A Phase 2, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group, Multicenter Trial to Evaluate the Safety and Tolerability, Efficacy, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of 2 Dose Regimens of ARGX-117 in Adults With Multifocal Motor Neuropathy

Published: 27-12-2021
Last updated: 05-04-2024

Rationale:Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities. MMN is considered a chronic immune-mediated neuropathy driven by the classical complement...

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

Summary

ID

NL-OMON54143

Source
ToetsingOnline

Brief title
A study with MMN patients comparing 2 doses of ARGX-117

Condition

- Autoimmune disorders
- Neuromuscular disorders

Synonym
Disease of the neuro muscular junction, serious muscle weakness

Research involving
Human

Sponsors and support

Primary sponsor: argenx BV
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: MMN, muscle disease, Phase 2

Outcome measures

Primary outcome

Primary Objectives:

To evaluate the safety and tolerability of ARGX-117 compared to placebo in

adult participants previously stabilized with IVIg •

Primary Endpoints:

Safety outcomes based on adverse event (AE) monitoring and other safety

assessments

Secondary outcome

Secondary Objectives:

• To evaluate the efficacy of ARGX-117 compared to placebo on muscle strength

and/or motor function in adult participants previously stabilized with IVIg

• To evaluate the efficacy of ARGX-117 on functional ability, arm and hand

function, quality of life, and fatigue in adult participants with MMN

• To evaluate the effect of ARGX-117 on health-related productivity and work

productivity

• To evaluate medication treatment satisfaction

• To assess the PK, PD, and immunogenicity of ARGX-117

Secondary Endpoints:

A. Time to the first retreatment with IVIg since the final IVIg treatment of the IVIg monitoring period

B. Time-to-relapse

C. AUC of the change from baseline in mMRC-10 sum score

D. Value and change from baseline in the average score of the 2 most important muscle groups as assessed by the mMRC-14 sum score

E. Value and change from baseline in the mMRC-14 sum score

F. Proportion of participants showing a deterioration of 1 or more points in at least 2 muscle groups as assessed by the mMRC-14 sum score

G. Proportion of participants with no deterioration in 2 or more muscle groups as assessed by mMRC-14 sum score

H. AUC of the change from baseline in GS

I. Proportion of participants with a GS decrease of 8 kilopascal (kPa) or more over 3 consecutive days

J. Values, change, and percent change from baseline in GS

K. Values and change from baseline in the Rasch-built overall disability scale for MMN (MMN*RODS©)

L. Values and change from baseline in the average time for the upper extremity (arm and hand) function (9-Hole Peg Test [9-HPT], or timed Peg Board Test)

M. Proportion of participants by level of severity on each dimension of the EQ-5D-5L scale

N. Value and change from baseline in EQ-5D-5L visual analog scale (VAS)

O. Values and change from baseline in the chronic acquired polyneuropathy patient reported index (CAP-PRI)

P. Values of the Patient Global Impression Change (PGIC) scale

Q. Values and change from baseline in the 9-item Fatigue Severity Scale (FSS)

R. Values and change for work-related and household core activities of the Heatlh-Related Productivity Questionnaire (HRPQ) at each visit:

* Hours lost because of absenteeism

* Hours lost because of presenteeism

* Total hours lost (absenteeism + presenteeism)

* Percentage of scheduled hours lost because of absenteeism

* Percentage of scheduled hours lost because of presenteeism

* Percentage of scheduled hours lost in total (absenteeism + presenteeism)

S. Effectiveness, side effects, convenience, and overall satisfaction scores as assessed by the Treatment Satisfaction 14-Item Questionnaire for Medication (TSQM)

