A Randomized, Double blind, Placebo Controlled Phase II Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX 113 in Patients with Myasthenia Gravis who have Generalized Muscle Weakness

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Primary Objective:* To evaluate the safety and tolerability of ARGX-113.Secondary Objectives:* To evaluate the clinical effect of ARGX-113 using:-Myasthenia Gravis-Activities of Daily Living (MG-ADL) score.-Quantitative-Myasthenia Gravis score (QMG...

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

Summary

ID

NL-OMON43317

Source
ToetsingOnline

Brief title
ARGX-113 in Patients with Myasthenia Gravis and generalized muscle weakness

Condition

- Autoimmune disorders
- Neuromuscular disorders

Synonym
Myasthenia Gravis, Severe Muscle Weakness

Research involving
Human

Sponsors and support

Primary sponsor: Argenx BVBA
Source(s) of monetary or material Support: Pharmaceutical Industry (Argenx BVBA)

Intervention

Keyword: ARGX 113, Generalized Muscle Weakness, Immunomodulator, Myasthenia Gravis

Outcome measures

Primary outcome

Primary endpoint:

* Evaluate the incidence and severity of adverse events (AEs) and serious AEs

(SAEs).

* Evaluate vital signs, electrocardiogram (ECG), and laboratory assessments.

Secondary outcome

Secondary endpoints:

* Score change from Baseline (defined as the score immediately prior to first

dose at Visit 1) at Visits 3, 5, 7, 9, 10, 11, 12, 14, and 16 for the following:

-MG-ADL

-QMG

-MGC

-MGQoL15r

* Maximum reduction from Baseline across visit days for MG-ADL, QMG, MGC, and

MGQoL15r score.

* Pharmacokinetic parameters of ARGX-113 including maximum observed

concentration (Cmax), time of maximum concentration (tmax), concentration prior

to dosing (Ctrough), half-life, (t1/2,*z), and accumulation ratio (Rac).

* Evaluation of PD markers: total IgG (and subtypes) and anti-AChR antibodies.

* Evaluate the incidence of anti-drug antibodies (ADA) to ARGX-113.

* Exploratory pharmacogenetic assessments in patients who sign a separate

pharmacogenetic ICF to examine FcRn polymorphisms.

Study description

Background summary

Myasthenia Gravis (MG) is an autoimmune disorder characterized in most cases by T cell and antibody responses to neuromuscular junction proteins such as skeletal muscle nicotinic acetylcholine receptor (AChR). Antibodies against epitopes of the AChR of the neuromuscular junction cause failure of neuromuscular transmission, resulting in the characteristic fatigue and weakness associated with this severe disorder. The muscle weakness fluctuates with activity, and periods of rest offer only a temporary reprieve.
Current short- and long-term treatments for MG have widely varying effectiveness with numerous adverse consequences.

Antibodies, especially IgG, play a predominant role in the pathogenesis and the treatment of many autoimmune diseases such as MG. In order to treat IgG-mediated autoimmunity, it would be beneficial to lower levels of pathogenic autoantibodies rapidly and sustainably. Antagonizing the neonatal Fc receptor (FcRn) could be a therapeutic approach to achieve this as FcRn is a multifunctional molecule primarily involved in IgG transport and homeostasis, that influences immunoglobulin G (IgG) serum levels and tissue distribution at all stages of life.
ARGX-113 is a human IgG1-derived Fc fragment of the za allotype that binds with nanomolar affinity to human FcRn, blocking FcRn-mediated recycling of IgGs. Given the essential role of the FcRn receptor in IgG homeostasis, inhibiting this FcRn function leads to rapid degradation of endogenous IgGs, which is expected to include autoantibodies in IgG-driven autoimmune diseases.

Pre-clinical data have validated the further development of ARGX-113 for assessing its therapeutic potential in IgG-driven autoimmune indications. To this end, a Phase I dose-escalation study in healthy volunteers was previously initiated. In this study ARGX-113 was administered to healthy volunteers in single doses (up to 50 mg/kg) as well as multiple doses (up to 25

mg/kg). ARGX-113 was proven to be safe and tolerable in this healthy volunteer study and pre-clinical PD parameters could be confirmed in a human setting.
The current proposed Phase II study aims to further establish the safety, efficacy, PK and PD of ARGX-113 in a patient setting, namely in patients with autoimmune MG with generalized muscle weakness, and thereby validating the concept of autoantibody reduction as a therapeutic treatment modality in this indication.

Study objective

Primary Objective:
* To evaluate the safety and tolerability of ARGX-113.

