A randomized, double-masked, multicenter, laser-controlled Phase III study assessing the efficacy and safety of ranibizumab (intravitreal injections) as adjunctive and mono-therapy in patients with visual impairment due to diabetic macular edema

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Primary objectiveto demonstrate superiority of ranibizumab 0.5 mg as adjunctive or mono-therapy to laser treatment in the mean change from baseline in BCVA over a 12-month treatment period.Secondary objectives* to evaluate whether ranibizumab (0.5...

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

Summary

ID

NL-OMON32224

Source
ToetsingOnline

Brief title
CRFB002D2301 RESTORE

Condition

- Retina, choroid and vitreous haemorrhages and vascular disorders

Synonym
diabetic macular edema, swelling of the retina

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma

Intervention

Keyword: diabetic macular edema, laser treatment, ranibizumab

Outcome measures

Primary outcome

The primary variable will be the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 12 and the baseline level of BCVA.

Secondary outcome

The mean change from baseline in BCVA will be analyzed for all post-baseline visits (Months 1-12) to evaluate the time-course of the treatment difference between the three treatments.

OCT (Central foveal thickness (CFT) and central retinal thickness (CRT), measured in microns): Mean change from baseline over time up to Month 12, percent change from baseline in edema (edema = CFT (CRT) * 175 microns) over time up to Month 12, proportion of patients with thickness of < 225 microns over time up to Month 12.

Proportion of patients with resolution of leakage (as assessed by the central reading center) at Month 12

Mean change in the area of retinal thickening (as assessed by the central

reading center) from baseline at Month 12.

Proportion of patients with a three-step change from baseline in the ETDRS

severity score at Month 12.

Mean change from baseline in the ETDRS severity score at Month 12.

Safety parameters will be adverse events, ophthalmic examinations, intraocular

pressure (IOP), vital signs, and laboratory results.

Study description

Background summary

Diabetes mellitus (DM) is the most common endocrine disease in developed countries, with prevalence estimates ranging between 2 to 5% of the world*s population. Diabetic retinopathy (DR) and diabetic macular edema (DME) are common microvascular complications in patients with diabetes and may have a sudden and debilitating impact on visual acuity (VA), eventually leading to blindness.

Laser photocoagulation is considered the current standard of care and has been demonstrated to slow the progression of vision loss. Photocoagulation is a destructive therapy and often causes symptomatic paracentral scotomas, which can become disabling after multiple treatments.

In a clinical trial, ranibizumab treatment did on average not result in a complete resolution of macular edema in the patients. The addition of ranibizumab intravitreal injections to laser treatment might result in a more complete resolution of macular edema. The addition of ranibizumab to laser treatment could also prevent VEGF-associated atrophic changes which are induced by thermal laser photocoagulation.

Study objective

Primary objective
to demonstrate superiority of ranibizumab 0.5 mg as adjunctive or mono-therapy to laser treatment in the mean change from baseline in BCVA over a 12-month treatment period.

Secondary objectives
* to evaluate whether ranibizumab (0.5 mg) as adjunctive or mono-therapy is superior to laser treatment:
- in the number of patients with visual acuity above 73 letters
and
- in the number of patients with improvement in BCVA.
* to evaluate the time course of BCVA changes on ranibizumab (0.5 mg) adjunctive and mono-therapy relative to laser treatment
* to evaluate the effects of ranibizumab (0.5 mg) adjunctive and mono-therapy on central retinal thickness and other anatomical changes relative to laser treatment
* to evaluate the effects of ranibizumab (0.5 mg) adjunctive and mono-therapy on patient-reported outcomes (PROs) relative to laser treatment
* to evaluate the safety of intravitreal injections of ranibizumab (0.5 mg) as adjunctive and mono-therapy in patients with DME overall and relative to laser treatment.

Study design

In this randomized, double-masked, multicenter, active control study of ranibizumab, consenting patients will participate in a screening period, lasting 3 to 14 days, to evaluate patient eligibility. After eligibility confirmation at baseline, patients will be randomized in a 1:1:1 ratio to one of the three treatment arms, i.e. to adjunctive administration of ranibizumab (0.5 mg) intravitreal injections to active laser, ranibizumab (0.5 mg) intravitreal injections (plus sham laser), or laser treatment (plus sham injections) for 12 months. Only one eye will be selected / treated as the study eye.

Intervention

There are three treatment groups:
Patients will be randomized in a 1:1:1 ratio to one of the three treatment arms, i.e. to adjunctive administration of ranibizumab (0.5 mg) intravitreal injections to active laser, ranibizumab (0.5 mg) intravitreal injections (plus sham laser), or laser treatment (plus sham injections).

* 0.5 mg ranibizumab (labeled as RFB002 0.5mg/0.05ml) intravitreal injection once per month during the first three months. Then treatment occurs based upon the monthly results of the different eye assessments.

