A Phase 2 Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Published: 25-03-2020
Last updated: 08-04-2024

Stage A (open-label, efgartigimod PH20 SC; 4-12 weeks [+ 1 optional additional week])Primary objective:• To assess the activity of efgartigimod PH20 SC (efgartigimod co formulated with recombinant human hyaluronidase PH20 [rHuPH20]) based on the...

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

Summary

ID

NL-OMON54028

Source
ToetsingOnline

Brief title
CIDP trial 1802

Condition

- Demyelinating disorders

Synonym
damaged myelin sheath of nerve fibers, Inflammation of peripheral nervous system

Research involving
Human

Sponsors and support

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

Intervention

Keyword: auto-immune desease, CIDP, efgartigimod, Phase2

Outcome measures

Primary outcome

Stage A

Primary endpoint: Percentage of patients with confirmed ECI.

Stage B:

Primary Endpoint :

• Time to first confirmed adjusted INCAT deterioration compared to Stage B baseline.

Note: Time to first confirmed adjusted INCAT deterioration is defined by the time from first dose of double-blind IMP to the first adjusted INCAT score increase of >=1 point compared to Stage B baseline, if the deterioration is confirmed at a consecutive visit 3-7 daysone week after fthe first adjusted INCAT score increase of >=1 point. For patients with an increase of 2 or more points on the adjusted INCAT score compared to Stage B baseline, no confirmation is required.

Secondary outcome

Stage A

Secondary endpoints:

• Evidence of clinical activity:

* Time to initial confirmed ECI.

* Change from Stage A baseline (D1A) over time in:

o Adjusted INCAT score

o Medical Research Council (MRC) Sum score.

o 24-item Inflammatory Rasch-built Overall Disability Scale (I-RODS) disability scores.

o Timed Up-and-go (TUG) score.

o Mean grip strength assessed by Martin vigorimeter.

• Safety:

* Exposure adjusted occurrence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by system organ class (SOC) and preferred term (PT);

* Incidence of clinically significant laboratory abnormalities.

• PK profile:

* Pre-dosing efgartigimod serum concentrations over time during Stage A.

• PD profile:

* Changes of serum IgG levels (total IgG) over time during Stage A.

• Immunogenicity:

* Percentage of patients with and titers of binding antibodies (BAb) towards efgartigimod and/or rHuPH20 during Stage A.

* Presence of neutralizing antibodies (NAb) against efgartigimod and titers of NAb against rHuPH20 during Stage A.

• Changes from D1A in EQ-5D-5L over time

Stage B

Secondary Endpoints:

• Clinical Efficacy:

* Time to CIDP disease progression.

Note: Time to CIDP disease progression is defined by the time from first dose of double-blind IMP to the first I-RODS score decrease >=4 points compared to Stage B baseline using the centile metric.

* Percentage of patients with improved functional level compared to Stage B baseline as measured by an increase in the 24-item I-RODS score up to Week 48.

* Change from Stage B baseline over time in:

o Adjusted INCAT score

o MRC Sum score.

o 24-item I-RODS disability scores.

o TUG score.

o Mean grip strength assessed by Martin vigorimeter.

* Time to 10% decrease in the 24-item I-RODS during Stage B.

• Safety:

* Incidence of TEAEs and SAEs by SOC and PT during Stage B.

* Incidence of clinically significant laboratory abnormalities during Stage B.

• PK Profile:

* Pre-dosing efgartigimod serum concentrations over time during Stage B.

• PD Profile:

* Changes of serum IgG levels (total IgG) over time during Stage B.

• Immunogenicity:

* Percentage of patients with and titers of BAb towards efgartigimod and/or

rHuPH20 during Stage B.

* Presence of NAb against efgartigimod and titers of NAb against rHuPH20 during

Stage B.