T. Serum concentrations and PK parameters for ARGX-117

U. Values and change from baseline in free C2, total C2, functional complement activity (CH50)

V. Incidence and prevalence of ADA against ARGX-117

Study description

Background summary

MMN is considered a rare chronic immune-mediated neuropathy involving progressive muscle weakness of mainly the hands, forearms, and lower legs. It is clinically characterized by progressive asymmetric weakness involving 2 or more nerves and partial motor conduction block. The estimated prevalence of MMN is between 0.6 to 2 per 100,000 people and typically presents as an asymmetrical upper limb pure motor neuropathy. The hallmark of the disease is the presence of multifocal motor conduction blocks, ie. impaired propagation of action potentials
along the axon, and patients often show high serum levels of immunoglobulin M (IgM) antibodies against the ganglioside GM1 (monosialotetrahexosylganglioside). GM1 is widely expressed in the nervous system by neurons, particularly around the node of Ranvier, and Schwann cells. The current prevailing view is that GM1 antibodies target the axolemma at the node of Ranvier. This is thought to interfere with axon-Schwann cell interactions, causing widening of the node, and direct damage to the axon.

The presence and titers of IgM anti-ganglioside GM1 (anti-GM1) antibodies and their complement activating properties, correlate with clinical features such as weakness and axonal damage. Moreover, the binding and subsequent classical complement pathway activation of
anti-GM1 IgM from patients with MMN to motor neurons derived from induced pluripotent stem cells causes disturbed calcium homeostasis and structural damage to these pluripotent cells in vitro, resembling the changes that occur in MMN.

Anti-GM1 (and other gangliosides) IgM antibodies are produced by a limited number of activated B cells; however, the mechanism of this B cell activation has not yet been established. Binding of these anti-GM1 antibodies to GM1 leads to activation of the classical complement
pathway, and subsequent MAC deposition. Consequently, this MAC deposition leads to disruption of Schwann cell-axolemma junctions, displacement of ion-channel clustering, and the disturbance of membrane integrity at the (para)nodal regions resulting in demyelination.
Anti-GM1 IgM antibodies are identified in at least 40% of patients with MMN.

These findings suggest that complements play an important role in the pathogenesis of MMN, therefore, the inhibition of complement activation may provide a new therapeutic option in this disease.

High dose IV immunoglobulin (IVIg) treatment is the only approved treatment for MMN. IVIg treatment often improves muscle strength; however, the efficacy of

IVIg in reducing MMN symptoms declines after several years and many patients report progressive neurological deficits. The mechanism of action of IVIg in MMN is not well understood; however, IVIg may have effects on humoral immunity beneficial to those with MMN. IVIg partially reduced complement activity in sera13 and may interfere with anti-GM1 IgM-mediated complement nerve deposition. Despite treatment with IVIg, MMN related disabilities will continue to progress due to ongoing axonal degeneration. Complement-modulating treatment was previously evaluated using eculizumab, a monoclonal antibody against complement factor 5 (C5) preventing
formation of MAC. Results showed that eculizumab was well tolerated, however, only a small improvement was seen in selected motor performance measurements. Considering the high levels of CD59 expression, iPSC-derived motor neurons show a high innate ability to inhibit the
terminal portion of the complement cascade. Thus, the use of a C5 inhibitor to preserve motor neuron function may be limited Moreover, C5 is downstream of C3, whereas the presence of C3aR on MNs suggest that complement activation upstream of C5 may have functional
consequences for MNs.

There is an unmet medical need for an efficacious treatment option with a more favorable safety and tolerability profile and lower duration of administration than the current standard of care.

Study objective

Rationale:
Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities. MMN is considered a chronic immune-mediated neuropathy driven by the classical complement pathway related to the presence of anti-ganglioside GM1 (monosialotetrahexosylganglioside [anti-GM1]) (and other gangliosides) immunoglobulin M (IgM) antibodies produced by a limited number of B cell clones. These antibodies activate the complement system's classical pathway and subsequently yield membrane attack complex (MAC) deposition leading to disruption of Schwann cell-axolemma junctions, displacement of ion-channel clustering, and disturbance of membrane integrity at the (para)nodal regions that result in demyelination and motor nerve conduction block.

Patients with MMN initially respond to the standard of care, intravenous immunoglobulin (IVIg); however, the disease will continue to progress despite treatment. There is an unmet medical need for an efficacious treatment option with a more favorable safety and tolerability profile and a lower duration of administration than the current standard of care.

