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CFZ533

Clinical Trial Protocol CCFZ533X2204

A multi-center, randomized, double-blind, placebo-controlled, parallel group study to preliminarily evaluate the safety, tolerability, pharmacokinetics and efficacy of CFZ533 in patients with moderate to severe myasthenia gravis

Personal Data

Document type:	Amended Protocol Version
EUDRACT number:	2015-000097-35
Version number:	v03 Clean (incorporating amendment 3)
Development phase:	IIa
Release date:	19-May-2016

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the Clinical Trial Leader.).

Contact information is listed in the SOM.

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List of abbreviations

AChR	Acetylcholine Receptors
ADA	Anti-drug antibodies
ADCC	Antibody dependent cell mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CDC	Complement dependent cytotoxicity
CFR	Code of Federal Regulation
CI	cholinesterase inhibitor
CI	confidence interval
CK	creatinine kinase
CRF	Case Report/Record Form (paper or electronic)
CRP	C-Reactive Protein
CTL	Clinical trial leader
CO_2	carbon dioxide
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
DLTs	dose limiting toxicities
FAS	full analysis set
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
γ-GT	Gamma-glutamyl transferase
h	hour
HIV	human immunodeficiency virus
IA	Interim Analysis
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IN	Investigator Notification
i.v. or IV	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
KLH	keyhole limpet hemocyanin
LFT	Liver function test
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living Scale
MGC	Myasthenia Gravis Composite
MG QOL-15	Myasthenia Gravis Quality of Life
ml	milliliter
MM	minimal manifestation
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MuSK	Muscle Specific Kinase

nACHR	nicotinic acetylcholine receptor
NHP	non-human primate
NOAEL	No observed adverse effect level
PA	posteroanterior
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PoC	Proof of Concept
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	partial thromboplastin time
QMG	Quantitative Mysthenia Gravis
RA	Rheumatoid Arthritis
RBC	red blood cell(s)
REB	Research Ethics Board
SAE	serious adverse event
s.c. or SC	subcutaneous
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SD	standard deviation
solCD40	soluble CD40
SOM	site operations manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TE	thromboembolic events
TEG	thromboelastography
totCD40	total CD40 (free CD40 and bound CD40)
TTx	tetanus toxoid
ULN	upper limit of normal
ULOQ	upper limit of quantification
WBC	white blood cell(s)
wk	week
WHO	World Health Organization

Pharmacokinetic definitions and symbols

AUCtau	The area under the plasma concentration-time curve from time zero to the end of the dosing interval tau [µg x day / mL]
AUCtau,ss	The area under the plasma concentration-time curve from time zero to the end of the dosing interval tau, at steady state [µg x day / mL]
Cav,ss	The average steady state plasma concentration during multiple dosing [µg / mL]
Cmax	The observed maximum plasma concentration following drug administration [µg / mL]
Cmax,ss	The observed maximum plasma concentration following drug administration at steady state [µg / mL]
Cmin,ss	The lowest plasma concentration observed during a dosing interval at steady state [µg / mL]
Tmax	The time to reach the maximum concentration after drug administration [day]

Protocol synopsis

Protocol number	CCFZ533X2204
Title	A multi-center, randomized, double-blind, placebo-controlled, parallel group study to preliminarily evaluate the safety, tolerability, pharmacokinetics and efficacy of CFZ533 in patients with moderate to severe myasthenia gravis
Brief title	Safety, tolerability, pharmacokinetics and efficacy of CFZ533 in moderate to severe myasthenia gravis patients.
Sponsor and Clinical Phase	Novartis Phase IIa
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to preliminarily evaluate safety, tolerability, pharmacokinetics/pharmacodynamics and efficacy of CFZ533 as an add-on therapy to standard of care in patients with moderate to severe myasthenia gravis (MG). The results of this study will provide preliminary data to evaluate a further development of CFZ533 in the treatment of myasthenia gravis.
Primary Objective(s)	To evaluate the safety and tolerability of CFZ533 as an add-on therapy to standard of care in moderate to severe MG patients. To evaluate the efficacy of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG after 24 weeks of treatment.
Secondary Objectives	To evaluate the efficacy of CFZ533 throughout the 24 weeks treatment period and the decay in efficacy throughout the 24 weeks follow-up period. To evaluate changes in patient's quality of life (QOL) throughout 24 weeks the treatment period. To evaluate the pharmacokinetics of CFZ533 To evaluate the pharmacodynamics of CFZ533 To assess immunogenicity of CFZ533
Study design	This is a randomized, double-blind, placebo controlled, non-confirmatory study in MG patients administered IV CFZ533 over a 24 weeks treatment period followed by other 24 weeks safety follow-up period.
Population	A total of approximately 44 male and female patients aged 18-85 (inclusive) years will be randomized in this study.
Inclusion criteria	Key inclusion criteria are listed: Diagnosis of MG class IIa to IVa inclusive (Myasthenia Gravis Foundation of America Clinical Classification). Quantitative Myasthenia Gravis (QMG) score of 10 or greater. If the QMG score is < 15 no more than 4 points may be derived from items 1 or 2 (ocular motility disturbance and ptosis). Presence of acetylcholine receptor (AChR) or Muscle Specific Kinase (MuSK) autoantibodies based on medical history and confirmed by autoantibodies diagnostic test performed at screening.

Inclusion criteria (cont'd)	Only one immunosuppressant or immunomodulatory drug at a stable dose is allowed during the study (i) azathioprine and mycophenolate mofetil must be stable for at least 4 months prior to randomization (ii) cyclosporine must be stable for at least 3 months prior to randomization. If the patient is on oral corticosteroids, methotrexate or tacrolimus at screening, the dose must be stable for at least 1 month prior to randomization. If the patient is on cholinesterase inhibitors at screening, the dose must be stable for at least 2 weeks prior to randomization. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, may be included in the study if they are using highly effective methods of contraception during the study and for 12 weeks after study treatment.
Exclusion criteria	Key exclusion criteria are listed: MGFA grade I, IVb, or V disease. Documented presence of unresected thymoma. Patients having undergone thymectomy or thymo thymectomy (resection of thymoma) within 6 months of screening. Patients having received any of the following treatments prior to randomization: IVIg or plasma exchange within 8 weeks; oral or IV cyclosphosphamide treatment within 3 months; IV corticosteroid bolus (dose higher than 1 mg/kg) within 3 months; belimumab within 6 months. For patients who received belimumab earlier, B cell count should be within normal range; rituximab within 12 months. For patients who received rituximab earlier, B cell count should be within normal range; any other biologic or an investigational drug within 1 month or five times the half-life, whichever is longer. Live vaccines within 4 weeks of study drug infusion. Patients who are at significant risk for TE as judged by the investigator or have any one of the following: History of either thrombosis or 3 or more spontaneous abortions with or without the presence of anti-cardiolipin autoantibodies; Presence of prolonged partial thromboplastin time (PTT).
Investigational and reference therapy	CFZ533 10 mg/kg IV infusion CFZ533 matching placebo IV infusion

Efficacy/PD assessments	Efficacy assessments: Quantitative Myasthenia Gravis (QMG) Score Myasthenia Gravis Composite (MGC) Score Quality of life questionnaires: MG-ADL and MG QOL-15 Pharmacodynamics assessments: Corporate Confidential Information
Safety assessments	Physical examination AEs Vital signs ECGs Hematology, blood chemistry, urinalysis Corporate Confidential Information
Data analysis	Analysis methods The primary efficacy variable is the change from baseline in QMG score after 24 weeks of treatment (at week 25 visit). The changes from baseline in QMG scores during the treatment period will be analyzed using a Bayesian model for repeated measurements. The model may investigate effects for treatment (CFZ533 or placebo), time (visit week), baseline QMG score, treatment by time and baseline by time interactions.

