A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenia Gravis

Published: 01-05-2019
Last updated: 09-04-2024

Main objective:To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile.Secondary objectives:• To assess the efficacy of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON52651

Source
ToetsingOnline

Brief title
ALXN1210-MG-306

Condition

- Autoimmune disorders

Synonym
Generalized Myasthenia Gravis (gMG)

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Generalized Myasthenia Gravis (gMG), Phase 3, Ravulizumab

Outcome measures

Primary outcome

Change from Baseline in MG-ADL total score in week 26 of the randomized

controlled period.

Secondary outcome

• Change from Baseline in QMG total score in week 26.

• Change from Baseline in the Revised 15 Component Myasthenia Gravis Quality of

Life (MG-QoL15r) score at Week 26.

• Change from Baseline in Neuro-QOL Fatigue score at Week 26.

• Improvement of at least 3 points in the MG-ADL total score from Baseline at

Week 26.

• Improvement of at least 5 points in the QMG total score from Baseline at Week

26.

Study description

Background summary

Generalized myasthenia gravis (gMG) is a rare disorder, which based on studies conducted in Europe, has an estimated prevalence between 145 to 278 per million inhabitants. Patients with gMG suffer from a devastating inflammatory

neuromuscular disorder with limited therapeutic options.
Generalized myasthenia gravis patients differ from the ocular myasthenia gravis (MG) population in that neuromuscular inflammation and the resultant clinical findings are not just limited to the ocular muscles, but involve all voluntary muscle groups: the bulbar, respiratory, head, neck, trunk, or peripheral muscles with or without involvement of the eyes. Profound weakness and devastating consequences, including slurred speech, dysarthria, dysphagia, disorienting vision, shortness of breath (both with activity and at rest), weakness of the upper and lower extremities, impaired mobility, marked reductions in the ability to perform activities of daily living (ADLs), extreme fatigue, and episodes of pulmonary failure requiring mechanical ventilation are hallmarks of gMG. Compared with patients with isolated ocular MG, patients with gMG have a greater incidence of morbidities and a higher burden of disease. Hospitalizations for gMG exacerbations are common, with the need for respiratory support, including mechanical ventilation secondary to respiratory failure (eg, myasthenic crisis) and gastrointestinal tube placement for nutritional support and prevention of dysphagia-associated aspiration. Patients with more advanced gMG have been reported to experience increased mortality of up to 40% at 10 years following diagnosis.

In difficult-to-control cases, patients with gMG experience unrelenting inflammation, tissue destruction, and consequent severe morbidities including profound muscle weakness, impaired mobility, shortness of breath, pulmonary failure, extreme fatigue, risk for aspiration, and markedly impaired ADLs. These patients are typically diagnosed in the prime of their adult lives, with a median age of onset ranging from 36 to 60 years As a result of the morbidities associated with gMG, many patients cannot work or have diminished work-capacity, experience difficultly caring for themselves and others, and require assistance speaking, eating, ambulating, breathing, and performing ADLs.

The study drug is being developed to treat gMG by blocking complement activity. In patients with gMG, abnormal complement activity is present, which causes damage to the structures in the body that are responsible for neuromuscular transmission. Ravulizumab IV has been previously tested in patients with other rare diseases called Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical Hemolytic Uremic Syndrome (aHUS). These diseases are also caused by abnormal complement activity. However, this study will be the first to test ravulizumab in patients with gMG.

Study objective

Main objective:
To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in the Myasthenia Gravis-
Activities of Daily Living (MG-ADL) profile.

Secondary objectives:
• To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in the Quantitative Myasthenia Gravis (QMG) total score.
• To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in quality of life measures.
• To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on other efficacy endpoints.

Study design

This is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab for the treatment in patients with gMG.

Intervention

Approximately 160 eligible patients will be stratified by region (North America, Europe, Asia-Pacific, and Japan) and randomized 1:1 to 1 of 2 treatment groups: (1) ravulizumab infusion or (2) placebo infusion.