ARGX-117, a therapeutic complement-inhibiting antibody that targets complement factor 2 (C2), is being developed to reduce tissue inflammation and attenuate the adaptive immune response by blocking both the lectin and classical

complement pathways. Inhibition of C2 in complement-mediated neuronal damage is a promising mechanism for preventing axonal and glial injury. In an ex vivo mouse model of acute neuropathy, the use of a C2 blocking antibody (Bro2) in GalNAcT-/--Tg (neuronal) mice prevented the loss of neurofilament staining at the nerve terminal, thereby maintaining axonal integrity. Additionally, C2 inhibition by Bro2 in GalNAcT-/--Tg(glial) mice resulted in the preservation of ankyrin B at the distal paranode. Using an in vitro model for MMN, ARGX-117 blocked IgM-mediated classical pathway complement activation on both motor neurons and Schwann cells, providing further support for developing ARGX-117 in patients with MMN.

The safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of single and multiple doses of ARGX-117 administered intravenously (IV), and ARGX-117 comixed with recombinant human hyaluronidase PH20 (rHuPH20) administered subcutaneously (SC), are being evaluated in the ongoing, first-in-human (FIH), phase 1 study, ARGX-117-1901.

This phase 2 clinical trial serves to evaluate the safety and efficacy of different dose regimens of ARGX-117 versus placebo, in participants with MMN previously stabilized with IVIg.

Study design

ARGX-117-2002 is a randomized, double-blinded, placebo-controlled, parallel-group, multicenter trial to evaluate the safety and tolerability, efficacy, PK, PD, and immunogenicity of different dose regimens of ARGX-117 in adults with MMN. Two cohorts of at least 24 participants each are planned for enrollment.

This trial consists of a screening period, an IVIg dependency period (if applicable), an IVIg monitoring period, a double-blinded treatment period (DBTP), and a safety follow-up period.

All participants will begin with a screening period and the diagnosis of MMN will be assessed by the MMN Confirmation Committee (MCC). The MCC will also assess IVIg dependency. Participants whose IVIg dependency is uncertain will enter an IVIg dependency period to assess the impact of a delayed IVIg administration on grip strength (GS) and/or motor function. The IVIg criterion is considered fulfilled in an individual stabilized to IVIg for longer than 3 months if a clinically meaningful deterioration from any of these 2 parameters is established. The IVIg criterion is also considered fulfilled if an individual stabilized to IVIg for less than 3 months demonstrates a clinical improvement following the initiation of IVIg therapy.

After completing the screening period (including the IVIg dependency period, if applicable), all participants will begin the IVIg monitoring period. Participants will receive IVIg during the IVIg monitoring period at a

frequency, duration, and dose established by their medical history. The IVIg monitoring period includes 3 IVIg treatment cycles, and will establish baseline values for all clinical endpoints assessed during the DBTP.
Participants will be randomized on day 1 of the DBTP in:
- a 2:1 ratio to ARGX-117 or placebo in cohort 1, and for option 1 (dose regimen 2: high dose ARGX-117) or option 2 (dose regimen 3: lower dose ARGX-117) in cohort 2
- in a 2:2:1:1 ratio to ARGX-117 (high dose), ARGX-117 (lower dose), placebo (high dose), or placebo (lower dose) for option 3 in cohort 2
Randomization will be stratified based on an individual*s IVIg dose frequency:
1. IVIg dosed every 2 or 3 weeks
2. IVIg dosed every 4 or 5 weeks

The dosing of ARGX-117 or placebo will begin on day 1 of the DBTP, 7 days after the final IVIg administration of the IVIg monitoring period.
Participants will be retreated with IVIg during the DBTP if there is a clinically meaningful deterioration in muscle strength and/or motor function. Investigational medicinal product (IMP) administration will continue throughout the DBTP. A clinically meaningful deterioration is defined as a >30% decline of the GS of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations) and/or a decline of at least 2 points on the modified Medical Research Council (mMRC)-10 sum score. Based on their clinical judgment, the investigator may choose to not re-treat the participant with IVIg. All trial participants can request IVIg retreatment anytime during the DBTP.