Data analysis (cont'd)	The target efficacy will be reached if at the end of the study, there is at least 90% probability that the difference between CFZ533 and placebo is ≥ 0 and 50% probability that the difference between CFZ533 and placebo is ≥ 3. The MGC composite is a key secondary endpoint. The changes from baseline in QMG scores at each visit of the treatment period (weeks 5, 9, 13, 17, 21 and 25) will be analyzed using a Bayesian model for repeated measurements.
Key words	CFZ533, Myasthenia Gravis

1 Introduction

1.1 Background

Acquired myasthenia gravis (MG) is an autoimmune disease that leads to fluctuating muscle weakness and fatigue. In the most common cases, muscle weakness is caused by circulating antibodies that bind to acetylcholine receptors at the postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter acetylcholine.

The disease incidence is 3-30 cases per million per year and rising, most likely as a result of increased awareness. The prevalence of MG in the USA is estimated to be between 100 and 150 per million (Trouth et al 2012). In MG, muscle weakness fluctuates with activity, and periods of rest offer only a temporary reprieve. The muscles that control eye and eyelid movement are particularly susceptible to weakness, but other muscles for chewing, talking, and swallowing are frequently involved. Patients may initially present with purely ocular MG, but this usually progresses to more severe, generalized disease with involvement of bulbar, axial, limb, and/or respiratory muscles (Trouth et al 2012). It is important to distinguish MG from congenital myasthenic syndromes that can present with similar symptoms but are due to genetically determined defects in neuromuscular junction proteins, and do not respond to immunosuppressive treatments.

In MG, the autoantibodies most commonly act against the nicotinic acetylcholine receptor (nAChR), the receptor at the motor end plate for the neurotransmitter acetylcholine that stimulates muscular contractions. A minority of antibodies has specificity for the acetylcholine binding site and thereby directly impairs the ability of acetylcholine to bind to receptors. Others lead to the loss of functional receptors, either by complement fixation and focal lysis of the endplate region, or by inducing the muscle cell to eliminate the receptors through endocytosis (Ha and Richmond 2014).

MG is treated medically with acetylcholinesterase inhibitors or immunosuppressants, and in selected cases, thymectomy. There is a high medical need in MG, and the disease can be life-threatening. In myasthenic crisis, patients can develop acute respiratory failure, due to paralysis of the respiratory muscles.

The use of corticosteroids and other immunomodulatory drugs (e.g., azathioprine, cyclosporine, and mycophenolate mofetil) have proven beneficial for some patients in the management of this disorder; however, the majority of the MG patients develop an increased risk of infections and other long-term complications (Mehndiratta et al 2014), therefore there is a medical need for new treatments.

Several lines of evidence suggest that inhibition of the CD40-CD154 co-stimulation pathway can be beneficial for the treatment of MG. In the majority of MG patients (85%), the production of pathogenic antibodies targeting muscle acetylcholine receptors (anti-AChR antibodies) is T cell dependent (Meriggioli and Sanders 2009). Most of these patients have thymic pathology usually in the form of hyperplasia, characterized by a hyper-proliferative thymus and ectopic germinal center formation with an activated B cell signature, including prominent CD40-CD154 signaling (Le Panse et al 2006).

Corp Risks and benefits of treatment with CFZ533 are outlined in Section 3.6

1.2 Study purpose

This study is designed to preliminarily evaluate safety, tolerability, pharmacokinetics/pharmacodynamics and efficacy of CFZ533 as an add-on therapy to standard of care in patients with moderate to severe myasthenia gravis (MG).

The results of this study will provide preliminary data to evaluate a further development of CFZ533 in the treatment of MG.

2 Study objectives

2.1 Primary objective(s)

Objective(s)	Endpoint(s)
To evaluate the safety and tolerability of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG throughout the study	• AEs / SAEs • Vital signs and body measurements • ECGs • Hematology, blood chemistry, urinalysis.
To evaluate the efficacy of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG	• Mean change from baseline in the QMG Score for Disease Severity after 24 weeks of treatment (primary endpoint). • Mean changes from baseline in the MGC Score for Disease Severity after 24 weeks of treatment. • Proportions of patients requiring rescue therapy (i.e. IV immunoglobulins or plasma exchange).

2.2 Secondary objective(s)

Objective(s)	Endpoint(s)
To evaluate the efficacy of IV CFZ533 using relevant MG related outcome measures throughout the 24 weeks treatment period To evaluate the decay in efficacy of IV CFZ533 using relevant MG related outcome measures throughout the 24 weeks follow-up period	• Mean Change from baseline in QMG Score and MGC Score. • Proportion of patients with improvement by ≥ 3 points in QMG score. • Proportion of patients with worsening by ≥ 3 points in QMG score. • Proportion of patients intolerant to steroid taper. • Proportion of patients who discontinued due to inefficacy or worsening.
To evaluate changes in patient's quality of life (QOL) throughout the 24 weeks treatment period	Mean change from baseline in the MG-ADL and MG QOL-15.
To evaluate the PK of 2-hour IV infusion of CFZ533 at 10 mg/kg administered q4w for 6 doses	Free CFZ533 in plasma
To evaluate the PD of CFZ533 (CD40 saturation on B cells, extent/duration of target engagement)	Free CD40 on B cells, total CD40 on B cells and total soluble CD40 in plasma
To assess immunogenicity in CFZ533-treated patients and in placebo-treated patients (pre-existing anti-drug antibodies).	Quantitative analysis of anti-CFZ533 antibodies in plasma

3 Investigational plan

3.1 Study design

This is a randomized double-blind, placebo controlled, non-confirmatory study to preliminarily evaluate the safety, tolerability, PK/PD, and efficacy of IV CFZ533 administered every four weeks (q4w) over a 24 week treatment period in patients with moderate to severe MG. The investigational drug or placebo will be administered in addition to standard of care therapy for MG.

Patients should remain on their standard of care therapies and the dose should be maintained at a constant level during the study (Section 4.1 and Section 6.10). For patients that are receiving corticosteroids at baseline, a predefined steroid tapering will be allowed after achievement of minimal manifestations (MM) state (Jaretzki et al 2000).

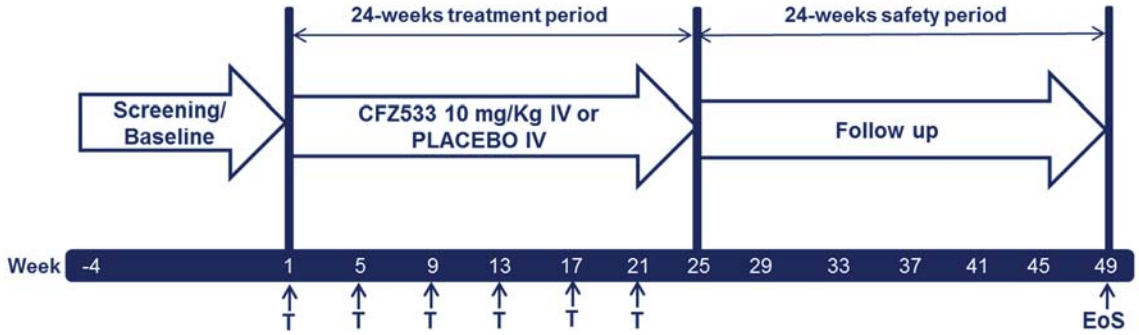
Patients on cholinesterase inhibitors (CI) should remain on stable doses throughout the study, but CIs should not be taken for at **least 12 hours prior** to QMG and MG composite testing at each visit, in order to reduce fluctuations in performance on functional tests due to the temporary symptomatic effects associated with CI use.

