A Phase 3, Multicenter, Open-label, Long-term Trial to Evaluate the Safety and Efficacy of Efgartigimod (ARGX-113) 10 mg/kg Intravenous in Adult Patients With Primary Immune Thrombocytopenia

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Primary Objective:* To evaluate the long-term safety of efgartigimod in adult patients with primary immune thrombocytopenia (ITP).Secondary Objectives:First 52-week treatment period only:* To evaluate the long-term efficacy of efgartigimod on...

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

Summary

ID

NL-OMON55305

Source
ToetsingOnline

Brief title
ADVANCE+ (ARGX-113-1803)
2682/0012

Condition

- Autoimmune disorders

Synonym
Primary Immune Thrombocytopenia;Werlhof's disease

Research involving
Human

Sponsors and support

Primary sponsor: argenx BV
Source(s) of monetary or material Support: The study sponsor as completed under B7

Intervention

Keyword: Efgartigimod, Open label, Phase 3, Primary Immune Thrombocytopenia

Outcome measures

Primary outcome

Frequency and severity of AEs, vital signs, and laboratory assessments.

Secondary outcome

First 52-week treatment period only:

1. Extent of disease control defined as the percentage of weeks in the trial

with platelet counts of *50×10^9/L.

2. Percentage of patients with overall platelet count response defined as

achieving a platelet count of *50×10^9/L on at least 4 occasions at any time

during the 52-week treatment period.

3. Mean change from baseline in platelet count at each visit.

4. For patients rolling-over from the ARGX-113-1801 trial with a platelet count

of <30×10^9/L: time to response is defined as the time to achieve 2 consecutive

platelet counts of *50×10^9/L.

5. The percentage of weeks in the with platelet counts of *30×10^9/L and at

least 20×10^9/L above baseline.

6. In patients with baseline platelet count of <15×10^9/L in the current trial

(ARGX-113-1803), the percentage of weeks in the trial with platelet counts of

*30×10^9/L and at least 20×10^9/L above baseline.

7. In patients with first exposure to efgartigimod: proportion of patients who achieve a sustained platelet response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the trial.

8. In patients with first exposure to efgartigimod: proportion of patients in the overall population achieving platelet counts of at least 50×10^9/L for at least 6 of the 8 visits between week 17 and 24 of the trial.

9. Rate of receipt of rescue therapy (rescue per patient per month).

10. Reduction in concurrent ITP therapy.

11. Incidence and severity of the WHO-classified bleeding events.

12. Change from baseline in PRO (FACIT-Fatigue, Fact-Th6) and QoL (SF-36) at planned visits.

13. Pharmacokinetic parameter of efgartigimod: serum concentration observed predose (Ctrough).

14. Pharmacodynamics markers: total IgG.

First 52-week treatment period and additional 52-week treatment periods:

15. Incidence of anti-drug antibodies (ADA) to efgartigimod.

Study description

Background summary

Efgartigimod (ARGX-113) is a modified human immunoglobulin (Ig) G1-derived crystallized fragment (Fc) of the za allotype that binds with nanomolar affinity to the human neonatal crystallized fragment receptor (FcRn). 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. Phase 2 trials in immune thrombocytopenia (ITP) and myasthenia gravis (MG) have indicated that efgartigimod administered by IV infusion is well tolerated; induces a specific, rapid, and profound PD effect (i.e. reduction in IgG levels, including autoantibody levels); and is associated with improvement in clinical signs and symptoms in ITP and MG patients, separately. Additionally, the safety and tolerability of efgartigimod is currently being evaluated for the treatment of patients with pemphigus in a phase 2 trial.

Primary ITP is an acquired autoimmune bleeding disorder characterized by an isolated low platelet count (<100×10^9/L) in the absence of other causes or disorders associated with thrombocytopenia. Prevalence of ITP is estimated at 9.5 per 100,000 adults, and incidence rates have been reported at 3.3 adults per 100,000 years. In adults, the prevalence of ITP increases with age. Adult ITP can persist for years. Even with best available care, patients rarely achieve long-term remission, and often require multiple treatment options.