• Changes from Stage B baseline in EQ-5D-5L over time

Study description

Background summary

Efgartigimod (ARGX-113) is a human immunoglobulin (Ig) G1-derived Fc of the za allotype that binds with nanomolar affinity to human neonatal Fc receptor (FcRn). Efgartigimod encompasses IgG1 residues D220-K447 (European Union [EU] numbering scheme) and has been modified with the so-called ABDEG* technology (ABDEG* = antibody that enhances IgG degradation)(27) to increase its affinity for FcRn at both physiological and acidic pH. The increased affinity for FcRn of efgartigimod at both acidic and physiological pH results in a blockage of FcRn mediated recycling of IgGs.
Given the essential role of the FcRn receptor in IgG homeostasis, inhibiting this FcRn function, as is achieved by efgartigimod, leads to rapid degradation of all IgGs, including disease associated autoantibodies of the IgG isotype. This approach is thought to result in alleviation of signs and symptoms in IgG-driven autoimmune diseases.
The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous (IV) administrations of efgartigimod have been investigated in the first-in-human trial ARGX 113 1501 in healthy adult subjects. A second trial ARGX-113-1702 in healthy adult subjects investigated the bioavailability, safety, tolerability, immunogenicity, PK, and PD following SC administration of efgartigimod and evaluated the reduction of the IV infusion time from 2 hours to 1 hour.
Phase 2 trials in immune thrombocytopenia (ITP; ARGX 113 1603) and myasthenia gravis (MG; ARGX 113 1602) have indicated that efgartigimod administered by IV infusion is well tolerated, induces a specific, rapid PD effect (ie, reduction in IgG levels, including autoantibody levels), and is associated with improvement in clinical signs and symptoms in patients with ITP and MG, separately.(10) Additionally, the safety and tolerability of efgartigimod is being evaluated for the treatment of patients with pemphigus in the Phase 2 trial ARGX-113-1701 and for the treatment of patients with MG in the Phase 3 trial ARGX 113 1704.
For this Phase 2 trial in patients with CIDP, a fixed dose of efgartigimod PH20

SC was selected based on the results of the Phase 1 trial ARGX 113 1901 in healthy subjects that achieved a similar pharmacodynamic effect as that observed in generalized myasthenia gravis (gMG) and ITP, ie, IgG reduction, at steady state as achieved by weekly 10 mg/kg IV infusions. Doses of 10 mg/kg efgartigimod IV have demonstrated a favorable safety and efficacy profile across Phase 2 trials in MG and ITP patients. To select the fixed SC dose, an open label, parallel group trial in healthy male patients subjects (ARGX-113-1901) has been performed to investigate the PK, PD, safety, and tolerability of different single fixed SC dose levels of efgartigimod co administered with rHuPH20.
In the current trial, efgartigimod is co formulated with the permeation enhancer rHuPH20 (efgartigimod PH20 SC). rHuPH20 acts as a spreading factor that increases the dispersion and absorption of other co administered drugs and allows SC dosing of greater volumes than without rHuPH20. SC injections of rHuPH20 with fluids, small molecules, peptides, and proteins (eg, IgG) were well-tolerated in all clinical trial populations studied to date

Study objective

Stage A (open-label, efgartigimod PH20 SC; 4-12 weeks [+ 1 optional additional week])
Primary objective:
• To assess the activity of efgartigimod PH20 SC (efgartigimod co formulated with recombinant human hyaluronidase PH20 [rHuPH20]) based on the percentage of patients classified as treatment responders.
Secondary objectives:
• To assess the time to clinical improvement.
• To determine the treatment effect of efgartigimod PH20 SC based on clinical functional assessments of motor function and muscle strength.
• To assess the short-term safety and tolerability of efgartigimod PH20 SC.
• To assess the pharmacokinetics (PK) of efgartigimod PH20 SC.
• To assess the pharmacodynamic (PD) effect of efgartigimod PH20 SC.
• To assess the immunogenicity of efgartigimod and rHuPH20.
• To assess the EuroQol 5 dimensions and 5 levels health-related qualityof-life questionnaire (EQ-5D-5L)

Stage B (double-blind, randomized-withdrawal, efgartigimod PH20 SC or placebo; up to 48 weeks)
Primary objective:
• To determine the efficacy of efgartigimod PH20 SC compared to placebo based on the time needed for the occurrence of the first evidence of clinical deterioration.
Secondary objectives:
• To determine the efficacy of efgartigimod PH20 SC compared to placebo based on clinical functional assessments of disease disability and motor function and muscle strength.
• To assess the safety and tolerability of efgartigimod PH20 SC.