For each patient, there will be two screening visits. Most of the screening assessments are done during Screening Visit 1 (Day -28 to Day -8), while Screening Visit 2 (Day -7 to Day -3) is performed to collect a blood sample to allow laboratory results (chemistry, hematology, and pregnancy test, if applicable) to be available prior to randomization on Day 1. All laboratory results, including the MG autoantibodies diagnostic test performed at screening, must be available prior to dosing (Day 1-Visit 3) and meet eligibility criteria. Once continued eligibility is confirmed, patients will be assigned a randomization number at Day 1 and receive CFZ533 or placebo via a 2-hour intravenous infusion. Patients will be dosed every four weeks (q4w) according to their randomization for a total of 6 doses on Day 1 ± 2 (Week 1), Day 29 ± 2 (Week 5), Day 57 ± 2 (Week 9), Day 85 ± 2 (Week 13), Day 113 ± 2

(Week 17) and Day 141 ± 2 (Week 21). The treatment period (24 weeks) will be followed by a safety follow-up period of other 24 weeks. The duration of the entire study including screening will be approximately 52 weeks.

An overview of the study design is given in Figure 3-1:

Figure 3-1 Study Design



T: Treatment 2 hours IV infusion
EoS: End of Study Visit

All infusions will take place at the investigative site in a suitable facility. Patients will remain at the clinic for at least 2 hours after the end of the infusion. The investigator will discharge the patient following satisfactory monitoring of safety parameters.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations, hematology, blood chemistry and urinalysis. Adverse Events (AEs) will be monitored throughout the study duration with special interest to infections. PK/PD and biomarkers will be evaluated during the study.

Details of the study procedures and samplings are provided in the Assessment Schedule (Table 8-1).

3.2 Rationale for study design

In this study, a randomized, double-blind approach will be used to eliminate potential bias on safety and clinical efficacy data. Patients will be randomized to IV CFZ533 or IV placebo in a 1:1 ratio.

Placebo will be used as comparator to provide objective evidence of safety and efficacy data from patients exposed to the experimental therapy. Use of placebo will be in addition to standard of care therapy so as not to leave patients without established treatment.

For patients that are receiving corticosteroids at baseline, a predefined steroid tapering (Table 6-1) will be allowed after achievement of minimal manifestations state (Jaretzki et al 2000). The steroid tapering is instituted to follow the common medical practice in MG to minimize steroid exposure and to mirror standard of care. The proportion of patients who are intolerant to steroid taper in the CFZ533 vs the placebo arm will be a secondary endpoint.

This study will use the Quantitative Myasthenia Gravis score (QMG) and MG Composite score (MGC) as key efficacy outcome measures. Both the scores are established and validated efficacy measure in MG trials (Jaretzki et al 2000, Howard et al 2013, Burns et al 2010) and therefore assumed sufficiently sensitive to provide preliminary evidence for efficacy after 24 weeks of treatment. This timeframe is consistent with previous trials of MG therapeutics in similar target populations (Howard et al 2013, Muscle Study Group 2008).

3.3 Rationale for dose/regimen, duration of treatment

Corporate Confidential Information

Safety and tolerability confirmed in humans: A Phase 1 study (CCFZ533X2101), testing single ascending doses (0.03 to 10 mg/kg) of CFZ533 IV and 3 mg/kg SC, is currently ongoing. Safety and tolerability data are presented in Section 1.1.1.3 Based on clinical experience so far, the 10 mg/kg IV q4w dosing regimen is anticipated to be safe and tolerable in MG patients.

Corporate Confidential Information

3.4 Rationale for choice of comparator

In this study, placebo will be used as comparator to provide objective evidence of safety and efficacy data from patients exposed to the experimental therapy. Patients should remain on their standard of care therapies and dose maintained at a constant level during the study (Section 6.10).

3.6 Risks and benefits

It is not known if there could be a benefit to patients from treatment with CFZ533.

The risk to subjects in this trial will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring, and targeted monitoring/follow-up visit safety assessments.

Hypersensitivity or infusion reactions can manifest with itching, flushing, headache, nausea/vomiting, hypotension, urticaria, bronchospasm, or angioedema. No such events were found in the Phase 1 study with CFZ533. In this study, CFZ533 will be administered as a 2-hour infusion where such hypersensitivity reactions can still occur. Subjects will be monitored up to 4 hours after the end of the infusion at each visit.

Subjects treated with CFZ533 may be at an increased risk of infection.

Administration of CFZ533 is expected to result in immunosuppression, with a decreased capacity to mount a response to novel immunogens requiring T cell-dependent B cell activation (potentially including bacterial, viral, fungal and parasitic origin) when full receptor occupancy has been achieved.

In addition, subjects will have adequate preformed antibody to maintain protective humoral response for extended periods of time (months). Subjects enrolled in this study will be carefully monitored for signs and symptoms of an infection.

Although not expected in this clinical study, the investigator will monitor for signs, symptoms and laboratory results consistent with clinically significant inflammation as well as for changes in renal function and signs of acute kidney injury as per local practice.

There has been no evidence that CFZ533 has an effect on clinical coagulation parameters, and no evidence from preclinical or clinical studies that CFZ533 presents an increased risk of thromboembolic events (TE).

Nevertheless, standard coagulation parameters and TEs will be carefully monitored throughout the study.

The overall risk-benefit supports further investigation in patients with autoimmune diseases such as MG patients. However, there may be unknown risks of CFZ533 which may be serious and unforeseen.

A maximum of approximately 600 mL of blood is planned to be collected over a period of 52 weeks (including screening, treatment and follow up period) from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

4 Population

A total of approximately 44 subjects will be enrolled in the study and randomized. At least 36 subjects are expected to complete the study.

Subject selection is to be established by checking all eligibility criteria at screening (Visit 1) and before randomization (Visit 3). A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site. No additional criteria should be applied by the investigator, in order that the study population will be representative of all

eligible subjects. Deviation from **any** entry criterion excludes a subject from enrollment into the study.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Able to provide signed informed consent.
2. 18-85 year old male or female patients.
3. Body mass index of 18-40 kg/m^2.
4. Diagnosis of MG class IIa to IVa inclusive (Myasthenia Gravis Foundation of America Clinical Classification).
5. Quantitative Myasthenia Gravis (QMG) score of 10 or greater. If the QMG score is < 15, no more than 4 points may be derived from items 1 or 2 (ocular motility disturbance and ptosis).
6. Presence of acetylcholine receptor (AChR) or Muscle Specific Kinase (MuSK) autoantibodies based on medical history and confirmed by autoantibodies diagnostic test performed at screening.
7. Only one immunosuppressant or immunomodulatory drug at a stable dose is allowed during the study (i) azathioprine and mycophenolate mofetil must be stable for at least 4 months prior to randomization (ii) cyclosporine must be stable for at least 3 months prior to randomization.
8. If the patient is on oral corticosteroids, methotrexate or tacrolimus at screening, the dose must be stable for at least 1 month prior to randomization.
9. If the patient is on cholinesterase inhibitors at screening, the dose must be stable for at least 2 weeks prior to randomization.
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, may be included in the study if they are using highly effective methods of contraception during the study and for 12 weeks after study treatment.
11. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment, confirmed by medical documentation. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening, with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.