Targeted and selective IgG reduction, as achieved by efgartigimod, has the potential as an effective new treatment in ITP seen the central role of IgG autoantibodies in the pathophysiology of ITP. It represents a novel mechanism of action distinct from that of other existing treatments which are either broadly immunosuppressive or stimulate thrombopoiesis.

Please refer to protocol section 1.1 for further details

Study objective

Primary Objective:
* To evaluate the long-term safety of efgartigimod in adult patients with primary immune thrombocytopenia (ITP).

Secondary Objectives:
First 52-week treatment period only:
* To evaluate the long-term efficacy of efgartigimod on overall platelet count response.
* To explore the potential for reduction in concurrent ITP therapy.
* To evaluate the effects of efgartigimod treatment on quality-of-life (QoL) measures and patient-reported outcomes (PRO).
To evaluate the incidence and severity of bleeding events while receiving treatment with efgartigimod.
To evaluate the use of rescue treatment while receiving treatment with efgartigimod.
* To assess the pharmacodynamic (PD) effects of efgartigimod.
* To evaluate the pharmacokinetics (PK) of efgartigimod.

First 52-week treatment period and additional 52-week treatment periods:
* To assess the immunogenicity of efgartigimod.

Study design

(This is a summary, for more detailed information please refer to the protocol)

This is a phase 3, multicenter, open-label, long-term extension of the phase 3 randomized, double-blinded, placebo-controlled, parallel-group trial (ARGX-113-1801; ADVANCE) to evaluate the safety and efficacy of efgartigimod 10 mg/kg intravenous (IV) treatment in adult patients with primary ITP.

The target population is the patients from the ARGX-113-1801 trial Patients will be offered the opportunity to enroll in this trial if they completed the 24 week trial period in trial ARGX-113-1801.

CHANGE IN EFGARTIGIMOD DOSING FREQUENCY
The assessment of dosing frequency of IV infusions of efgartigimod 10 mg/kg will continue as in the ARGX-113-1801 trial (i.e. weekly or every other week [q2w]). If patients were on a fixed dosing frequency in the ARGX-113-1801 trial, a change in dosing frequency is permitted as from visit 1 (baseline).

EARLY DISCONTINUATION
Patients who have an *insufficient response* by visit 12 will exit the trial.
An *insufficient response* is defined as a platelet count of <30×10^9/L in all of the last 4 visits between visit 9 and visit 12 (both visits inclusive).
Any patient prematurely discontinuing the trial (with the exception of patients who withrdraw their consent) should perform the assessments listed for the Early Discontinuation visit 1 week after the last visit performed in the treatment period as specified in the SoA (Table 1) and complete the 4-week treatment-free follow-up after the Early Discontinuation visit.

SAMPLE SIZE
The maximum number of patients will be the number of patients who completed the 24-week trial period of the ARGX-113-1801 trial.

CONCURRENT ITP THERAPY
As from the start of the trial, for patients already receiving permitted concurrent ITP therapy, a decrease in the dose and/or schedule of permitted concurrent ITP therapy is allowed (permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, fostamatinib, and/or oral thrombopoietin receptor agonists [TPO-RAs]).
New concurrent ITP therapy cannot be started.

RESCUE THERAPY
Rescue therapy is allowed post-baseline and throughout the trial for patients with a platelet count of <30×10^9/L and 1 of the following:

- an immediate risk of bleeding or a clinically significant bleeding, or wet purpura
- requirement for urgent or emergent surgery (elective surgeries must be postponed until trial completion)

Intervention

IV infusions of efgartigimod 10 mg/kg will continue as in the ARGX-113-1801 trial (i.e. weekly or biweekly). If patients were on a fixed dosing frequency in the ARGX-113-1801 trial, a change in dosing frequency is permitted as from visit 1 (baseline).