* sham injection (labeled as RFB002 0mg/0ml)
* laser photocoagulation Laser treatment (active or sham) will be administered at Day 1. Subsequent laser treatments (together with ranibizumab or sham injections) may be re-administered in accordance with the ETDRS guidelines at intervals no shorter than 3 months from the last treatment if deemed necessary by the treating investigator.
* sham laser

Study burden and risks

The average duration of a study visit is three hours. During each visit (14x), blood pressure and pulse will be measured and a standard ophthalmologic exam will be performed. At visit 2, 5, 8 and 14 the patient will be asked to complete a questionnaire. This will take about 15 minutes per questionnaire. During visits 2, 8 and14 and as needed during the other visits, a color fundus photograph will be taken and a fundus angiogram will be performed. During all visits an Optical coherence tomography (OCT) will be performed.
Ten milliliters of blood will be collected from patients who agree to participate in the pharmacogenetics study. In the future, genetic markers may be found in these blood samples that can show a relationship between the genetic information and predict relative possibility interactions with Lucentis and predict side effects. From non-menopausal female patients, 4 ml of blood will be withdrawn once to perform a pregnancy test. The risks of Lucentis treatment to an unborn fetus are unknown and therefore, pregnant women will be excluded from this study.
The side-effects of Lucentis include an increased eye pressure, eye infections and eye inflammations.

Potential complications of laser treatment include permanent visual impairment (scotomas),
scars on the retina which can lead to new edemas and leakage, retinal fibrosis, and impairment
of color vision.

The eye pressure will be carefully monitored during the trial and treated if necessary. The intravitreal injection procedure will be performed under sterile circumstances and the patient will be asked to use antimicrobial eye drops three days prior to and three days after a Lucentis injection, to lower the chance on infections.

Contacts

Public
Novartis

Raapopseweg 1
6824 DP Arnhem
Nederland
Scientific
Novartis

Raapopseweg 1
6824 DP Arnhem
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female patients *18 years of age who have signed an informed consent
- Patients with Type 1 or Type 2 diabetes mellitus (according to ADA or WHO guidelines) with HbA1c not more than 10.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes.
- Patients with visual impairment due to focal or diffuse DME in at least one eye who are eligible for laser treatment in the opinion of the investigator. If both eyes are eligible, the one with the worse visual acuity, as assessed at Visit 1, will be selected for study treatment unless, based on medical reasons, the investigator deems the other eye the more appropriate candidate for study treatment. The study eye must fulfill the following criteria at Visit 1:
- BCVA score between 78 and 39 letters, inclusively, using ETDRS-like visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/160)
- Decrease in vision is due to DME and not due to other causes, in the opinion of the investigator
- 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.

Exclusion criteria

Ocular concomitant conditions/ diseases
- Concomitant conditions in the study eye which could, in the opinion of the investigator, prevent the improvement of visual acuity on study treatment
- Active intraocular inflammation (grade trace or above) in either eye
- Any active infection (e.g. conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) in either eye
- History of uveitis in either eye
- Structural damage within 0.5 disc diameter of the center of the macula in the study eye likely to preclude improvement in visual acuity following the resolution of macular edema, including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudate plaques
- Ocular disorders in the study eye that may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the 12-month study period, including cataract, retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause (e.g., AMD, ocular histoplasmosis, or pathologic myopia)
- Uncontrolled glaucoma in the either eye (IOP > 24 mmHg on medication or according to investigator*s judgment)
- Neovascularization of the iris in either eye
- Evidence of vitreomacular traction in either eye
- Active proliferative diabetic retinopathy in the study eye
- Patients who are monocular or have a BCVA score in the non-study eye (fellow eye) - Panretinal laser photocoagulation in the study eye within 6 months prior to or during the study
- Focal/grid laser photocoagulation in the study eye within 3 months prior to study entry
- Treatment with anti-angiogenic drugs (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) within 3 months prior to randomization
- Any intraocular surgery in the study eye within 3 months prior to randomization
- History of vitrectomy in study eye
- History of intravitreal corticosteroid treatment in phakic study eye
- Intravitreal coricosteroids in post-cataract surgery study eye (aphakic or pseudophakic, without damaged posterior capsule) within 3 months prior to randomization.
- Ocular conditions in the study eye that require chronic concomitant therapy with topical ocular or systemically administered corticosteroids;Systemic conditions or treatments
- History of stroke
- Renal failure requiring dialysis or renal transplant OR renal insufficiency with creatinine levels > 2.0 mg/dl
- Untreated diabetes mellitus
- Blood pressure systolic > 160 mmHg or diastolic > 100 mmHg
- Untreated hypertension or change in antihypertensive treatment within 3 months preceding Baseline
- Current use of or likely need for systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Chloroquine/ hydroxychloroquine (Plaquenil), Tamoxifen, Phenothiazines and Ethambutol

Known hypersensitivity to ranibizumab or any component of the ranibizumab formulation or fluorescein
- any type of advanced, severe or unstable disease or it's treatment, that may interfere with primary and/or secondary variable evaluations including any medical condition that could be expected to progress, recur, or change to such an extend that it may bias the assessment of the vlinical status of the patient to a significant degree or put the patient at special risk.;Compliance/ Administrative
- Previous participation in any clinical studies of investigational drugs (excluding vitamins and minerals) within 1 month (or a period corresponding to 5 half-lives of the investigational drug, whatever is longer) prior to randomization
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant. including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method or a barrier method plus a hormonal method. Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent.
- Pregnant or nursing (lactating) women
- Inability to comply with study or follow-up procedures.

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:	Pending
Start date (anticipated):	01-10-2008
Enrollment:	15

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Lucentis
Generic name:	ranibizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-07-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-09-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2009
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	EUCTR2007-004877-24-NL
CCMO	NL23426.018.08