Study burden and risks

For full details see table 1 in the protocol (schedule of assessments) page 18-23

The patient participation in this study will last approximately2.5 years. During this time the patient will visit the hospital approximately 25 times. The visits will take about 2-4 hours.
During these visits the following tests and procedures will take place:
- physical examinations will be done and questions will be asked about medical history.
- ECGs will be done
- weight, height, blood pressure, temperature, heartbeat will be measured
- blood and urine sampling will be taken.
- The research physician will also test female pa rticipants of childbearing potential for pregnancy.
- Subjects need to complete several questionnaires
Possible side effects that are already known are described in the IB and patient information letter.

Contacts

Public

Alexion Pharmaceuticals

Seaport Boulevard 121
Boston MA 02210
US
Scientific
Alexion Pharmaceuticals

Seaport Boulevard 121
Boston MA 02210
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male and female patients must be aged >= 18 years of age at the time of signing the informed consent
2. Diagnosed with MG at least 6 months (180 days) prior to the date of the Screening Visit
3. Confirmation of eligibility by:
a. Positive serologic test for anti-AChR Abs as confirmed at screening, and
b. One of the following (either historical or during screening):
• Abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation
• Positive anticholinesterase test (eg, edrophonium chloride test)
• Demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating physician
4. Myasthenia Gravis Foundation of America Clinical Classification Class II to IV at screening
5. MG-ADL profile must be >= 6 at screening and randomization (Day 1)
6. Patients receiving treatment with any of the following must have been receiving treatment and on a stable dose for the time periods specified below

prior to the date of the Screening Visit:
• Azathioprine (AZA): Must have been on AZA for >= 6 months (180 days) and have been on a stable dose for >= 2 months (60 days)
• Immunosuppressive therapies (ie, mycophenolate mofetil [MMF], methotrexate [MTX], cyclosporine [CYC], tacrolimus [TAC], or cyclophosphamide [CY]), must have been on the IST for >= 3 months (90 days) and have been on a stable dose for >= 1 month (30 days)
• Oral corticosteroids, must have been on a stable dose for >= 4 weeks (28 days)
• A cholinesterase inhibitor, at the time of the Screening Visit, must have been on a stable dose for >= 2 weeks (14 days)
7. To reduce the risk of meningococcal infection (N meningitidis), all 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
8. Body weight >= 40 kg at the time of screening
9. Patients of childbearing potential and patients with partners of childbearing potential must follow protocol-specified contraception guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug
10. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol

Exclusion criteria

1. Any active or untreated thymoma or history of thymic carcinoma or thymic malignancy
Note: Treated patients with history of thymoma other than thymic carcinoma corresponding to clinical stage 1 and 2 with no evidence of recurrence as defined by a recent negative imaging study (CT scan with IV contrast or MRI scan within 6 months of randomization) are eligible for enrollment.
2. History of thymectomy, thymomectomy, or any thymic surgery within the 12 months prior to screening
3. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins
4. History of N meningitidis infection
5. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer)
6. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the patient*s full participation in the study, pose any additional risk for the patient, or confound the assessment of the patient or outcome of the study
7. History of hospitalization for >= 24 hours, for any reason, within the 4

weeks (28 days) prior to screening
8. Clinical features that, in the opinion of the Investigator, consistent with MG crisis/exacerbation or Clinical Deterioration, at the time of the Screening Visit or at any time prior to randomization
9. Female patients who plan to become pregnant or are currently pregnant or breastfeeding
10. Female patients who have a positive pregnancy test result at screening or on Day 1
11. Use of the following within the time period specified below:
• IVIg within the 4 weeks (28 days) prior to randomization (Day 1)
• Use of PE within the 4 weeks (28 days) prior to randomization (Day 1)
• Use of rituximab within the 6 months (180 days) prior to screening
12. Patients who have received previous treatment with complement-inhibitors (eg, eculizumab)
13. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of the study drug, whichever is greater
14. History of unexplained infections
15. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1
16. Presence of fever >= 38°C (100.4°F) within 7 days prior to study drug administration on Day 1

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:	Recruiting
Start date (anticipated):	20-01-2020

Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ravulizumab
Generic name:	Ravulizumab

Ethics review

Approved WMO Date:	01-05-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2022
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	EUCTR2018-003243-39-NL
CCMO	NL69039.018.19