A phase 2b randomized, double-masked, controlled trial to establish the safety and efficacy of intravitreous administration of Fovista® (Anti-PDGFBB pegylated aptamer) administered in combination with Avastin® compared to Avastin® monotherapy in subjects with subfoveal neovascular age-related macular degeneration.

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The objective of this trial is to evaluate the safety and efficacy of the combination of Fovista® intravitreous administration with Avastin® compared to Avastin® monotherapy.

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

Summary

ID

NL-OMON43730

Source
ToetsingOnline

Brief title
OPH1007

Condition

- Vision disorders

Synonym
retina aging

Research involving
Human

Sponsors and support

Primary sponsor: OPHTHOTECH CORPORATION
Source(s) of monetary or material Support: OPHTHOTECH CORPORATION

Intervention

Keyword: age-related wet macular degeneration, choroidal neovascularization, eye disorder

Outcome measures

Primary outcome

The primary efficacy endpoint is the mean change in visual acuity (ETDRS

letters) from baseline at the Month 18 visit.

Secondary outcome

Efficacy Endpoints:

* The proportion of subjects in each treatment group gaining 20 or more ETDRS

letters from baseline at the Month 18 visit.

* The proportion of subjects in each treatment group gaining 25 or more ETDRS

letters from baseline at the Month 18 visit.

* The proportion of subjects in each treatment group losing 5 or more ETDRS

letters from baseline at the Month 18 visit.

* The mean change in visual acuity (ETDRS letters) from baseline at the Month 5

and Month 11 visit.

Safety Endpoints

* Adverse events (AEs) and serious adverse events (SAEs)

* Vital signs (pulse, systolic and diastolic blood pressure)

* Ophthalmic variables (IOP, ophthalmic examination, fluorescein angiograms and

OCT)

* ECG (12-lead)

* Laboratory variables (blood: hematology, renal function, hepatic function,

and electrolytes; urinalysis)

Study description

Background summary

Age-related macular degeneration is a disease characterized by progressive degenerative abnormalities in the macula of the eye, a small area in the central portion of the retina. It is characteristically a disease of individuals >50 years of age and is the leading cause of visual loss in developed countries.
Neovascular proliferation is the key step in wet AMD development. These abnormal vessels consist of endothelial cells, pericytes, and inflammatory cells. Two factors that play important roles in proliferation and maintenance of abnormal blood vessels are VEGF and Platelet Derived Growth Factor (PDGF). VEGF is an endothelial cell survival factor and a key mediator in the process of neovascularization. It is also one of the most potent inducer of vascular permeability in biologic systems.
PDGF is a growth factor responsible for pericyte survival, maturation and regulation.
The neovascularization process is complex and anti-VEGF resistance may result from multiple mechanisms including endothelial cell protection by pericytes. Simultaneous and selective inhibition of both VEGF and PDGF has the potential to have significantly more impact on abnormal vessels than inhibition of the VEGF alone [9].
Pharmacology studies indicate that Fovista® binds to PDGF-B with high specificity and affinity and inhibits the functions of PDGF-B both in vitro and in vivo. In a highly powered, randomized controlled Phase 2 trial combining Fovista® with an anti-VEGF agent in the treatment of neovascular AMD, combination therapy proved superior in terms of mean visual gain when compared to eyes that were treated with anti-VEGF monotherapy

Study objective

The objective of this trial is to evaluate the safety and efficacy of the combination of Fovista® intravitreous administration with Avastin® compared to Avastin® monotherapy.

Study design

Subjects will be treated with study treatment, i.e., active Fovista® or sham (an empty syringe without a needle) in combination with Avastin®, every month for the first 6 doses and bimonthly thereafter.
Depending on how the patient reacts to the treatments, additional treatments may be given. (see schedule of assessments in chapter 3 of the protocol)

The study is 18 months in duration (17 months treatment, 1 month follow-up) preceeded by a screening period of 14 days to see if the patient is eligible.