- Combination of any two of the following (a+b or a+c, or b+c):
    a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), e.g. hormone vaginal ring or transdermal hormone contraception.
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal/suppository
- In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. MGFA grade I, IVb, or V disease.
2. Documented presence of unresected thymoma.
3. Patients having undergone thymectomy or thymothymectomy (resection of thymoma) within 6 months of screening.
4. Patients having received any of the following treatments prior to randomization:
    - IVIg or plasma exchange within 8 weeks;
    - oral or IV cyclosphosphamide treatment within 3 months;
    - IV corticosteroid bolus (dose higher than 1 mg/kg) within 3 months;
    - belimumab within 6 months. For patients who received belimumab earlier, B cell count should be within normal range;
    - rituximab within 12 months. For patients who received rituximab earlier, B cell count should be within normal range;
    - any other biologic or an investigational drug within 1 month or five times the half-life, whichever is longer.
5. Live vaccines within 4 weeks prior to randomization.
6. History of tumor, infection, or interstitial lung disease on chest CT, MRI, or CXR.
7. History of malignancy within 3 years prior to screening, with the exception of basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix.

8. History or presence of any medically significant cardiac condition which according to the investigator may jeopardize the patient in case of participation in the study including ischemic heart disease, congestive heart failure or cardiomyopathy, myocardial infarction or stroke.
9. Sitting vital signs outside of the following ranges at baseline: oral temperature: 35.0 - 37.5°C, systolic blood pressure: 90 - 145 mmHg, diastolic blood pressure: 50 - 90 mmHg, pulse rate 50 - 100 bpm.
10. Patients who are at significant risk for thromboembolic events as judged by the investigator or have any one of the following:
    - History of either thrombosis or 3 or more spontaneous abortions with or without the presence of anti-cardiolipin autoantibodies;
    - Presence of prolonged partial thromboplastin time (PTT).
11. Pancreatic injury or pancreatitis as indicated by abnormal signs or symptoms of pancreatitis or clinically significant elevations in amylase or lipase at screening.
12. Have had signs or symptoms of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to randomization.
13. Any significant concurrent medical condition such as pulmonary, renal or liver disease that, in the opinion of the principal Investigator, could affect the patient's ability to tolerate or complete the study.
14. Evidence of active or latent tuberculosis as assessed by quantiferon testing at screening (PPD is not recommended as immunosuppression may result in false negative result).
15. Positive serology for HIV antibodies, hepatitis B surface antigen or hepatitis C antibodies (confirmed by an appropriate licensed test) at screening.
16. Any of the following abnormal laboratory values at screening:
    - total white blood cell count (WBC) outside the range of 1,500-15,000/mm^3 (1.5-15.0 x 10^9/L)
    - total white blood cell count (WBC) outside the range of 1,500-20,000/mm^3 (1.5-20.0 x 10^9/L), only for patients taking corticosteroids
    - platelets <100,000/mm^3 (<100 x 10^9/L)
    - Hgb <8.0 g/dL
    - lymphocyte count <500/mm^3 (<0.5 X 10^9 / L)
    - neutrophil count <1500/mm^3 (<1.5 X 10^9 / L)
17. Hypoalbuminemia (serum albumin of less than 2.0 g/dL) at screening.
18. Clinical evidence of liver disease or liver injury or any of the following hepatic conditions:
    - known history of alcohol abuse, chronic liver or biliary disease
    - conjugated bilirubin greater than the upper limit of normal (ULN)
    - alkaline phosphatase (ALP) greater than 2 x ULN
    - AST (SGOT), ALT (SGPT) greater than 2 x ULN
    - gamma-glutamyl-transferase (γ -GT) greater than 2 x ULN

19. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening.
20. Have donated blood or experienced a loss of blood >500 mL within 4 weeks of study drug infusion.
21. Allergy to murine or human antibodies.
22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

5 Restrictions for Study Subjects

Subjects must be informed and reminded of the restrictions reported in the following paragraphs.

5.1 Contraception requirements

Please refer to inclusion criteria (Section 4.1) for details of contraception requirements for the study. In consideration of the patient population and overall risk benefit profile, women of childbearing potential must utilize highly effective contraception to avoid becoming pregnant while receiving CFZ533 and for 12 weeks after the last dose or until data from the reproductive toxicity studies suggest otherwise.

5.2 Prohibited treatments

Use of the treatments in Table 5-1 is not allowed during the study and until at least four weeks after the last administration of study drug.

In case of rescue therapy (IVIg or plasma exchange), study treatment should be interrupted but patient can remain in the study for the safety follow-up period or at least complete the End of Study (EoS) visit (Visit 777) assessments.

If any other prohibited treatment is given during the course of the trial, patients should be **discontinued** from the study and complete EoS visit (Visit 777) assessments as per Assessment Schedule (Table 8-1).

Table 5-1 Prohibited treatments

Medication	Wash-out	Action to be taken
IVIg or plasma exchange	*8 weeks prior to randomisation*	*Investigational treatment discontinued, but patient can remain in the study for the safety follow-up period*
Oral or IV cyclosphosphamide; IV corticosteroid bolus (dose higher than 1 mg/kg)	*3 months prior to randomisation*	*Patient's discontinuation and EoS assessments to be undertaken*
Belimumab	*6 months prior to randomisation*	*Patient's discontinuation and EoS assessments to be undertaken*
Rituximab	*12 months prior to randomisation*	*Patient's discontinuation and EoS assessments to be undertaken*

Medication	Wash-out	Action to be taken
Any other biologic or an investigational drug	*1 month or five times the half-life, whichever is longer prior to randomisation*	*Patient's discontinuation and EoS assessments to be undertaken*
Live vaccination	*4 weeks prior to randomisation*	*Patient's discontinuation and EoS assessments to be undertaken*

Please, refer to Section 6.10 for standard of care treatment instructions (e.g. corticosteroids, immunosuppressants and cholinesterase inhibitors) and other concomitant treatments.

5.3 Dietary restrictions and smoking

Subjects will maintain their usual diet and life habits during the entire study.

5.4 General restrictions

No general restrictions are required in this study.

6 Treatment

6.1 Study treatment

6.1.1 Investigational treatment

The investigational drug (CFZ533) and placebo will be prepared by Novartis and supplied to the Investigative site as open-label bulk medication. CFZ533 will be provided as lyophilisate in vial (150 mg) and the placebo as liquid in vials.

To maintain the blind, the investigational treatments will be prepared by an unblinded pharmacist/designee and the investigational treatment will only be administered by blinded study personnel to patient treatment allocation.

Instructions for infusion preparation, storage and handling of CFZ533 vials and placebo are described in the Pharmacy Manual, provided as a separate document. Once the active or placebo will be diluted there will be no possibility to differentiate the two solutions for injection.

Study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated staff have access.

Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels. Storage conditions must be adequately monitored and appropriate temperature logs maintained as source data. Appropriate documentation of the subject specific dispensing process must be maintained.

Medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the patient.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply. Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction.

6.2 Treatment arms

Subjects will be assigned to CFZ533 or matching placebo according to a 1:1 randomization scheme, as follows:

- CFZ533 10 mg/kg IV infusion every 28 days (q4w), for a treatment duration of 24 weeks (6 doses).
- CFZ533 matching placebo IV infusion every 28 days (q4w), for a treatment duration of 24 weeks (6 doses).

Both infusions (drug and vehicle) will be at matched volumes, constant rates, and given over 2 hours. In case of any adverse event please refer to Section 6.8 treatment of adverse events.

6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments or interruptions are not permitted. In case of an AE or for any reason (e.g., non-compliance, operational hurdle) resulting in a deviation from the required dosing scheme, agreement with Novartis will be necessary to decide whether the subject can continue or needs to be discontinued from the study.

6.4 Treatment assignment

Prior to dosing, eligible patients will be randomized via an IRT system to one of the two treatment arms. Randomization numbers will be generated in ascending, sequential order by a validated IRT system.

The site personnel (e.g. PI or delegate or unblinded pharmacist) will log into the IRT system to randomize the patient. The IRT will then assign a randomization number to the patient and will indicate to the unblinded site personnel the treatment to be assigned to the patient.

