, study conduct, and study progress. The DSMB may suggest changes to the protocol or consent form to the Study Chair as a consequence of AEs. The DSMB may also make recommendations to NINDS concerning continuation, modification, or termination of the study. The frequency and format of DSMB meetings, reports, and guidelines for interim analysis will be agreed upon prior to study subject enrollment.

11.4 Study Hold Rules (Safety)

Individual study subjects may be withdrawn from the study medication, but continue to be followed for safety, if subjects develop a grade 3 or more suspected toxicity as graded by the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 or an SAE related to study medication as determined by the MSM. Grade 3 adverse events are severe or medically significant, but not immediately life-threatening and may cause hospitalization or prolongation of hospitalization indicated. Descriptions of CTCAE grading criteria are included in the Manual of Operations and SAEs are specifically defined in section 2.2. Subjects will be allowed to resume participation in the study if their suspected toxicity or AE resolves completely, and in the judgement of the investigator and MSM it is safe for the subject to continue.

12. INTERIM STOPPING RULES

The study will be permanently stopped, and no further administration of rituximab will be given, if the investigator, CIRB, DSMB, and/or any other institutional or regulatory body deems it inappropriate for the study to resume due to a significant number of randomized subjects developing safety concerns that cannot otherwise be attributed to MG, infections, disease relapse, or pre-existent comorbidities as deemed by the MSM.

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TREATMENT EMERGENT SAEs	RITUXIMAB			PLACEBO			P-VALUE
	No. (% subjects)	No. of Events	Rate	No. (% subjects)	No. of Events	Rate	
Worsening of MG	1 (4%)	1	0.003	3 (11.1%)	4	0.013	0.36
Pulmonary embolism	1 (4%)	1	0.003	1 (3.7%)	1	0.003	0.96
Leucopenia	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Hypersensitivity	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Diverticulitis	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Septic shock	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Vascular pseudoaneurysm	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Decreased platelet count	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Hyperglycemia	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Psychotic disorder	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Nephrolithiasis	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Menorrhagia	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Hypotension	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Venous thrombosis in limb	1 (4%)	1	0.003	0 (%)	0	0.000	0.48
Anemia	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Congestive heart failure	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Coronary artery disease	0 (0%)	0	0.000	1 (3.7%)	2	0.003	1.00
Colonic obstruction	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Intestinal diverticulum	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Small intestinal obstruction	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Chest pain	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Pyrexia	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Neck abscess	0 (0%)	0	0.000	1 (3.7%)	2	0.007	1.00
Cellulitis	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
C. difficile colitis	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Pneumonia	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Sepsis	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Spinal compression fracture	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Hyperkalemia	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Prostate cancer	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Dyspnea	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Micrographic skin surgery	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00
Thrombosis	0 (0%)	0	0.000	1 (3.7%)	1	0.003	1.00

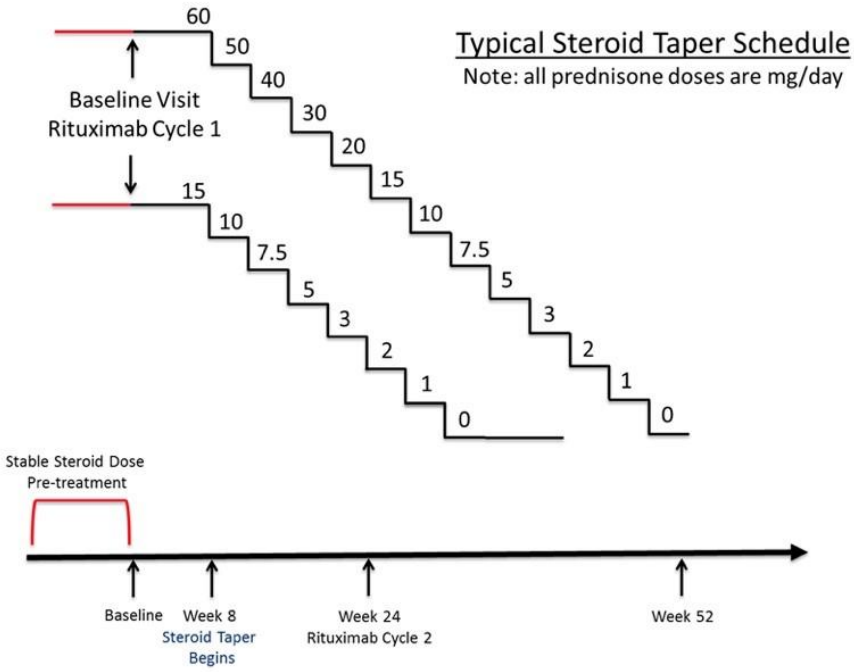
eTable 1: Treatment emergent serious adverse events (SAEs) during the 52-week study period. *The table shows the number and percentage of participants in either of the two treatment groups who ever had an SAE during the study as well as the number of SAEs per 30 days. * Preferred term in the Medical Dictionary for Regulatory Activities.*

