AN OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ECULIZUMAB IN PEDIATRIC PATIENTS WITH REFRACTORY GENERALIZED MYASTHENIA GRAVIS

Published: 14-12-2020
Last updated: 08-04-2024

The primary objectiveTo evaluate the efficacy of eculizumab in the treatment of pediatric refractory generalized myasthenia gravis (gMG) based on change from Baseline in the Quantitative Myasthenia Gravis score for disease severity (QMG).The...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON54896

Source
ToetsingOnline

Brief title
ECU-MG-303

Condition

- Autoimmune disorders

Synonym
Generalized Myasthenia Gravis (gMG), muscle weakness disease

Research involving

Human

Sponsors and support

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

Intervention

Keyword: eculizumab, open-label, pediatric patients, refractory Generalized Myasthenia Gravis (gMG)

Outcome measures

Primary outcome

Change from Baseline in the QMG total score over time regardless of rescue

treatment.

Secondary outcome

* Change from Baseline in the MG-ADL total score over time regardless of rescue

treatment

* Proportion of patients with * 3-point reduction in the MG-ADL total score

over time with no rescue treatment

* Proportion of patients with * 3-point reduction in the MG-ADL total score

over time regardless of rescue treatment

* Proportion of patients with * 5-point reduction in the QMG total score over

time with no rescue treatment

* Proportion of patients with * 5-point reduction in the QMG total score over

time regardless of rescue treatment

* Change from Baseline in the MGC total score over time regardless of rescue

treatment

* Change from Baseline in EQ-5D-Y over time regardless of rescue treatment

* Change from Baseline in Neuro-QoL Pediatric Fatigue over time regardless of rescue treatment

* MGFA Post-Interventional Status over time regardless of rescue treatment

Total number and percentage of patients with clinical deteriorations, myasthenic crises, and rescue therapy use over time

Extension Period Efficacy Endpoints:

* Total number and percentage of patients with clinical deteriorations and/or myasthenic crises during the study

* Total number and percentage of patients needing rescue therapy during the study

* Change from Baseline in the QMG total score regardless of rescue treatment

* Change from Baseline in the MG-ADL total score regardless of rescue treatment

* Change from Baseline in the MGC total score regardless of rescue treatment

* Change from Baseline in Neuro-QoL Pediatric Fatigue regardless of rescue treatment

* Change from Baseline in EQ-5D-Y regardless of rescue treatment

* Change from Baseline in MGFA Post-Interventional Status regardless of rescue treatment

Safety Endpoints:

* Frequency of adverse events (AEs) and serious adverse events (SAEs)

* Frequency of adverse events leading to discontinuation

* Incidence of antidrug antibodies (ADA)

* Changes from Baseline in vital signs

* Change from Baseline in electrocardiogram parameters

* Change from Baseline in laboratory assessments

Pharmacokinetic and Pharmacodynamic Endpoints:

* Pharmacokinetic/PD parameters including maximum plasma drug concentration (Cmax), terminal half-life (t*), trough (Ctrough), clearance, free complement protein 5 (C5), and in vitro hemolytic assay; assessed at Baseline and various time points including 24 hours (Day 2), Week 12, and Week 26 during treatment

Farmacokinetische en farmacodynamische eindpunten:

* Farmacokinetische/PD-parameters met inbegrip van maximale plasma-geneesmiddelenconcentratie (Cmax), terminale halfwaardetijd (t*), dal (Cdal), klaring, vrij complementeiwit 5 (C5) en in-vitro hemolyse test; beoordeeld bij de baseline en op verschillende tijdstippen, waaronder na 24 uur (dag 2), in week 12 en week 26 tijdens de behandeling.

Study description

Background summary

Myasthenia gravis (MG) is a rare, chronic, autoimmune disease of neuromuscular transmission that manifests clinically in both children and adults as fluctuating weakness in voluntary muscles that is exacerbated during periods of activity and improves after periods of rest (Barnett, 2014; Sieb, 2014)
Although adults and juveniles with MG share aspects of presentation and pathophysiology, there are differences in epidemiology and prognosis. Additionally, the ongoing development of children and adolescents complicate therapeutic decision making in young patients with MG.