End of Trial/Rollover
After completing the 16-week DBTP, participants may enroll in a long-term extension (LTE) study and receive ARGX-117; otherwise, participants will enter the 9-month safety follow-up period.
The following interim database locks will occur:
- After the completion of the 16-week DBTP by all participants included in cohort 1.
- After the completion of the 16-week DBTP by all participants included in cohort 2.
A final database lock will occur when all participants have completed the safety follow-up period, or have rolled over to the LTE study, if applicable.

Intervention

The first IMP administration will begin 7 days after the final IVIg administration at the end of the IVIg monitoring period.

IMP includes:
• ARGX-117 administered by IV infusion
• Placebo administered by IV infusion

ARGX-117 and placebo will be administered by an IV infusion over approximately 2 hours at visit 1. ARGX-117 and placebo will be administered by an IV infusion over approximately 1 hour for all subsequent administrations.

Dose regimen 1 will be assessed in cohort 1. Dose regimen 1 will include an ARGX-117 dose of 30 mg/kg on day 1, followed by a dose of 10 mg/kg every 7 days for 4 weeks (4 infusions total), and a dose of 10 mg/kg every 14 days (5 infusions total) until the end of the DBTP.

Three options are available as the dose regimen for cohort 2, of which 1 will be assessed per the decision of the EDRT:
• Option 1*Dose regimen 2 (high dose): a single dose of 60 mg/kg ARGX--117 or placebo on day 1, followed by 4 weekly doses of 30 mg/kg ARGX--117 or placebo on days 8, 15, 22, and 29 (4 total infusions), and a dose of 30 mg/kg ARGX-117 or placebo every 2 weeks until the end of the DBTP, starting from day 43 (5 total infusions in total).).
• Option 2*Dose regimen 3 (lower dose): a single dose of 15 mg/kg ARGX-117 or placebo on day 1, followed by 4 weekly doses of 5 mg/kg ARGX-117 or placebo on days 8, 15, 22, and 29 (4 total infusions), and a dose of 5 mg/kg ARGX-117 or placebo every 4 weeks, on days 57 and 85, until the end of the DBTP (2 total infusions). Additionally, placebo will be given every 4 weeks, on days 43, 71, and 99.
• Option 3*Dose regimens 2 and 3

Study burden and risks

There was 1 reported serious adverse event (SAE) of *abscess* which was considered not related to IMP (ARGX-117 or placebo).

No SAEs considered related to blinded treatment have been reported.

No deaths or life-threatening events have been reported.

Contacts

Public
argenx BV

Industriepark Zwijnaarde 7
Zwijnaarde (Ghent) B-9052
BE
Scientific
argenx BV

Industriepark Zwijnaarde 7
Zwijnaarde (Ghent) B-9052
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Participants are eligible to be included in the trial only if all of the following criteria apply:
1. Capable of giving signed informed consent as described in Appendix 1, Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol (including consent for the use and disclosure of research-related health information). Participants must be able to read and write and be willing and able to comply with the trial protocol procedures (including attending the required trial visits).
2. Male/female at least 18 years of age at the time the ICF is signed
3. Probable or definite MMN according to the EFNS/PNS 2010 guidelines (Appendix 8: Section 10.8) at screening confirmed by the MCC
4. Receiving a stable IVIg regimen for at least 3 months before screening or recently initiated IVIg treatment (refer to inclusion criterion 5.1a) and both of the following:
a. IVIg treatment interval of 2 to 5 weeks
b. IVIg dose of 0.4 to 2.0 grams per kg body weight and infusion
5.1 IVIg treatment dependency confirmation by the MCC at screening or after IVDP when applicable, based on 1 of the following:
a. Recently initiated IVIg treatment (less than 3 months):
- Clinical improvement following IVIg initiation documented in the participant*s medical record
b. Maintenance therapy with IVIg (longer than 3 months), based on 1 of the following:

- Clinical deterioration following IVIg withdrawal, IVIg dose reduction, or IVIg delayed administration within 12 months prior to screening (documented in the participant*s medical record)
- Clinical deterioration following IVIg delayed administration during the IVDP
6. Immunization with the first meningococcal vaccine and pneumococcal vaccine, and the single Haemophilus influenza type B vaccine must be performed at least 14 days before IMP administration at V1 according to local country-specific immunization schedules. A documented history of vaccination against Neisseria meningitides, Haemophilus influenza type B, and streptococcus pneumonia will be permitted.
7. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies
a. Male participants must agree to not donate sperm from the time the ICF is signed until 15 months after the last IMP administration
b. Women of childbearing potential (WOCBP) (defined in Appendix 4, Section 10.4.1.1) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before IMP can be administered
The contraceptive requirements for WOCBP are described in Appendix 4, Section 10.4.2).