The screening number will be maintained as unique identifier for each patient throughout the study and will be entered into the CRF (details in the SOM).The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and from the blinded site staff. A patient randomization list will be produced by a Contract research Organisation (CRO) using a validated system that automates the random assignment of treatment arms.

The patient randomization list will be reviewed and approved by a member of the Novartis randomization office. After approval the randomization list will be integrated into the IRT system.

Patients will not be replaced.

6.5 Treatment blinding

This is a double blind study: subjects, investigators performing the assessments and data analysts will remain blind to the identity of study treatments according to the specifications provided in Appendix 3 of the SOM. Randomization data are kept strictly confidential, and are accessible only to authorized personnel, until unblinding of the trial.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

The bioanalyst will request a copy of the randomization to facilitate analysis of the samples. The bioanalyst will provide the sample data to the team under blinded conditions. The bioanalyst will keep this information confidential until IA or final clinical database lock.

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The DMC will receive unblinded data as described in the DMC charter.

Corporate Confidential Information

Otherwise, unblinding will only occur in the case of patient emergencies (Section 6.6), at the time of the IA and C the conclusion of the study.

6.6 Emergency breaking of assigned treatment code

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency unblinding of a patient is managed via the IRT system. Study site personnel will be trained on the Emergency Unblinding Procedure in IRT prior to study start. **The unblinded treatment code should not be recorded on the CRF.** The investigator must also immediately inform the Novartis local monitor that a patient has been unblinded. Unblinded patients will be discontinued from the study.

If appropriate, the investigator will inform the subject how to contact his/her trained backup in cases of emergency when he/she is unavailable.

An assessment will be done by the appropriate site personnel and the Sponsor after an emergency unblinding to assess whether or not study drug should be discontinued for a given subject and, if applicable, whether the subject can continue into the next trial phase.

6.7 Treatment exposure and compliance

Compliance with treatment administration will be collected in the eCRF. Exposure to CFZ533 will be measured by appropriate PK parameters as detailed in Section 8.5.

6.8 Recommended treatment of adverse events

Parenteral administration of monoclonal antibodies can be associated with acute, severe reactions (occurring within the first few hours post dose) secondary to hypersensitivity, immunogenicity, or ADCC-mediated cell depletion.

In this study, CFZ533 will be administered as a 2-hour infusion. No systemic infusion reactions have been noted with CFZ533 in healthy volunteers or RA patients (Study CCFZ533X2101); however, investigators should be aware of the possibility and be prepared to treat such events.

In case of any signs of an acute reaction, clinical treatment will be provided as determined by the treating physician on a case-by-case basis and depending on the severity, using symptomatic treatment, antihistamines, NSAIDs, acetaminophen, intravenous fluids, corticosteroids, or adrenaline. Patients will be monitored at the site for at least 6 hours post dose or longer at the discretion of the Investigator to ensure adequate safety monitoring.

For the management of allergic reaction, anaphylaxis and cytokine release, it is recommended to follow the guidelines by the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE/v4.03, Reference http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue medication

Rescue therapy (IVIg or plasma exchange) is instituted due to worsening of myasthenic weakness that in the opinion of the treating physician requires immediate therapy. This usually involves acute worsening of oropharyngeal or respiratory function so that compromise of the airway or ventilator function is judged to be imminent.

In case of rescue therapy, study treatment should be discontinued but the patient can remain in the study or for the safety follow-up period or at least complete the EoS visit (Visit 777) assessments.

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

6.10 Concomitant treatment

Patients should remain on their standard of care therapies (if not prohibited) and dose should be maintained stable, unless changes are judged to be necessary based on history and clinical examination after discussion between the investigator and Novartis.

Corticosteroid

If the patient is on oral corticosteroids, methotrexate or tacrolimus at screening the dose must be stable for at least **1 month** prior to randomization.

For patients that are receiving corticosteroids, a predefined steroid tapering (Table 6-1) will be allowed after achievement of MM state (Jaretzki et al 2000). In patients whose disease substantially worsens after tapering, the previous steroid dose will be reinstituted, and no further dose reduction will be attempted in the study.

Table 6-1 Predefined tapering scheme

Baseline daily dose (x)*	Week 13	Week 17	Week 21	After Week 25
x ≤ 10 mg	No change	No change	↓ by 2.5 mg	As needed #
10 < x ≤ 20mg	No change	↓ by 2.5 mg	↓ by 2.5 mg	As needed #
x > 20 mg	↓ by 5 mg	↓ by 5 mg	↓ by 2.5 mg	As needed #

* Or equivalent alternate day dose

According to usual standard of care

↓ Decrease

Immunosuppressant or immunomodulatory drugs

In addition to corticosteroids, only one immunosuppressant or immunomodulatory drug **at a stable dose** is allowed during the study. Azathioprine and mycophenolate mofetil must be at a stable dose for at least 4 months prior to randomization. Cyclosporin should be at a stable dose for at least 3 months prior to randomization.

Cholinesterase inhibitors

Patients on cholinesterase inhibitors must be on a stable dose for at least 2 weeks prior to randomization.

Cholinesterase inhibitors **will be held at least 12 hours prior** to QMG and MGC testing at each study visit. It may be necessary for patients to remain overnight at the study site for observation during this time, if the investigator deems it necessary.

Other concomitant medications

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies section of the CRF. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

Patients may voluntarily discontinue the study treatment for any reason at any time.

The Investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

- Study treatment **must** be discontinued and patients followed up for safety, if possible, if the following occur:
- In case of non-detectable AChR or MuSK autoantibodies for patients enrolled prior to this amendment.
- Significant increase in MG disease activity requiring treatment outside of a clinical trial setting.
- Worsening of MG with severe oropharyngeal or respiratory weakness (MGFA class IVb or V).
- Rescue medication use (IVIg or plasma exchange).
- Pregnancy.
- Severe or life threatening infusion reaction.
- Major worsening of renal function (e.g. >40% increase from baseline creatinine level).
- Acute infection as a severe AE as judged by the investigator.
- Major elevations (>4.0 x ULN) in amylase or lipase or any abnormal signs or symptoms suggesting pancreatic injury.
- Significant changes in standard coagulation parameters, including prothrombin time (PT), activated partial thromboplastin time (aPTT) suggesting an increased risk for hypercoagulability or any sign or symptom of a TE.
- Any other AE or complication where continued dosing of the patient is considered to be placing them at excess risk.
- Patient withdraws consent (when patient must also be withdrawn from the study).

Patients who are withdrawn from the study for any reason will not be replaced.

Study patients who discontinue participation for any reason or who decide they do not wish to participate in the study further should not be considered withdrawn from the study unless they withdraw their consent (see Section 7.3). Where possible, they should return for their EoS visit assessments (Visit 777). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in Section 7.2.1 Any unresolved AEs will be followed by the investigator until resolution.

7.2 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject completes the EoS visit (Visit 777), and any assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

After study participation, the patients will continue to be treated by his/her general practitioner according to the local standard clinical management related to the underlying disease. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

7.2.1 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled EoS visit would have occurred.

7.3 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore, does not want any further visits or assessments or study related contact and does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

7.4 Study stopping rules

As a guidance, dose limiting toxicities (DLTs) will be assessed according to the standardized toxicity grading scale.