Intervention

Subjects will be randomized in a 1:1 ratio to the following dose groups:

* Fovista® 1.5 mg/eye + Avastin® 1.25 mg/eye
* Fovista® sham + Avastin® 1.25 mg/eye

Study burden and risks

The study drug and procedures in this study have risks, discomforts, and side effects associated with them. Side effects are any undesirable actions or effects of a drug.

Effects from the Intravitreous Injection
Participants receiving an injection of Fovista®or Avastin® may experience some side effects that may be related to the pre-injection preparation procedure (eyelid speculum, anesthetic drops or injection, dilating drops, antibiotic drops, and povidone-iodine drops) or the injection itself. These side effects may include eye pain, bloodshot eye (subconjunctival hemorrhage), vitreous floaters (small dark shapes that float through your field of vision), irregularity or swelling of the cornea, inflammation of the eye, cataract (clouding of the lens of the eye), increased pressure within the eye, and visual disturbances. If you have a history of glaucoma, you may be at more risk for experiencing increased pressure within your eye after an injection of any substance. Although not common, injections into the eye can cause side effects such as infections, retinal detachment (retina separates from the back of the eye), or bleeding.

General Effects of Avastin®

The following side effects have been observed in treatment with Avastin®:

Eye-related events
Avastin® has been studied in humans in previously completed research studies. Temporary redness of the injected eye, minor bleeding at the injection site that resolves on its own (doesn*t require treatment), dull pain in the injected eye, sensitivity to light, mild and temporary burning and stinging, vision disturbances including decrease in vision, bleeding inside the injected eye that resolves on its own, infection outside the treated eye, and mild and self-resolving inflammation on the inside of the eye.

Less frequent side effects include infection inside the eye (endophthalmitis), severe inflammation in the inside of the eye (uveitis), blockage of the blood flow in the main vein inside the eye (central retinal vein occlusion), temporary increase in the pressure inside the eye (intraocular pressure), damage to the lens inside the eye (cataract formation), a tear through the retinal tissue in the eye (retinal tear/detachment), a rip in the pigment cell layer that lies beneath and nourishes the retina (retinal pigment epithelial [RPE] tear), and inadequate response of the pupil to light entering the eye. Some of the complications listed above may result in permanent loss of vision or loss of the eye.

Non-eye related events
Tests have shown that low levels of Avastin® can reach your blood stream after injection into the eye. The significance of this is not well understood. The risk of having another side effect involving a body system other than the eye is unknown but is believed to be very small. Additional serious side effects have been associated with Avastin® when it is given at high levels (more than 300 times the amount injected into the eye) directly into the blood stream for cancer patients. Strokes, transient ischemic attacks (TIAs), heart attacks, and angina (heart-related chest pain) were 2 to 3 times more common in cancer patients receiving Avastin® than in cancer patients not receiving Avastin®. In addition, intestinal perforations, wound healing complications, bleeding, high blood pressure, protein in the urine, infections, and congestive heart failure have been more common in cancer patients receiving Avastin®. Avastin® may have side effects that are unknown.

General Effects of Fovista®
Fovista® has been tested in combination with Lucentis® (ranibizumab) in 22 research participants in a Phase 1 study. These participants received up to three monthly intravitreal injections of Fovista® at one of four doses (0.03, 0.3, 1.5 or 3 mg/eye) in combination with Lucentis® 0.5 mg/eye. In this Phase 1 study, Fovista® combined with Lucentis® was well tolerated. No dose-limiting toxicity or drug-related side effects were reported at any of the dose levels investigated. Almost all participants with side effects experienced these effects in the study eye, which are expected and which were related to the

injection procedure and not to Fovista®. No side effects in the eye or the rest of the body were related to Fovista®. The most frequently occurring side effects, regardless of cause, were events that occurred in the study eye, including foreign body sensation in the eye, conjunctival hemorrhage (bleeding in the clear tissue that surrounds the white of the eye), eye irritation, and punctate keratitis (irritation of the cornea). Almost all side effects were attributed to the intravitreal injection procedure, and none were attributed to Fovista®. The majority of side effects were mild in severity.