• To assess the PK of efgartigimod PH20 SC.
• To assess the PD effect of efgartigimod PH20 SC.
• To assess the immunogenicity of efgartigimod and rHuPH20.
• To assess the EQ-5D-5L

Study design

After a screening period for all patients and a run-in period for applicable patients (not for treatment-naïve patients), all patients will enter the open-label Stage A at baseline (D1A) and receive weekly trial treatment (efgartigimod PH20 SC) for up to 12 weeks (with optional 1 additional week). The trial will include the following periods:
• Screening period: up to 28 days
• Run-in period: 4-12 weeks (not for treatment-naïve patients;
• Stage A will be a period of up to 12 weeks (with optional 1 additional week) of open label treatment of efgartigimod PH20 SC (weekly trial visits).
• Stage B will be a period of up to 48 weeks of double-blind, randomized-withdrawal treatment of efgartigimod PH20 SC or of placebo (trial visits once every 4 weeks) ().
• Follow-up: 28 days after the last dose of investigational medicinal product (IMP) or the Week 48 visit if the patient does not intend to roll over into the open-label extension (OLE) trial ARGX-113-1902.

Total trial duration for each patient can be up to 81 weeks with a maximum of 61 weeks on IMP.
An independent DSMB will be used in this trial
During the different trial periods (run in, Stage A, and Stage B), there is a permissible window of ±2 days for the trial visits (and ±3 days for the safety follow-up visit) as described in the schedule of activities
Patients who discontinue early from treatment, after they have completed the assessments of the current visit will be encouraged to return for all remaining scheduled visits as per SoA , unless they withdraw consent

Intervention

Patients eligible for Stage A will receive open-label IMP as weekly SC administrations of efgartigimod PH20 SC for up to 12 weeks

Stage B is a double blind, randomised treatment of efgartigimod PH20 SC or placebo

Study burden and risks

Risks
No major safety findings have arisen in the ongoing and completed trials, nor any pattern of adverse events (AEs) which would raise concerns or alter the

potential benefit-risk profile of efgartigimod.
In clinical trials to date, efgartigimod has been well-tolerated in healthy adult subjects and patients with gMG and ITP, separately: the majority of treatment-emergent adverse events (TEAEs) were considered to be mild (grade 1) in severity. No TEAEs of grade >=3 have been reported. The most common TEAE suspected to be related to efgartigimod is headache; however, there is no evidence that headache occurs more frequently in patients administered efgartigimod than in patients administered placebo.

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

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. Ability to understand the requirements of the trial, provide written informed consent, willingness and ability to comply with the trial protocol procedures.
2. Male or female patient aged 18 years or older, at the time of signing the informed consent.
3. Diagnosed with probable or definite CIDP according to criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS, 2010),(11) progressing or relapsing forms.
4. CIDP Disease Activity Status (CDAS)(14) score >=2 at screening.
5. An INCAT score >=2, with a score of 2 exclusively from leg disability, at the first run-in visit (RI-V1; for patients entering run-in) or Stage A baseline (A-V1; for treatment-naïve patients with documented evidence for worsening on the total adjusted INCAT disability score within 3 months prior to screening).
6. Fulfilling any of the following treatment conditions:
• Currently treated with pulsed corticosteroids, oral corticosteroids equivalent to prednisolone/prednisone <=10 mg/day, and/or IVIg or SCIg, if this treatment has been started within the last 5 years before screening, and the patient is willing to discontinue this treatment at the first run-in visit (RI-V1); OR
• Without previous treatment (treatment-naïve); OR
• Treatment with corticosteroids and/or IVIg or SCIg discontinued at least 6 months prior to screening.
Note: Patients not treated with monthly or daily corticosteroids, IVIg or SCIg for at least 6 months prior to screening are considered as equal to treatment naïve patients.
7. Women of childbearing potential who have a negative serum pregnancy test at screening and a negative urine pregnancy test up to Stage A baseline (D1A).
8. Women of childbearing potential must use an acceptable method of contraception from signing the ICF until the date of the last dose of IMP.
9. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a condom and his partner must use a highly effective method of contraception from screening to 90 days after the last administration of IMP. Male patients practicing true sexual abstinence (when this is in line with the preferred and usual life style of the participant) can be included. Sterilized male patients who have had vasectomy with documented aspermia post-procedure can be included. In addition, male patients are not allowed to donate sperm from screening to 90 days after the last administration of IMP.