There are currently no approved therapies specific for the treatment of refractory gMG in pediatric patients. Since complement activation plays a pivotal role in the pathophysiology of MG (Vincent, 2002; Conti-Fine, 2006), eculizumab, a terminal complement inhibitor, may benefit patients who continue to have generalized weakness and bulbar signs and symptoms despite current standard of care.

The favorable benefit-risk for eculizumab in the treatment of adult patients with refractory gMG that was established in the adult clinical program provides the basis for studying eculizumab in the pediatric patient population.

Study objective

The primary objective

To evaluate the efficacy of eculizumab in the treatment of pediatric refractory generalized myasthenia gravis (gMG) based on change from Baseline in the Quantitative Myasthenia Gravis score for disease severity (QMG).

The secondary objectives of the study are to:
* Evaluate the safety and tolerability of eculizumab in the treatment of pediatric refractory gMG
* Evaluate the efficacy of eculizumab in the treatment of pediatric refractory gMG based on change from Baseline in the following measures:
- Myasthenia Gravis Activities of Daily Living profile (MG-ADL)
- Myasthenia Gravis Composite score (MGC)
* Evaluate the effect of eculizumab on the following quality of life measures:
-European Quality of Life 5-Dimension Youth (EQ-5D-Y) Questionnaire * EQ-5D-Y Proxy version for patients < 8 years of age or EQ-5D-Y version for patients * 8 years of age
- Neurological Quality of Life Pediatric Fatigue (Neuro-QoL Pediatric Fatigue) Questionnaire for patients * 8 years of age
- PROMIS Parent Proxy Item Bank v2.0 * Fatigue * Short Form 10a for patients < 8 years of age
* Evaluate MGFA Post-Interventional Status over time
* Describe the total number and percentage of patients with clinical deteriorations, myasthenic crises, and rescue therapy use over time
* Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab treatment in pediatric refractory gMG patients to confirm the pediatric dosing regimen selected through modeling and simulation following 26 weeks of eculizumab treatment

The Extension Period objectives are to:
* Characterize long-term safety beyond 26 weeks of eculizumab treatment in pediatric patients with refractory gMG
* Characterize long-term efficacy beyond 26 weeks of eculizumab treatment in

pediatric patients with refractory gMG

Study design

This is an open-label, multicenter study to evaluate the efficacy, safety, PK, and PD of intravenous eculizumab in pediatric patients aged 6 to < 18 years with acetylcholine receptor (AChR)-antibody (Ab) positive refractory gMG. There will be 4 periods in this study: Screening Period (2 to 4 weeks), Primary Evaluation Treatment Period (26 weeks), Extension Period (up to an additional 208 weeks), and Follow-up Period (8 weeks). All patients who complete Week 26 of Study ECU-MG-303 will continue receiving eculizumab in the Extension Period of this study for up to an additional 208 weeks. The 8-week Follow-up Period is required following the last dose of study drug for all patients upon withdrawal or discontinuation from the study or upon completion of the study when the patient is not continuing to receive eculizumab treatment.
Patients may continue use of acetylcholinesterase inhibitors (AChI), intravenous immunoglobulin (IVIg), and supportive immunosuppressive therapies (ISTs) during the study where applicable under certain restrictions.

Intervention

Weight-based Dosing Regimen of Eculizumab are available in the protocol table 1 body weight is categorized into * 40 kg, 30 to < 40 kg, 20 to < 30 kg and 10 to < 20 kg with different induction doses and maintenance doses

Supplemental Doses
For patients who enter the study on maintenance IVIg treatment, a series of supplemental doses of eculizumab will be administered to account for the anticipated approximately 50% increase in eculizumab clearance according to Table 2 of the protocol

If a patient continues to receive IVIg treatment at a dose cycle interval equal to or more frequent than every 4 weeks during eculizumab treatment, a supplemental dose will be administered at the same time that each scheduled dose of eculizumab is administered.
* If a patient receives IVIg treatment at a dose cycle interval less frequent than every 4 weeks during eculizumab treatment, a supplemental dose will be administered following the last dose of the IVIg infusion cycle at the next scheduled eculizumab dose.