The study will be placed on hold with no further dosing pending full safety review if *any* of the following criteria are met:

- One (1) patient with CFZ533-related death.
- Three (3) or more patients presenting with a serious adverse event that is related to CFZ533.
- One (1) patient presenting with CFZ533-related cytokine release syndrome.
- One (1) patient presenting with a CFZ533-related thromboembolic events that is at least of moderate severity.
- More than one (1) patient with a severe allergic reaction within the first 5 treated subjects or an incidence of >20% thereafter.
- Any treatment-related, severe adverse event considered drug related by the Investigator with the following exceptions:
    - Events not requiring treatment, and diagnostic procedures involving elective or non-urgent hospital admission,

  - Disease Specific Events that are due to the patients underlying MG diagnosis,
  - AEs/SAEs unrelated to the experimental compound as determined by the Investigator or Novartis.
- Two (2) or more patients presenting with:
  - Acute severe exacerbation of MG symptoms requiring hospitalization for treatment.
  - Progressive renal insufficiency or acute kidney injury defined as a moderate increase in serum creatinine (1.5 X ULN) in the setting of euvolemia at any time during the study related to CFZ53.
  - Emergent hypogammaglobulinemia defined as a reduction in total serum IgG or IgM concentration by 50% or more from baseline.
  - Severe systemic infection or opportunistic infection that requires treatment, e.g., sepsis, urosepsis, mycoses, pneumonia.
- Clinically significant (according to the Investigator), study drug-related persisting changes from baseline in vital signs, ECGs, or relevant persistent changes in laboratory parameters (not due to existing co-morbidities), in more than one (1) patient within the first 5 treated patients or an incidence of >20% thereafter.
- Other clinically significant changes or effects in the opinion of the Investigator or Sponsor that are deemed unsafe to continue dosing.

All blinded safety data, including disease specific events, will be evaluated by the Sponsor and Investigator on an ongoing basis and at scheduled meetings. The study may be put on hold pending further data analysis, if the principal investigator or the Sponsor considers that the number and/or severity of AEs justify discontinuation of the study.

In addition, a DMC will be instituted (see Section 10.3) with the aim to review safety data regularly (and efficacy data, if required) as outlined in their charter and at ad hoc meetings. The DMC can recommend stopping the entire trial if it is considered unsafe or unethical to continue administering CFZ533.

7.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject and complete their EoS visit assessments as per Assessment Schedule (Table 8-1). The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

Visits should be scheduled within the allowed visit/assessment window as specified in the Assessment Schedule (Table 8-1).

PK samples should be taken at the time points as specified in the Assessment Schedule. When other assessments are scheduled to be performed at the same time-point, these will be taken after the PK samples.

The preferred sequence of data collection during study visits is safety, ECG, followed by vital signs and blood sampling.

Table 8-1 Assessment Schedule

Study phase	Screening 1	Screening 2	Treatment Period						Follow-up period						EoS*
Visit Numbers (internal use only)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V777
Week	W-4 to W-1		W1	W5	W9	W13	W17	W21	W25	W29	W33	W37	W41	W45	W49
Day	D-28 to D-8	D-7 to D-3	D1	D29	D57	D85	D113	D141	D169	D197	D225	D253	D281	D309	D337
Visit Window (days)				± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2
Obtain informed consent	X		X[a]												
Inclusion/Exclusion criteria	X		X												
Relevant medical history	X														
Current medical condition	X				X							X			
Demography	X														
Physical examination	X				X							X			
Adverse Events	X				X							X			
Concomitant meds/Therapies	X				X							X			
Body height	X														
Body weight	X				X							X			
ECG evaluation	X		X												X
Body temperature	X				X							X			
Blood pressure / Pulse rate	X				X							X			
Hepatitis and HIV screen	X														X
Quantiferon testing	X														
Urine drug screen & alcohol test	X														X
Serum pregnancy test	X	X													X
Urine pregnancy test					X						X				
Corporate Confidential Information	X														
Hematology, Blood chemistry, Urinalysis	X[a]	X[a]	Predose[a]						X[a]						
Confirm cholinesterase inhibitors withdrawal (at least 12 hours before QMG/QMC)	X		Predose						X						
QMG score	X		Predose						X						
MGC score	X														
QoL scales: MG-ADL and MG QOL15															
Corporate Confidential Information			Predose					Predose				X			X
Randomisation			X												
Drug administration			X	X	X	X	X	X							

Assessment Schedule (cont'd)

Study phase	Screening 1	Screening 2	Treatment Period						Follow-up period						EoS*
Corporate Confidential Information			Predose, 2h[a]						X	X	X	X			X
			Predose, 2h[a]						X	X	X	X			X
			Predose[b]						X	X	X	X			X
			Predose[b]						X	X	X	X			X
			Predose[b]						X	X	X	X			X
			Exploratory biomarkers												
			Predose[c]	Predose[c]		Predose[c]			X			X			X
	X		Predose[c]	Predose[c]		Predose[c]		Predose[c]		X		X		X	X
			Predose[c]	Predose[c]		Predose[c]			X			X			X
			Predose[c]	Predose[c]		Predose[c]			X						
			X[#]												

a: First sample to be collected within 1h pre-dose, second sample to be taken within 1h from end of infusion (2h infusion)
b: One sample to be collected within 1h pre-dose (same time of the PK/PD samples)
c: One sample to be taken after PK/PD samples

Corporate Confidential Information

#: Overnight fast for at least 10 hours before your screening visit

Corporate Confidential Information

*End of Study: End of Study assessments should be performed also in case of patient discontinuation for any reason (except in case of consent withdrawal)

8.1 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If incapable of doing so, in cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: date of birth, age, sex, race, predominant ethnicity.

Relevant medical history/current medical conditions data includes data prior to signature of informed consent. Where possible, diagnoses and not symptoms should be recorded.

The date of original diagnosis of Myasthenia Gravis and the MG class will be recorded in the CRF.

Medical history of MG and the autoantibodies diagnostic test results (performed at V1) will be maintained/recorded in the source data.

Hepatitis screen, HIV screen

All subjects will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies.

Evaluation for HIV seropositivity will be performed, and if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Appropriate subject counseling will be made available by the Investigator in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

Results will be available as source data and will not be recorded within the eCRF.

Alcohol test, Drug screen

Subjects will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates).

Results will be available as source data and will not be recorded within the eCRF.

8.3 Efficacy / Pharmacodynamics

Exploratory efficacy and PD assessments are described in this section. Assessments will be performed and samples collected at the visits/timepoint(s) defined in the Assessment Schedule (Table 8-1).

8.3.1 Quantitative Myasthenia Gravis (QMG) score

The Quantitative Myasthenia Gravis (QMG) score is an established and validated measure of disease severity used in MG trials (Jaretzki et al 2000). This scoring system is based on quantitative testing of sentinel muscle groups by means of a 4 point scale ranging from 0 (no symptoms) to 3 (severe symptoms).

The scale measures ocular, bulbar, respiratory, and limb function, grading each finding, and the total score ranges from 0 (no myasthenic findings) to 39 (maximal myasthenic deficits). Its reliability and longitudinal validity have been demonstrated in several studies (Sharshar et al 2000, Bedlack et al 2005). It has been used as the primary outcome measure in several recent randomized trials in MG (Zinman et al 2007, Barth et al 2011, the Muscle Study Group 2008).

8.3.2 Myasthenia Gravis Composite (MGC) score

The MG Composite score (MGC) is another key efficacy outcome measure. It is reliable and demonstrates concurrent and longitudinal construct validity in the MG practice care setting (Burns et al 2010). The MGC scale covers 10 important functional domains most frequently involved in patients with MG. The proportion of bulbar and respiratory items reflect the clinical importance of these domains in the disease, and are appropriately weighted.

The assessment of each of the 10 test items provides immediate insight into the status of that particular functional domain.

8.3.3 Quality of Life questionnaires

The MG-QOL15 is a 15-item survey, completed by the patient that is designed to assess some aspects of quality of life related to MG (Burns et al 2011).

The MG-ADL is an 8-item survey to assess functional performance of daily activities that are sometimes impaired by MG (Muppidi et al 2011).

Patients will be asked to complete a paper copy of the questionnaires in their local language. The printed copy will serve as source data and the subject's responses will be transcribed into the eCRF.

