A Two-Year, Two-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Diabetic Macular Edema

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Retina, choroid and vitreous haemorrhages and vascular disorders
Study type	Interventional

Summary

ID

NL-OMON50742

Source
ToetsingOnline

Brief title
CRTH258B2301 (KESTREL)

Condition

- Retina, choroid and vitreous haemorrhages and vascular disorders

Synonym
Diabetic Macular Edema DME

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: Aflibercept, Brolucizumab, Diabetic Macula Edema

Outcome measures

Primary outcome

To demonstrate that brolucizumab is noninferior to aflibercept with respect to

the visual outcome after the first year of treatment. Measured as change from

baseline in BCVA at Week 52.

Secondary outcome

- To demonstrate that brolucizumab is noninferior to aflibercept with respect

to visual outcome during the last 3 months of the first year of treatment

- To estimate the proportion of patients treated at q12w frequency with

brolucizumab

- To estimate the predictive value of the first q12w cycle for maintenance of

q12w treatment with brolucizumab

- To evaluate the functional and anatomical outcome with brolucizumab relative

to aflibercept

- To evaluate the effect of brolucizumab relative to aflibercept on the

Diabetic Retinopathy status

- To assess the safety and tolerability of brolucizumab relative to aflibercept

- To evaluate the effect of brolucizumab relative to aflibercept on

patient-reported outcomes (VFQ-25)

Study description

Background summary

Diabetic retinopathy (DR) and diabetic macular edema (DME) are common microvascular complications in patients with diabetes and may have a debilitating impact on visual acuity (VA), eventually leading to blindness.
For anti-VEGF agents like ranibizumab or aflibercept a favorable benefit risk ratio was demonstrated with superior efficacy versus the previous standard of care (laser photocoagulation) in large Phase 3 programs that consequently led to their approval for the treatment of DME. Anti-VEGF treatment led to clinically relevant improvements of BCVA, reduction of fluid accumulation and decreased severity of diabetic retinopathy.
The current treatment options for patients with DME are: laser photocoagulation, IVT corticosteroids, IVT corticosteroid implants, or IVT anti-VEGF. Due to the efficacy and safety profile of anti-VEGF therapy, it has become the first-line treatment. Corticosteroids are used as a second line treatment and focal / grid laser photocoagulation remains a therapeutic option, but with a lower expected benefit compared with steroid and anti-VEGF therapy. Despite the treatment success of existing anti-VEGFs, there remains a need for further treatment options to improve response rate and/or reduce resource use and injection frequency in patients with DME.
Brolucizumab is a humanized single-chain fragment variable (scFv), binding to VEGF-A.

Study objective

In this study we want to find out how safe and effective is the new product brolucizumab. Brolucizumab is administered in this study to subjects with decreased sight due to diabetes macular edema. The effects of brolucizumab are compared with those of the long-standing drug aflibercept (brand name Eylea). We want to assess the effects of both treatments. At this moment we do not know which of the two treatments works best. That is why we are going to compare the effects.

Study design

This study investigates the effects of brolucizumab and aflibercept in patients with visual impairment due to fluid accumulation in the macula of the eye due to diabetes. The research takes about 2 years. The study consists of the screening of 2 weeks and a treatment period of approximately 100 weeks. There are 29 visits in which various examinations are conducted to monitor the

patient's health and to investigate the effect and safety of the medication.
There are 3 study arms: 3 and 6 mg brolucizumab and 2mg aflibercept. Patients are randomized into one of the treatment arms in the 1: 1: 1 ratio.

Intervention

The investigational treatments used in this study are:
* Brolucizumab 3 mg/0.05 mL
* Brolucizumab 6 mg/0.05 mL
The control treatment is:
* Aflibercept 2 mg/0.05 mL

-Brolucizumab 3 mg/0.05 mL 5 x q 6w loading then q12w/q8w maintenance
-Brolucizumab 6 mg/0.05 mL 5 x q6w loading then q12w/q8w maintenance
-Aflibercept 2 mg/0.05 mL 5 x q4w loading then q8w maintenance

Study burden and risks

Patients will have to come to the clinic 29 times in 102 weeks. Each visit will take approximately 3 hours. All study procedures conducted at each visit are standard medical procedures:
-Injection into the eye
-Eye drops used for eye examination
-OCT imaging and Fundus Photography
-Blood draws

No major complications caused by the study procedures or treatment are expected

Expected benefit is that sight of patients will improve. In this study placebo is also an anti-VEGF treatment so there is no risk of sub-optimal treatment.

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

General
- Patients must give written informed consent before any study related assessments are performed
- Patients *18 years of age at baseline
- Patients with type 1 or type 2 diabetes mellitus and HbA1c of *10% at screening
- Medication for the management of diabetes must have been stable within 3 months prior to randomization and is expected to remain stable during the course of the study
Study Eye:
- Visual impairment due to DME with:
*BCVA score between 78 and 23 letters, inclusive, using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320), at screening and baseline
*DME involving the center of the macula, with central subfield retinal thickness (measured from RPE to ILM inclusively) of *320 *m on SDOCT at screening If both eyes are eligible, the eye with the worse visual acuity will be selected for study eye. However, the investigator may select the eye with better visual acuity, based on medical reasons or local ethical requirements.

Exclusion criteria

- Previous treatment with any anti-VEGF drugs or investigational drugs in the

study eye
- Active proliferative diabetic retinopathy in the study eye as per the investigator
- Concomitant conditions or ocular disorders in the study eye at screening or baseline which could, in the opinion of the investigator, interfere with study results
- Any active intraocular or periocular infection or active intraocular inflammation in study eye at screening or baseline
- Structural damage of the fovea in the study eye at screening likely to preclude improvement in visual acuity following the resolution of macular edema.
- Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP)> 25 mmHg on medication or according to investigator*s judgment, at screening or baseline
- Neovascularization of the iris in the study eye at screening or baseline
- Evidence of vitreomacular traction in the study eye at screening or baseline which, in the opinion of the investigator, affect visual acuity

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-11-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Beovu
Generic name:	brolucizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Eylea
Generic name:	aflibercept
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-04-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-09-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	21-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-004742-23-NL
ClinicalTrials.gov	NCT03481634
CCMO	NL64794.056.18