Study burden and risks

Efgartigimod has been shown to effectively reduce IgG antibodies in several clinical trials, including healthy volunteers, patients with MG, and with ITP. In clinical trials to date, efgartigimod has been well-tolerated in healthy adult subjects and patients with MG and ITP, separately: the majority of treatment-emergent AEs (TEAEs) were considered to be mild (grade 1) in severity. In the completed phase 1 trials ARGX 113 1501, ARGX 113 1702, and ARGX 113 1901 in healthy volunteers, and in the phase 2 trial ARGX-113-1602 in patients with MG, no grade *3 TEAEs were reported and no TEAE led to discontinuation. In patients with ITP, 1 TEAE with grade 4 was reported (thrombocytopenia), considered unrelated to treatment, and led to treatment discontinuation.

No clinically significant changes in vital signs and/or electrocardiogram (ECG) findings have been observed in clinical trials to date.
Safety for use during pregnancy has not been established. Therefore, efgartigimod should not be administered to pregnant or lactating women. Reproductive toxicity trials are completed and in reporting phase.

Please refer to protocol section 1.2 for further details.

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. Ability to understand the requirements of the trial, to provide written informed consent (including consent for the use and disclosure of research-related health information), and to comply with the trial protocol procedures (including required trial visits).
2. Patients enrolled in the ARGX-113-1801 trial who completed the 24 week trial period.
3. Women of childbearing potential must have a negative urine pregnancy test at baseline before trial medication (infusion) can be administered. Women are considered of childbearing potential unless they are post-menopausal (defined by continuous amenorrhea) for at least 1 year with a follicle-stimulating hormone (FSH) of >40 IU/L or are surgically sterilized (i.e. women who had a hysterectomy, a bilateral salpingectomy, both ovaries surgically removed, or have a documented permanent female sterilization procedure including tubal ligation). Follicle-stimulating hormone can be used to confirm post-menopausal status in amenorrheic patients not on hormonal replacement therapy.
4. Women of childbearing potential should use a highly effective or acceptable method of contraception during the trial and for 90 days after the last administration of the IMP. They must be on a stable regimen, for at least 1 month:
* combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
o oral
o Intravaginal
o Transdermal

* progestogen-only hormonal contraception associated with inhibition of ovulation:
o Oral
o Injectable
o Implantable
* intrauterine device (IUD)
* intrauterine hormone-releasing system
* bilateral tubal occlusion
* vasectomized partner (provided that the partner is the sole sexual partner of the trial participant and that aspermia was documented post procedure)
* continuous abstinence from heterosexual sexual contact. Sexual abstinence is only allowable if it is the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.
* male or female condom with or without spermicide
* cap, diaphragm, or sponge with spermicide
5. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use an acceptable method of contraception, ie, a condom. Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle 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 during this period from signing of informed consent form, throughout the duration of the trial, and for 90 days after the last administration of IMP.

In addition to the above criteria, for patient who want to continue receiving efgartigimod during an additional 52-week treatment period (only applicable in case efgartigimod is not yet commercially available for patients with primary ITP, or becomes available through another patient program for patients with primary ITP:
6. Ability to understand the requirements of the additional 52-week treatment period of the trial, to provide written informed consent (including consent for the use and disclosure of research-related health information), and to comply with the trial protocol procedures (including required trial visits).
7. Patient has completed a 52-week treatment period.

Exclusion criteria

1. Introduction or continuation of non-permitted medications during the ARGX-113-1801 trial (such as anti-CD20 therapy, romiplostim, monoclonal antibodies, Fc fusion proteins, or live/live-attenuated vaccines).
2. Pregnant or lactating women, and those intending to become pregnant during the trial or within 90 days after the last dosing.
3. Patients with known medical history of hypersensitivity to any of the ingredients of efgartigimod.

4. Use of any other investigational drug or participation in any other investigational trial.

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:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Efgartigimod
Generic name:	N/A

Ethics review

Approved WMO Date:	07-01-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-05-2020
Application type:	First submission

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-03-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-03-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2019-002101-21-NL
ClinicalTrials.gov	NCT04225156
CCMO	NL71448.100.19