Secondary Objectives:
* To evaluate the clinical effect of ARGX-113 using:
-Myasthenia Gravis-Activities of Daily Living (MG-ADL) score.
-Quantitative-Myasthenia Gravis score (QMG).
-Myasthenia Gravis Composite score (MGC).
* To evaluate the impact of ARGX-113 on quality of life using 15-item quality of life scale for Myasthenia Gravis (MGQoL15r [revised version]).
* To investigate the pharmacokinetics (PK) of ARGX-113.
* To assess the pharmacodynamic (PD) markers (e.g., total immunoglobulin G (IgG) and subtypes, anti-acetylcholine receptor [AChR] antibodies).
* To evaluate the immunogenicity of ARGX-113.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter Phase II study to evaluate the safety, efficacy, and pharmacokinetics of ARGX-113 for the treatment of autoimmune Myasthenia Gravis (MG) with generalized muscle weakness.
Approximately 24 patients will be randomized in up to 25 sites globally.
The study will include a Screening period of maximum 15 days, a Treatment period of 3 weeks from Visit 1 to Visit 7 and a Follow-Up (FU) period of 8 weeks starting after completion of Visit 7 (total duration 13 weeks).
During the Treatment period, eligible patients will be randomized at a 1:1 ratio to receive ARGX-113 (10 mg/kg) or placebo in 4 infusions administered one week apart in addition to Standard of Care (SoC).
This study is exploratory and not powered to address any predefined hypothesis.
The safety and efficacy analysis will be performed on the safety analysis set, which includes all patients who received at least one infusion of ARGX-113 or placebo.

Intervention

Following screening, all subjects that meet the entry criteria will be randomized at a 1:1 ratio to receive ARGX-113 (10 mg/kg) or placebo. This will be administered intravenously once a week for up to 4 times. Each infusion will take 2 hours, and the subject will need to stay at the clinic for observation for 2 hours following the infusion.

Study burden and risks

Including screening and follow-up the study will consist of 17 clinic visits (of which 4 are optional) over a period of 13 weeks. During the treatment period subjects will receive weekly intravenous infusions for a period of 4 weeks. Each visit will last from 0,5 to 5 hours and during these visits the subject will be subjected to questions about their physical/mental well-being and current medications, physical examinations (including vital signs), urine tests, blood tests, pregnancy tests (if applicable), ECGs and questionnaires/efficacy assessments (MGQoL15r, MG ADL, QMG and MGC). Subjects will be expected to not take part in other medical studies, keep their appointments for visits, fast for up to 8 hours prior to certain study visits, stop taking certain MG medications, stay at the clinic for 2 hours after the infusions, carry a participant card with them and to use appropriate forms of contraception up to 90 days after the last dose of study drug.

During this study, subjects will receive either ARGX-113 or placebo as an add-on therapy to the routine SoC. The most common side effects of ARGX-113 include changes to the level of white blood cells (not associated with clinical symptoms), increase in C-reactive protein (not associated with clinical symptoms), headache and common cold. As with all biologic medications an immune reaction cannot be excluded. Though not seen in other studies, treatment with ARGX-113 might make the body more prone to infections and may potentially reactivate any hidden infections.
Also, the study drug may have side effects that are still unknown.

Since patients with autoimmune MG eligible for this study continue to have significant residual symptoms that affect their quality of life whilst on SoC, this study offers an opportunity to receive ARGX-113 (50% chance) that may offer additional benefit on top of their routine SoC. Preliminary blinded data from a previous Phase I study indicate ARGX-113 is generally safe and tolerable based on data from healthy volunteers. During the study, all adverse events, vital signs and laboratory data will be collected and reviewed by the Principal Investigator and clinical research staff on an ongoing basis. The study is designed to ensure overall patient safety and every effort will be made to monitor the study closely and take appropriate actions as needed. The data generated from this study will support further development of ARGX-113 for the treatment of MG.

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

1.Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study protocol procedures (including required study visits).
2.Male or female patients aged *18 years.
3.Diagnosis of autoimmune MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II, III or IVa, and likely not in need of a respirator for the duration of the study as judged by the Investigator. The confirmation of the diagnosis should be documented and supported
by:
* Positive serologic test for anti-AChR antibodies before Screening and
* at least 1 of the following 3 tests:

(i) History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation or
(ii) History of positive edrophonium chloride test, or
(iii) Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors as assessed by the treating physician.
4.A total score of *5 on the MG ADL at Screening and Baseline with more than 50% of this score attributed to non-ocular items.
5.Patients are required to be on a stable dose of their MG treatment prior to randomization. For patients receiving AZA, other NSIDs, steroids, and/or cholinesterase inhibitors as concomitant medications the following conditions will apply:
*AZA: treatment initiated at least 12 months ago and no dose changes in the last 6 months before Screening.
*Other NSIDs (e.g., methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide): treatment initiated at least 6 months ago and no dose changes in the last 3 months before Screening.
*Steroids: treatment initiated at least 3 months prior to and no dose changes in the last month before Screening.
*Cholinesterase inhibitors: to be on a stable dose for >2 weeks before Screening.
Note: cholinesterase inhibitors must be held for at least 12 hours consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA]1, before the MGQoL15r, MG ADL, QMG, and MGC assessments.
6.Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Visit 1 prior to administration of IMP. Female of childbearing potential are defined as all female participants unless they are postmenopausal (defined by continuous amenorrhea) for at least 2 years with a Follicle stimulating hormone (FSH) >40 IU/L or are surgically sterile (i.e., who had a hysterectomy, bilateral oophorectomy, or have current
documented tubal ligation or any other permanent female sterilization procedure). Determination of FSH levels can be used to confirm postmenopausal status in amenorrheic patients not on hormonal
replacement therapy if the test result is within the postmenopausal range per the central laboratory.
7.Female participants of childbearing potential must agree to use a highly effective method of contraception (i.e., pregnancy rate of less than 1% per year) during the study and for 90 days after the discontinuation of the IMP. Adequate contraceptive methods include combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine devices (IUDs), intrauterine hormonereleasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal
occlusion, or a female participant who is not of childbearing potential. Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment for at least 4 weeks before Screening.
8.Sterilized male patients who have had vasectomy a year back with documented aspermia post procedure can be included. In addition, male patients must be advised not to donate

sperm during this period from signing of Informed Consent Form (ICF), throughout the duration of the
study, and for 90 days after the last administration of IMP. Nonsterilized male patients who are sexually active with a female partner of childbearing potential must use effective method of double barrier contraception (e.g., condom with spermicidal cream or jelly, 1 hormonal plus 1 barrier method or 2 simultaneous barrier methods). Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included.

Exclusion criteria

1.Females who are pregnant or lactating.
2.MGFA Class I, IVb, and V.
3.Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening; or history of or known infection with human
immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or Mycobacterium tuberculosis. Patients must have negative test results for HBV surface antigen, HBV core antibody, HCV antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON® TB Gold test at Screening. Patients with an indeterminate QuantiFERON® TB Gold result will be allowed one retest; if not negative on retesting, the patient will be excluded.
4.At Screening, have clinically significant laboratory abnormalities or as below:
*Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2 x upper limit of normal (ULN).
*Total serum bilirubin of >1.5 x ULN (except for Grade 1 hyperbilirubinemia solely due to a medical diagnosis of Gilbert's syndrome).
*Serum creatinine >1.5 mg/dL and creatinine clearance <50 ml/min (using the Chronic Kidney Disease Epidemiology [CKD-EPI]-Creatinine formula).
*Clinically significant proteinuria (i.e.,> 3x ULN)
*Hemoglobin *9 g/L
*Thyroid stimulating hormone or thyroglobulin outside of the central laboratory normal range
*International normalized ratio (INR) or activated partial thromboplastin time (aPTT) >1.2x ULN
*Total immunoglobulin G level <6 g/L.
5.Body Mass Index (BMI) at screening * 35 kg/m2.
6.Use of rituximab, belimumab, eculizimab or any monoclonal antibody for immunomodulation within 6 months prior to first dosing. Patients with prior exposure to rituximab must have CD19 counts within the normal range per the central laboratory at Screening.
7.Use of any biological therapy or investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) before Screening.
8.Immunoglobulins given by IV (IVIg), or intramuscular route, or plasmapheresis/plasma exchange (PE) within 4 weeks before Screening.
9.Have known autoimmune disease other than MG that would interfere with the course and

conduct of the study (such as uncontrolled thyroid disease or severe RA).
10.Have received vaccinations within 4 weeks before Screening or have any vaccinations planned during the study.
11.Have a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders at any time, unless deemed cured by adequate treatment with no evidence of recurrence for *5 years before Screening. Patients with completely excised nonmelanoma skin cancers (such as basel cell carcinoma or squamous cell carcinoma) or cervical carcinoma in situ would be permitted at any time.
12.Have a history of cerebrovascular accident or myocardial infarction within the last 12 months before Screening, or current severe/unstable angina, arrhythmia, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV, or uncontrolled hypertension.
13.Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious diseases) which, in the opinion of the Investigator, could confound the results of the study or put the patient at undue risk.
14.Major past surgery (e.g., heart valve replacement, hip replacement) that, in the opinion of the Investigator, poses a risk to patient's safety or interferes with the study evaluation, procedures or completion.
15.Thymectomy when performed < 3 months prior to screening.
16.History or presence of alcoholism or drug/chemical/substance abuse within 2 years before Screening per Investigator's opinion.

Study design

Design

Study phase:	2
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):	30-12-2016

Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	03-10-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-12-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2016-002938-73-NL
CCMO	NL59159.058.16