RELATED AND ANTICIPATED SAEs (N=17)			
RITUXIMAB	**No. of events**	**PLACEBO**	**No. of events**
Diverticulitis	1	Worsening of MG	2
Hypersensitivity	1	Neck abscess	1
Hypotension	1	Congestive Cardiac failure	1
Leukopenia	1	Cellulitis	1
Worsening of MG	1	Intestinal diverticulum	1
Decreased platelet count	1	Pneumonia	1
Pulmonary embolism	1	Pulmonary embolism	1
		Pyrexia	1
		Sepsis	1
UNANTICIPATED BUT NOT RELATED SAEs (N=14)			
RITUXIMAB	**No. of events**	**PLACEBO**	**No. of events**
Hyperglycemia	1	Clostridium difficile colitis	1
Nephrolithiasis	1	Colonic obstruction	1
Septic shock	1	Dyspnea	1
Vascular pseudoaneurysm	1	Hyperkalemia	1
Venous thrombosis in limb	1	Micrographic skin surgery	1
		Prostate cancer	1
		Small intestinal obstruction	1
		Spinal compression fracture	1
		Thrombosis	1
RELATED AND UNANTICIPATED SAE (N=0)			

eTable 2: Serious adverse events (SAEs) during the 52-week study period across both treatment groups. *The table shows the number and descriptions of the SAEs that were potentially related and anticipated, unanticipated but not related, and related but unanticipated to study intervention as deemed by the independent medical monitor. * Preferred term in the Medical Dictionary for Regulatory Activities.*

eFigure 1: Predetermined steroid taper schedule for rituximab and placebo groups. In each participant, the dose was gradually reduced at every 4-week assessment beginning at week 8 only after confirming clinical improvement or stable symptoms based on the MGC score (≤2-point increase) as compared to the baseline visit or prior study visit score. If the MGC score worsened by ≥3 points, the forced steroid taper was stopped, and the dose was increased until symptoms resolved, or patient achieved baseline visit MGC score.

eFIGURE 1: Steroid Taper



Daily Prednisone Dose (mg)	Taper to Dose (mg):
100	90
90	80
80	70
70	60
60	50
50	40
40	30
30	20
20	15
15	10
10	7.5
7.5	5
5	3
3	2
2	1
1	0

Every Other Day Prednisone Dose (mg)	Taper to Dose (mg):
200	180
180	160
160	140
140	120
120	100
100	80
80	60
60	40
40	30
30	20
20	15
15	10
10	7.5
7.5	5
5	2.5
2.5	0

eFigure 2: Futility analysis. A clinically relevant increase associated with the primary futility hypothesis being tested in this trial is that participants treated with rituximab will achieve at least an absolute 30% increase in the frequency of favorable responses (e.g. $p_R \geq 70\%$). Under these assumptions ($p_P = 40\%$ & $P_R = 70\%$), this corresponds to an odds ratio of 3.5. Therefore, the primary futility hypothesis was assessed using a logistic regression model, adjusted for the two stratification variables, to estimate the log-odds of primary endpoint success in each group. As previously mentioned, rejecting the null hypothesis suggests 'futility' in the sense that it appears unlikely that conducting a future phase 3 clinical trial would lead to a significant effect with a magnitude at least as large as the specified clinically meaningful effect of interest. If we did not reject the null hypothesis, this would have provided one of the "go" conditions for conducting a future phase 3 study. The table shows the power computed across a range of assumed values for the true response rate in the rituximab group. The calculations assume a type I error rate of 10%, $p_P = 0.40$, and a conservative assumption of up to 20% missing data. The table demonstrates the benefits of using the futility design. When the true success rate for rituximab is near or below the true success rate for placebo, the study will declare "futility" with high probability (in red). Likewise, when the true success rate for rituximab is well above the true success rate for placebo, the study has a very low chance of incorrectly declaring "futility" (in green).

Rituximab Response Rate (p_R)	30%	35%	40%	45%	50%	60%	70%	80%	90%
Probability of declaring futility (%)	92%	84%	74%	63%	50%	25%	10%	2%	<1%