Exclusion criteria

1. Pure sensory atypical CIDP.
2. Polyneuropathy of other causes, including the following:
-Multifocal motor neuropathy;
-Monoclonal gammopathy of uncertain significance with anti-myelinassociated

glycoprotein immunoglobulin M (IgM) antibodies;
-Hereditary demyelinating neuropathy;
-Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin change syndromes;
-Lumbosacral radiculoplexus neuropathy;
-Polyneuropathy most likely due to diabetes mellitus;
-Polyneuropathy most likely due to systemic illnesses;
-Drug- or toxin-induced polyneuropathy.
3. Any other disease that could better explain the patient's signs and symptoms.
4. Any history of myelopathy or evidence of central demyelination.
5. Current or past history (within 12 months of screening) of alcohol, drug or medication abuse.
6. Severe psychiatric disorder, history of suicide attempt, or current suicidal ideation that in the opinion of the investigator could create undue risk to the patient or could affect adherence with the trial protocol.
7. Patients with clinically significant active or chronic uncontrolled bacterial, viral, or fungal infection at screening, including patients who test positive for an active viral infection at screening with:
* Active Hepatitis B Virus (HBV): serologic panel test results indicative of an active (acute or chronic) infection;
* Active Hepatitis C Virus (HCV)
* Human Immunodeficiency Virus (HIV) positive serology associated with an Acquired Immune Deficiency Syndrome (AIDS)-defining condition or with a cluster of differentiation 4 (CD4) count <=200 cells/mm3.
8. Total IgG level <6 g/L at screening.
9. Treatment with the following:
-Within 3 months (or 5 half-lives of the drug, whichever is longer) before screening: plasma exchange or immunoadsorption, any concomitant Fccontaining therapeutic agents or other biological, or any other investigational product;
-Within 6 months before screening: rituximab, alemtuzumab, any other monoclonal antibody, cyclophosphamide, interferon, tumor necrosis factor-alpha inhibitors, fingolimod, methotrexate, azathioprine, mycophenolate, any other immunomodulating or immunosuppressive medications, and oral daily corticosteroids >10 mg/day.
Note: Patients using IVIg, SCIg, pulsed corticosteroids, and oral daily corticosteroids <=10 mg/day can be included.
-Patients who (intend to) use prohibited medications and therapies during the trial.
10. Pregnant and lactating women and those intending to become pregnant during the trial.
11. Patients with any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of CIDP.
12. Patients who received a live-attenuated vaccine fewer than 28 days before screening. Receiving an inactivated, sub-unit, polysaccharide, or conjugate vaccine any time before screening is not exclusionary.
13. Patients who have a history of malignancy unless deemed cured by adequate

treatment with no evidence of recurrence for >=3 years before the first IMP administration. Patients with the following cancer can be included anytime:
-Adequately treated basal cell or squamous cell skin cancer,
-Carcinoma in situ of the cervix,
-Carcinoma in situ of the breast, or
-Incidental histological finding of Prostate cancer
14. Patients who previously participated in a trial with efgartigimod and have received at least one administration of IMP.
15. Patients with known medical history of hypersensitivity to any of the ingredients of IMP.
16. Patients with clinical evidence of other significant serious disease or patients who underwent a recent or have a planned major surgery, or any other reason which could confound the results of the trial or put the patient at undue risk.

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):	30-09-2021
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	efgartigimod PH20 SC

Generic name:	efgartigimod PH20 SC

Ethics review

Approved WMO Date:	25-03-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-01-2022
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2019-003076-39-NL
CCMO	NL72659.078.20