Further details can be found in the SOM.

8.4 Safety

Safety assessments are specified below and in the Assessment Schedule (Table 8-1).

8.4.1 Physical examination

The Physical examination will include the following:

- Eyelid closure
- Extra-ocular movements
- Facial strength
- Palatal elevation
- Tongue protrusion
- Jaw closure
- Neck flexion/extension
- Strength in upper and lower extremities (proximal and distal muscles)

8.4.2 Vital signs

- Body temperature
- Blood pressure (BP)/ Pulse rate

If vital signs are out-of-range at baseline, the Investigator may obtain two additional readings, so that a total of up to three consecutive assessments are made, with the subject seated quietly for approximately five minutes preceding each repeat assessment.

At least the last reading at baseline must be within the ranges provided above in order for the subject to qualify.

8.4.3 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]^2)

8.4.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening (Visit 1 or 2), the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the subject is excluded from the study.

In the case where a laboratory range is outside the reference range for the laboratory at screening or baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

The blood sample for hematology and clinical chemistry should be taken in fasting conditions.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes, including reticulocyte counts) and platelet count will be measured.

Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, CK, γ-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid, free Hbg and haptoglobin. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Prothrombin time (PT/INR), activated partial thromboplastin time (aPTT) and C-Reactive Protein (CRP) will be measured.

Urinalysis

A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for protein, nitrite, leucocytes or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

Serum IgG and IGM

Serum total immunoglobulin G (IgG) and M (IgM) will be assessed in the study.

8.4.5 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs, appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, be appropriately signed and dated to confirm review and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the Sponsor.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions if known prior to informed consent signature or in the AE eCRF page (if the abnormality is detected after informed consent signature).

The following data will be collected in the eCRF:

- date and time of ECG
- heart rate
- PR interval
- QT uncorrected
- QTcF
- QRS duration

8.4.6 Pregnancy and assessments of fertility

Pregnancy tests are required of all female subjects regardless of reported reproductive/menopausal status.

Serum pregnancy tests will be performed at the screening visits and at the end of the study. The result of this test must be received before the subject may be dosed. At all other times urine pregnancy tests will be performed.

If a urine pregnancy test is performed and is found to be positive, this will require immediate performing a serum β-hCG. If positive, the Sponsor and Investigator will decide if discontinuation from the trial is required or whether study assessments can continue without compromising the patient's safety.

In case the subject will be aware of pregnancy anytime during the study, the subject should contact the investigator immediately.

8.4.7 Other safety evaluations

All occurrences of infections must be carefully monitored by the investigator. Significant findings, which meet the definition of infection, must be recorded in the eCRF.

8.5 Pharmacokinetics

PK blood samples will be collected from all patients, at baseline and during the treatment and follow-up periods at the timepoints defined in the Assessment Schedule (Table 8-1).

Untreated samples (placebo-treated patients) will not be analyzed unless a safety issue suggests otherwise or there is clinical suspicion of treatment group misclassification.

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Cmax,ss, Cmin,ss, Tmax, AUCtau, AUCtau,ss and Cav,ss from the plasma concentration-time data.

The linear trapezoidal rule will be used for AUC calculation.

A SOM accompanies this protocol, providing operational details for study conduct (incl. subject numbering, blood log with sample numbers). Further details on sample collection, processing and shipment will be provided in the Central Lab Manual. The detailed methods of analysis and data will be provided in the Bioanalytical Data Report.

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in Section 9.3.

Adverse events must be recorded on the Adverse Events CRF for subjects that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade:
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. its relationship to the study treatment (no/yes), or investigational treatment (no/yes), or other study treatment (non-investigational) (no/yes), or both or indistinguishable,
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE). See Section 9.2 for definition of SAE
5. action taken regarding study treatment.

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  a. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  b. elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  c. treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  d. social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis **within 24 hours** of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted **within 24 hours** of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information*)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department, notifying the Clinical Trial Leader. Contact information is listed in the SOM.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 9-1 and Table 9-2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in in Table 9-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to Section 7.1, if appropriate)
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.

Table 9-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
Liver laboratory triggers	3 x ULN < ALT / AST ≤ 5 x ULN
	1.5 x ULN < TBL ≤ 2 x ULN
Liver events	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity*

Table 9-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for *more than 2 weeks*, discontinue the study drug Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks

Criteria	Actions required	Follow-up monitoring
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study drug immediately Hospitalize the patient Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF	Investigator discretion

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

9.4 Renal safety monitoring

Renal events are defined as one of the following:

- confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- new onset (≥1+) proteinuria, hematuria or glucosuria; or as a
- doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

The following two categories of abnormalities/adverse events have to be considered during the course of the study:

- serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
- urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

Table 9-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Serum creatinine increase ≥ 50 % compared to baseline	Follow up within 24-48h if possible Consider drug interruption Consider patient hospitalization /specialized treatment
Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; New dipstick proteinuria ≥ 1+ Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider drug interruption / discontinuation
New dipstick glucosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
Document contributing factors: co-medication, other co-morbid conditions, and additional diagnostic procedures performed in the CRF	
Monitor patient regularly (frequency at investigator's discretion) until one of the following: Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

9.5 Pregnancy reporting

To ensure patient safety, each pregnancy in a subject on study drug must be reported to Novartis **within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued and the patient should be discontinued. Discontinued pregnant women will complete the EoS visit (Visit 777) assessments as described in the Assessment Schedule (Table 8-1).

Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

9.6 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be

summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (CRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic CRF are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

The CRO working on behalf of Novartis reviews the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff are required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the CRO working on behalf of Novartis who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results sent electronically to the designated CRO.

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

10.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be instituted. The DMC will be responsible for reviewing the safety results from the interim and final analyses, as well as overseeing the safety data accruing in the trial at regular intervals. It is expected that the DMC will consist of a myasthenia gravis specialist, a neurologist, an immunologist and a statistician.

Details of the working procedures of the DMC are described in the DMC Charter.

10.4 Adjudication Committee

Not required.

11 Data analysis

Analysis of the data will be under the direction of Novartis personnel. Full statistical details will be presented in the Reporting and Analysis Plan (RAP), which will be finalized prior to database lock.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The full analysis set (FAS) will include all patients who received any study drug.

The safety analysis set will include patients who received any study drug.

The PD analysis set will include all patients who received any study drug and with no protocol deviations with relevant impact on efficacy data.

The PK analysis set will include patients with available PK data and no protocol deviations with relevant impact on PK data.

Patients with non-detectable AChR or MuSK autoantibodies will be excluded from the PD and PK analysis sets.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration, rescue medication and concomitant therapies will be listed by treatment group and subject.

11.4 Analysis of the primary variable(s)

The primary objectives of this study are to preliminarily evaluate the safety, tolerability and efficacy of IV CFZ533 in moderate to severe Myasthenia Gravis patients after 24 weeks of treatment as an add-on therapy to standard of care as compared to placebo.

11.4.1 Variable(s)

The safety variables and analysis are detailed in Section 11.5.2.

The primary efficacy variable is the change from baseline in QMG score after 24 weeks of treatment (at week 25 visit). The baseline value will be the predose assessment on Day 1. It is assumed that the change from baseline in QMG score is normally distributed.

11.4.3 Handling of missing values/censoring/discontinuations

No imputation of missing data for dropouts will be done. Corporate Confidential Information

11.4.4 Supportive analyses

In order to assess the robustness of the results, the primary analysis will be repeated on the FAS.

In addition, the changes from baseline in QMG scores at each visit of the treatment period (weeks 5, 9, 13, 17, 21 and 25) will be analyzed using a mixed effect model for repeated measurements. The model may investigate effects for treatment (CFZ533 or placebo), time (visit week), baseline QMG score, treatment by time and baseline by time interactions. An unstructured covariance matrix may be used to model the correlations between the measurements in the same subject. In case of convergence issues, the covariance matrix that best fit the data will be chosen. The estimated treatment differences at each visit will be provided with 90% CI and 2-sided p-values.

