A randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of eculizumab in subjects with refractory generalized myasthenia gravis (gMG)

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Main Objective:Assess the efficacy of eculizumab as compared with placebo in the treatment of refractory gMG based on the improvement in the MG specific Activities of Daily Living profile (MG-ADL).Secondary Objectives: - Safety and tolerability of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON40159

Source
ToetsingOnline

Brief title
ECU-MG-301

Condition

- Other condition

Synonym
alter, Antibodies block, or destroy the receptors for acetylcholine at the NMJ (neuromuscular junction); Neuromuscular Disease

Health condition

Refractory generalized myasthenia gravis

Research involving
Human

Sponsors and support

Primary sponsor: Alexion Pharmaceuticals
Source(s) of monetary or material Support: Pharmaceutical industry.

Intervention

Keyword: Eculizumab, Efficacy, Myasthenia gravis, Safety

Outcome measures

Primary outcome

Primary Efficacy Endpoint:

The primary efficacy endpoint is change from baseline in the MG-ADL total score

at Week 26 for eculizumab as compared with placebo.

Secondary outcome

- Change from baseline in QMG total score

- Proportion of subjects with at least a 3-point reduction in the MG-ADL total

score and with no rescue therapy

- Proportion of subjects with at least a 5 point reduction in the QMG total

score

- Change from baseline in the Myasthenia Gravis Composite (MGC) scale total

score

- Change from baseline in MG-QOL-15

Study description

Background summary

Myasthenia Gravis is a rare, debilitating, acquired autoimmune disease of the neuromuscular junction (NMJ), caused by the failure of neuromuscular transmission, which results from the binding of auto-antibodies (Abs) to proteins involved in signaling at the neuromuscular junction (NMJ). Myasthenia Gravis is clinically characterized by weakness and fatigability of skeletal muscles. The prevalence of MG is estimated to be between 14-20 per 100,000 people in the United States. In the MG patient population, there is a wide range of disease severity. Although many patients with MG can be managed with anticholinesterase inhibitor therapy and immunosuppressants, there is a cohort of patients who continue to have marked generalized weakness and bulbar signs and symptoms of the disease despite adequate dosing of immunosuppressant therapy. For these patients,
there is a medical need for alternative treatment strategies targeting different pathophysiological aspects of the disease. Since complement activation plays a pivotal role in the pathophysiology of MG, eculizumab, a terminal complement inhibitor, as such may benefit patients who continue to have generalized weakness and bulbar signs and symptoms despite current standard of care. Alexion has completed a phase II, randomized, double-blind, placebo-controlled, pilot trial (cross-over design), protocol number C08-001, to establish safety and efficacy of eculizumab in 14 subjects with refractory gMG. In this phase 2 clinical trial, 86% (6/7) subjects in the eculizumab arm had >=3-point reduction in the Quantitative MG (QMG) score vs. 57% (4/7) in placebo arm, 86% (6/7) had >=2-point change in the MG activities of the Activities of Daily Living profile (MG-ADL) vs 57% (4/7) in the placebo arm and the mean change from baseline in MG-ADL was -4.1 points. The data from the pilot trial (C08-001) provide preliminary evidence of the safety and efficacy of eculizumab in the treatment of refractory gMG and warrants further investigation.

Study objective

Main Objective:
Assess the efficacy of eculizumab as compared with placebo in the treatment of refractory gMG based on the improvement in the MG specific Activities of Daily Living profile (MG-ADL).

Secondary Objectives:
- Safety and tolerability of eculizumab as compared with placebo in gMG subjects
- Efficacy of eculizumab compared with placebo
- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab
- Characterize the effect of eculizumab as compared with placebo on Quality of Life measures

Study design

This is a randomized, double-blind, parallel-group, placebo-controlled,

multicenter trial to evaluate the safety and efficacy of eculizumab for the treatment in subjects with refractory gMG. Approximately 92 eligible subjects will be randomized on Day 1 on a 1:1 ratio to one of two treatment arms, (1) eculizumab infusion or (2) placebo infusion. Subjects may continue to receive stable dose/type of supportive immunosuppressive therapy (IST), but no new ISTs and no increase in IST dosage are permitted during the trial. There will be 3 periods in this study: Screening Period, Study Period, and Follow-up Period (for subjects who withdraw from this trial or who do not enter the extension trial). Subjects may be provided the opportunity to participate in an extension trial (separate protocol) to receive eculizumab after completion of this trial.

Intervention

Investigational Product (IP), eculizumab or placebo, will be intravenously administered according to the following regimen:

Induction Phase:
eculizumab or placebo; 3 vials of IP (placebo or equivalent to 900 mg of eculizumab) weekly x 4 (every 7 days ±2 days) followed by 4 vials of IP (placebo or equivalent to 1200 mg of eculizumab) one week later for the fifth dose.

Maintenance Phase: eculizumab or placebo: 4 vials of IP (placebo or equivalent to 1200 mg of eculizumab) every two weeks (every 14 days ±2 days).

Supplemental Doses:
If PE is administered due to a clinical deterioration (as defined by this protocol), supplemental IP (2 vials) will be administered within 60 minutes after the end of each PE session. Per-protocol, scheduled IP administration will be continued according to the specified dose-administration schedule for the subject. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose should be administered within 60 minutes after the end of the PE session.

Study burden and risks

The proposed phase III clinical trial includes only patients with refractory generalized MG. The inclusion criteria are designed to select patients who continue to have clinical symptoms, including oropharyngeal/respiratory symptoms despite treatment with immunosuppressive agents or chronic use of IVIG or Plasma Exchange to maintain clinical stability. This is a small subset of the broader MG population, but is the population with greatest unmet medical need.

The lack of effective treatment, the new and targeted mechanism of action of eculizumab and the promising efficacy data achieved in clinical Phase II study

support the potential benefit of eculizumab in this population.

This clinical development program is designed to assess the efficacy of eculizumab as compared with placebo in the treatment of refractory gMG based on the improvement in the MG-specific Activities of Daily Living profile (MG-ADL).

The safety profile of eculizumab has been extensively characterized in PNH and aHUS patients. The most significant risk associated with the use of eculizumab is the risk of meningococcal infection and key mitigation measures have been put in place. The risk of meningococcal infection observed to date in Soliris® (eculizumab) treated patients is less than 0.5 events/100 patient years of treatment.

In addition, strict requirements for contraception are also mandated to minimize the risk of unintended pregnancies during the study period and in the 5 months following the last dose of study drug as per currently approved Soliris® (eculizumab) SmPC.

In summary, the benefit-to-risk balance is considered as favorable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Male or female subjects >=18 years old
- Diagnosis of MG
- MGFA Clinical Classification Class II to IV at screening
- MG-ADL total score must be >=6 at screening

Exclusion criteria

- History of thymoma or other neoplasms of thymus
- History of thymectomy within 12 months prior to screening
- Weakness only affecting ocular or peri-ocular muscles (MGFA Class I)
- MG crisis at screening (MGFA Class V)
- Pregnancy or lactation
- Unresolved meningococcal infection

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-03-2015
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Soliris
Generic name:	Eculizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-003589-15-NL
ClinicalTrials.gov	NCT01997229
CCMO	NL47104.018.14