If a patient receives IVIg treatment within 4 weeks prior to receiving the first dose of eculizumab, a supplemental dose of eculizumab will be administered at the same time that the first dose of eculizumab is administered (ie, the total dose is the supplemental dose plus the first scheduled dose).

When IVIg is administered as acute rescue therapy for clinical deterioration,

no supplemental dose of eculizumab should be administered. However, if a patient receives more than 1 dose cycle of IVIg as rescue therapy within a 12-week period, supplemental eculizumab should be administered after the last dose of the second IVIg cycle and at the end of each subsequent IVIg dose cycle within the 12-week period in accordance with Table 2.

Study burden and risks

For full details see table 1-6 in the protocol (schedule of assessments) page 32-56

The patient participation in this study will last approximately 4.7 years. During this time the patient will visit the hospital approximately 122 times. The visits will take about 2-6 hours for all children below 18

During these visits the following tests and procedures will take place:
- Physical exam, vital signs, demographic and medical history
- ECG
- vaccinations (meningococcal, Haemophilus influenzae (H influenzae) type b and Streptococcus pneumoniae (S pneumoniae) if no vaccination before. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
- Questionnaires
- Blood and urine tests
- Pregnancy tests in women of childbearing potential
- Female patients: no breastfeeding allowed. Effective methods of birth control must be used from the time of signing the ICF, throughout the entire study and for 5 months following the last dose of the study drug.
- Male patients: due to the potential risk of the effect on the sperm appropriate method of contraception must be used starting at screening and continuing for at least 5 months following the last dose of study drug

Possible side effects that are already known are described in the IB and patient information letter.

Contacts

Public
Alexion Pharmaceuticals

Seaport Boulevard, Suite 400 121
Boston MA 02210
US

Scientific
Alexion Pharmaceuticals

Seaport Boulevard, Suite 400 121
Boston MA 02210
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

* Male or female pediatric patients 6 to < 18 years of age at time of assent/consent.
* Diagnosis of MG confirmed by positive serologic test for anti-AChR-Ab at Screening, and one of the following:
a. History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation, or
b. History of positive anticholinesterase test (eg, edrophonium chloride or neostigmine test), or
c. Patient demonstrated improvement in MG signs on oral AChIs, as assessed by the Investigator.
* Presence of refractory gMG, defined as patients with gMG who have one or more of the following:
a. Failed treatment * 1 year with at least 1 IST
b. Require maintenance PE or IVIg to control symptoms
c. In the opinion of the Investigator, MG poses a significant functional burden despite current MG treatment.
* All MG-specific treatment has been administered at a stable dosing regimen of adequate duration prior to Screening.
* Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of Class II to IV at Screening

In patients aged 12 to 18 years, QMG total score * 12 at Screening; in patients aged 6 to 11 years, no minimum QMG is required for inclusion; however, patients must have documented limb weakness in at least one limb.
* Patients must be vaccinated against meningococcal infections within the 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
* Documented vaccination against H influenzae and S pneumoniae infections prior to dosing as per local and country specific immunization guidelines for the appropriate age group.

Exclusion criteria

* Any active or untreated thymoma. History of thymic carcinoma or thymic malignancy unless deemed cured by adequate treatment with no evidence of recurrence for *5 years before Screening.
* History of thymectomy within 12 months prior to Screening.
* Weakness only affecting ocular or periocular muscles (MGFA Class I).
* Myasthenia Gravis crisis or impending crisis at or during Screening (MGFA Class V).
* Any unresolved acute, or chronic, systemic bacterial or other infection, which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics.
* Unresolved meningococcal infection.
* Patients who are under 15 kg and are receiving maintenance IVIg.
* For patients who are not receiving a stable maintenance dose of IVIg, as described in the Inclusion Criteria, use of IVIg (eg, as rescue therapy) within 4 weeks prior to first dose.
* Use of PE within 4 weeks prior to first dose.
* Use of rituximab within 6 months prior to first dose.
* Hypersensitivity to murine proteins or to one of the excipients of eculizumab.

Study design

Design

Study phase:	3
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO

Date:	14-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	13-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	23-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	09-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	11-10-2021
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	EUCTR2016-001384-37-NL
ClinicalTrials.gov	NCT03759366
CCMO	NL75134.018.20