Other potentially influent factors such as sex, age at onset of the disease, makers of baseline severity of the disease or prednisone dose may be explored.

11.5 Analysis of secondary and exploratory variables

11.5.1 Efficacy / Pharmacodynamics

The MGC composite is a key secondary endpoint. The changes from baseline in QMG scores at each visit of the treatment period (weeks 5, 9, 13, 17, 21 and 25) will be analyzed using a Bayesian model for repeated measurements. The model may investigate effects for treatment (CFZ533 or placebo), time (visit week), baseline QMG score, treatment by time and baseline by time interactions. An unstructured covariance matrix may be used to model the correlations between the measurements in the same subject. In case of convergence issues, the covariance matrix that best fit the data will be chosen. The estimated treatment differences at each visit will be provided with 90% CI and 2-sided p-values.

Other secondary efficacy variables include:

- proportions of patients requiring rescue therapy (i.e. IV immunoglobulins or plasma exchange)
- mean change from baseline in QMG Score and MGC Score at all visits
- proportion of patients with improvement by ≥ 3 points in QMG score
- proportion of patients with worsening by ≥ 3 points in QMG score
- proportion of patients intolerant to steroid taper
- proportion of patients who discontinued due to inefficacy or worsening
- Mean change in the Myasthenia Gravis Activities of Daily Living Scales (MG-ADL, MG QOL-15).

The changes from baseline in MG-ADL and MG QOL-15 at each visit until week 25 will be analyzed using the main mixed model as described above for MGC.

The proportions of patients requiring rescue therapy between Week 1 and Week 25 (i.e. IV immunoglobulins or plasma exchange) will be described. Time to first rescue therapy will be described using Kaplan-Meier curves and compared between CFZ533 and placebo using the log-rank test. In case of dropouts, the data will be censored at the last visit before or at Week 25.

The proportion of patients with improvement by ≥ 3 points in QMG score at Week 25, the proportion of patients with worsening by ≥ 3 points in QMG score at week 25, the proportion of patients intolerant to steroid taper and the proportion of patients who discontinued due to inefficacy or worsening before week 25 will be analyzed via logistic regression with treatment as a factor compared between CFZ533. Additional covariates such as sex, gender, age at onset of MG, QMG score at baseline will be explored. Odds ratios together with 90% CI and p-values will be provided for comparisons of CFZ533 versus placebo utilizing the logistic regression model fitted.

The statistical analysis for exploratory efficacy and PD variables will be described in the RAP.

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

11.5.3 Pharmacokinetics

Free CFZ533 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and will not be considered for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. PK parameters will be calculated as described in Section 8.5 and will be listed by treatment and subject.

Population modeling of PK data using compartmental, non-linear or mechanistic approaches (i.e. together with PD endpoints), may be performed as appropriate, and will be reported in a separate, standalone modeling and simulation report. During modeling activities, the broad principles outlined in the FDA Guidance for Industry: Population PK, will be followed.

11.6 Sample size calculation

The sample size is based on the primary efficacy endpoint and the primary analysis described in Section 11.4.2

A sample size of 36 evaluable patients (18 on CFZ533, 18 on placebo) was determined, assuming a SD of 5.5 (Zinman et al 2007) for the QMG endpoint. To account for approximately 20% anticipated dropouts, 44 patients will be randomized in this study (22 on CFZ533 and 22 on placebo).

To account for potential discontinuations due to non-detectable AChR or MuSK autoantibodies, the sample size might be increased to compensate the discontinued seronegative patients.The operating characteristics of this design are shown on Figure 11-1 below. The probability of reaching the target efficacy (success) at final analysis is about 8% if CFZ533 is equal to placebo, and it is >80% if the true difference between CFZ533 and

placebo is ≥ 4.5. At the planned IA the probability of success is 42% if the true difference between CFZ533 and placebo is ≥ 4.5 and the probability of stopping for futility is 5% if CFZ533 is equal to placebo. This sample size was considered adequate to preliminarily evaluate the efficacy of CFZ533 in the treatment of myasthenia gravis.

Figure 11-1 Operating characteristics for the planned interim and final analyses

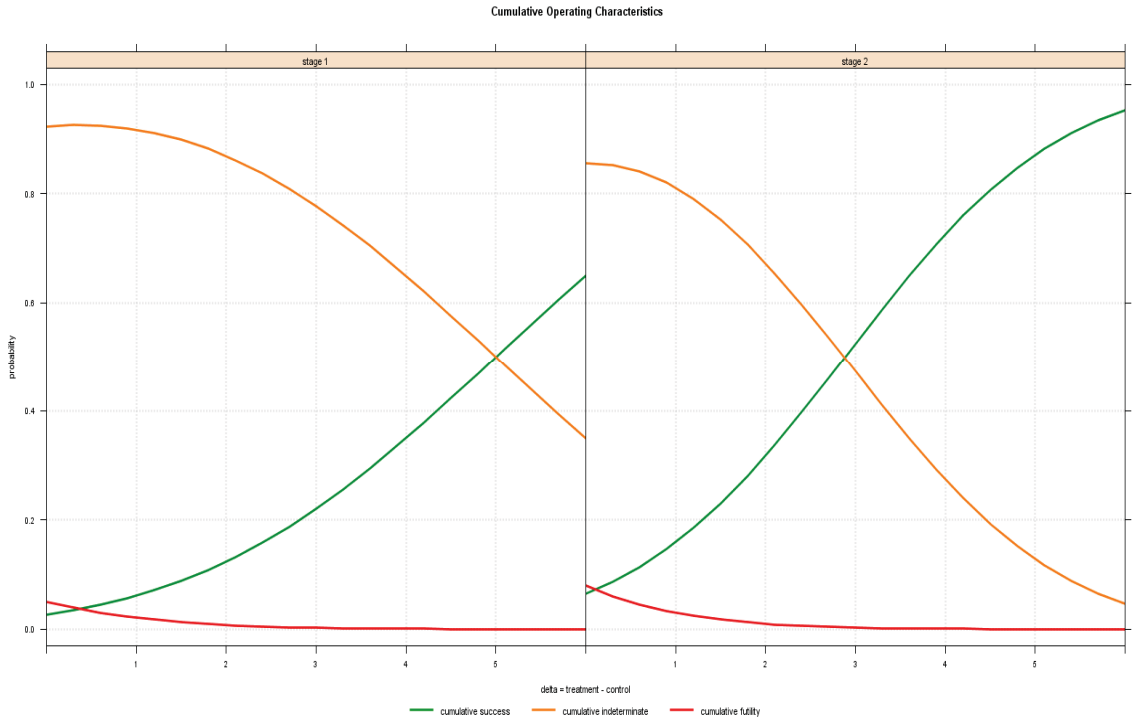

Figure 11-1 shows the operating characteristics curves for the planned interim and final analyses. The horizontal axis shows the difference CFZ533 minus placebo in mean QMG change from baseline (from 0 to 6). The vertical axis displays the probabilities (i) success (target efficacy, green curves)), (ii) futility (red curves), and (iii) indeterminate (neither success nor futility achieved (yellow curves).

11.7 Power for analysis of key secondary variables

MGC score is a key secondary variable. It ranges from 0 to 53, with a SD of 6.6. The change form baseline is assumed to be normally distributed. With 36 patients, the study will have more than 80% power to detect a difference of 4.7 between CFZ533 and placebo mean change from baseline using a 1-sided t-test at 10% significance level.

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated

agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

14 References

Available upon request

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