Exclusion criteria

Participants are excluded from the trial if any of the following criteria apply:
1. Any coexisting condition which may interfere with the outcome assessments (eg, diabetic neuropathy, CIDP, inflammatory arthritis, or osteoarthritis affecting the hand)
2. Clinical signs or symptoms suggestive for neuropathies other than MMN such as motor neuron disease (eg, bulbar signs or brisk reflexes) or other inflammatory neuropathies (eg, sensory neuropathy)
3. Severe psychiatric disorder (such as severe depression, psychosis, bipolar disorder), history of suicide attempt, or current suicidal ideation that in the opinion of the investigator could create undue risk to the participant or could affect adherence with the trial protocol. See Section 8.2.6.
Note: At screening, suicidality will be assessed using the Columbia-suicide severity rating scale (C SSRS) (see Section 8.2.6.1); participants with a high suicide risk will be excluded from the trial (ie, participants will be excluded with a positive answer to questions #4 and/or #5 of the suicidal ideation subscale [over the past 3 months]; and/or any positive answer to the suicidal behavior subscale [over the past year]). Any positive answer to the these questions under *Lifetime/time he/she felt most suicidal* should be carefully evaluated for any current risk of suicide by the investigator prior to trial entry.
4. Clinically significant uncontrolled active or chronic bacterial, viral, or

fungal infection during the screening and/or IVMP.
5. Any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of MMN or put the participant at undue risk (eg, SLE).
6. History of malignancy unless resolved by adequate treatment with no evidence of recurrence for >=3 years before the first administration of the IMP.
Participants with the following carcinomas will be eligible:
a. Adequately treated basal cell or squamous cell skin cancer
b. Carcinoma in situ of the cervix
c. Carcinoma in situ of the breast or
d. Incidental histological finding of prostate cancer (TNM stage T1a or T1b)
7. Clinical evidence of other significant serious diseases, (including splenectomy at any time), have had a recent major surgery, or who have any other condition in the opinion of the investigator, that could confound the results of the trial or put the participant at undue risk
8. Prior/concomitant therapy
a. Cyclophosphamide and/or rituximab and/or eculizumab and/or mycophenolate mofetil within 3 months prior to screening
b. Use of an investigational product within 3 months or 5 half-lives (whichever is longer) before the first dose of the IMP.
9. Positive serum test at screening for an active viral infection with any of the following conditions:
a. Hepatitis B virus (HBV) that is indicative of an acute or chronic infection (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf)
b. Hepatitis C virus (HCV) based on HCV antibody assay
c. HIV based on test results that are associated with an AIDS-defining condition or a CD4 count <200 cells/mm3
10. Current or history of (ie, within 12 months of screening) alcohol, drug, or medication abuse
11. Known hypersensitivity reaction to 1 of the components of the IMP or any of its excipients
12. Female participants with a positive serum or urine pregnancy test, lactating females, and those who intend to become pregnant during the trial or within 12
months after last dose of the IMP
13. ALT or AST >=2 × upper limit of normal and total bilirubin >=1.5 × upper limit of normal of the central laboratory reference range, or any other clinically significant
laboratory abnormality. These tests will be performed by the central laboratory
14. An estimated glomerular filtration rate of <=60 mL/min/1.73m2 calculated by the central laboratory using the 4-variable Modification of Diet in the Renal-Disease
(MDRD) equation

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:	Recruiting
Start date (anticipated):	12-12-2022
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ARGX-117-IV
Generic name:	ARGX-117-IV

Ethics review

Approved WMO Date:	27-12-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-02-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	22-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2021-003302-50-NL
ClinicalTrials.gov	NCT05225675
CCMO	NL79411.028.21