A Phase 2 study has recently been completed of Fovista® given in combination with Lucentis® (ranibizumab) in a total of 449 research participants. Participants received six monthly intravitreous injections of Fovista® given in combination with Lucentis®. They were randomized in a 1:1:1 (equal) ratio to the following dose groups: Fovista® 0.3 mg/eye + Lucentis® 0.5 mg/eye, Fovista® 1.5 mg/eye + Lucentis® 0.5 mg/eye, or Fovista® sham + Lucentis® 0.5 mg/eye. Combination therapy in this Phase 2 study was well tolerated. The most common ocular side effects were, as expected in intravitreal studies, related to the intravitreal preparation and injection procedure and were not drug-related, for example, conjunctival hemorrhage (bleeding in the clear tissue that surrounds the white of the eye), punctate keratitis (irritation of the cornea), and eye pain. There were no events of endophthalmitis (infection inside the eye), retinal detachment (retina separates from the back of the eye), retinal tear (a tear in the retina), or traumatic cataract (clouding of the lens of the eye directly due to the injection procedure). As expected, the mean intraocular pressure (IOP) increased after each intravitreal injection consistent with the increase in volume after the injection. However, the mean IOP returned to pre-injection level at the next visit, including at the end of the study. Some of these side effects may cause decreased vision.

Non-eye related events
The safety profile of the combination of Fovista®/Lucentis® was similar to that of Lucentis® given alone. Fovista® may have side effects that are unknown.

Fovista® has also been tested in animals, and there were no significant ocular or systemic (general body) safety issues noted. Full testing in animals to see if Fovista® causes cancer in animals has not been done. The risk of cancer to humans is not known.

Risk of Allergic Reaction
There is a chance of allergic reaction when taking any medication (dilation drops, antibiotic drops, betadine, fluorescein dye, Fovista®, Avastin®, etc.). Symptoms of any allergic reaction can include a rash, hives, itching, and/or difficulty breathing, closing of the throat, swelling of the lips, tongue or face, and rarely death. If you experience any difficulty breathing, closing of the throat, swelling of the lips, tongue or face, or hives, you should immediately seek emergency medical attention. You should tell your study doctor if you are allergic to tropicamide (such as Mydriacyl®), phenylephrine

(such as Neo-Synephrine®), fluoroquinolone antibiotics (such as Cipro®), tetracaine, lidocaine, or povidone-iodine (such as Betadine®). These medications may be used during this study. There are trained medical personnel and emergency equipment and medicines available at the study center to treat you in the event of a severe allergic reaction.

In general, allergic reactions to medicines are more likely to occur in people who have allergies to other drugs, foods, or things in the environment, such as dust or grass. If you have allergies to other medicines, foods, or other things in the environment, or if you have asthma, you should let your study doctor know.

Contacts

Public
OPHTHOTECH CORPORATION

One Penn Plaza 19th Floor
New York NY 10119
US
Scientific
OPHTHOTECH CORPORATION

One Penn Plaza 19th Floor
New York NY 10119
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

General Inclusion Criteria
1. Subjects of either gender aged * 50 years.
2. Performance Status 2 according to Eastern Cooperative Oncology Group (ECOG) / World Health Organization (WHO) scale .
3. Women must agree to be using two forms of effective contraception, be post-menopausal for at least 12 months prior to trial entry, or surgically sterile; if of child-bearing potential, a serum pregnancy test must be performed within 14 days prior to the first injection with a negative result. The two forms of effective contraception must be implemented during the trial and for at least 60 days following the last dose of test medication.
4. Provide written informed consent.
5. Ability to comply with study and follow-up procedures and return for all trial visits.;Ophtalmic Inclusion Criteria ;1. Presence of subfoveal "active CNV". "Active CNV* is defined as the presence of fluorescein leakage consistent with choroidal neovascularization.
2. Presence of subretinal or intraretinal fluid in the anatomic fovea by OCT.
3. Best corrected visual acuity in the study eye between 20/63 and 20/200, inclusive.
4. Total area of the lesion (including blood, neovascularization, and scar/atrophy) must be * 9 disc areas (DA), of which at least 50% must be active CNV.
5. Clear ocular media and adequate pupillary dilatation to allow collection of fundus photographs and fluorescein angiograms of a sufficient quality to be analyzed.
6. Intraocular pressure (IOP) of 21 mmHg or less.

Exclusion criteria

General Exclusion Criteria
1. Any of the following underlying conditions or diseases including:
* A definitive diagnosis of diabetes mellitus or diabetic retinopathy (regardless of HbA1c level)
* HbA1c value of *6.5%* (*If the HbA1c value is * 6.5% and * 6.9%, and the patient has no signs or symptoms of diabetes mellitus, has a normal creatinine, has no diabetic retinopathy and no glycosuria, then the patient may have an oral glucose tolerance test (OGTT) at the discretion of the investigator. If the 2-hour glucose value on OGTT is <200 mg/dL (<11.1mmol/L), then the patient may be enrolled)
* History of other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.
* History or evidence of severe cardiac disease (e.g., NYHA Functional Class III or IV - see Appendix 17.6), history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction or coronary artery revascularization within 6 months, or ventricular tachyarrythmias requiring ongoing treatment.
* Stroke (within 12 months of trial entry).
* Any major surgical procedure within one month of trial entry.

2. Any treatment with an investigational agent in the 60 days prior to randomization for any condition.
3. Known serious allergies to the fluorescein dye used in angiography (mild allergy amenable to treatment is allowable), or to the components or formulation of either Fovista® or Avastin®.;Opthalmic Exclusion Criteria
1. Any prior treatment for AMD in the study eye prior to the Day 1 visit, except oral supplements of vitamins and minerals.
2. Any prior intravitreal treatment in the study eye prior to the Day 1 visit, regardless of indication (including intravitreal corticosteroids).
3. Subjects with subfoveal scar or subfoveal atrophy (by OCT and/or by Fundus Photography)
4. More than 50% of the total lesion size consisting of subretinal hemorrhage.
5. Presence of retinal angiomatous proliferation (RAP).
6. Presence of significant serous pigment epithelial detachments (PEDs), such as large PEDs that constitute greater than 50% of the total lesion or have a vertical height of * 500 *m.
7. Presence of pure PED.
8. Presence of pigment epithelial tears or rips.
9. Presence of intraocular inflammation (* trace cell or flare), significant epiretinal membrane (causing distortion of macular anatomy and/or opacification), significant vitreomacular traction (causing distortion of macular anatomy), macular hole (full or partial thickness) or vitreous hemorrhage.
10. Aphakia or absence of the posterior capsule. Absence of an intact posterior capsule is allowed if it occurred as a result of YAG laser posterior capsulotomy in association with prior posterior chamber IOL implantation.
11. History of idiopathic or autoimmune-associated uveitis in either eye.
12. Significant media opacities, including cataract, which might interfere with visual acuity, assessment of toxicity, or fundus photography in the study eye. Subjects should not be entered if there is likelihood that they will require cataract surgery in the study eye in the next 12 months.
13. Presence of other causes of choroidal neovascularization, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25mm or more), the ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.
14. Any intraocular surgery or thermal laser within three (3) months of trial entry. Any prior thermal laser in the macular region, regardless of indication.
15. Any photodynamic therapy within three (3) months of trial entry.
16. Any ocular or periocular infection in the past twelve (12) weeks.
17. History of any of the following conditions or procedures in the study eye: Rhegmatogenous retinal detachment, pars plana vitrectomy, filtering surgery (e.g. trabeculectomy), glaucoma drainage device, corneal transplant.
18. Previous therapeutic radiation in the region of the study eye.

Study design

Design

Study phase:	2
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):	16-03-2016
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fovista
Generic name:	pegpleranib sodium

Ethics review

Approved WMO Date:	22-06-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2015
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2015-000518-23-NL
CCMO	NL53527.018.15