A 2 year randomized, single-masked, multicenter, controlled phase IIIb trial assessing the efficacy and safety of 0.5 mg ranibizumab in two *treat and extend* treatment algorithms vs. 0.5 mg ranibizumab as needed in patients with macular edema and visual Impairment secondary to diabetes mellitus

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Primary objective:To demonstrate that the mean change from baseline in Best Corrected Visual Acuity (BCVA) over a 12 month treatment period obtained with either a 0.5 mg ranibizumab *Treat and Extend* (TE) dosing regimen with adjunctive laser, and/…

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

Summary

ID

NL-OMON36659

Source
ToetsingOnline

Brief title
RETAIN

Condition

- Eye disorders NEC

Synonym
macular edema

Research involving
Human

Sponsors and support

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

Intervention

Keyword: diabetes mellitus, macular edema, ranibizumab

Outcome measures

Primary outcome

To demonstrate that the mean change from baseline in Best Corrected Visual Acuity (BCVA) over a 12 month treatment period obtained with either a 0.5 mg ranibizumab *Treat and Extend* (TE) dosing regimen with adjunctive laser, and/or with 0.5 mg ranibizumab TE dosing regimen alone is at least non-inferior to 0.5 mg ranibizumab alone given PRN in patients with visual impairment due to DME to cover a potential superiority claim. The condition for the interpretation of these results is the assessment of the extent to which the TE dosing regimens could be maintained during the study duration.

Secondary outcome

*To evaluate whether the mean change from baseline in BCVA over a 24-month period in patients with visual impairment due to DME obtained with either a 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, or with 0.5 mg ranibizumab TE dosing regimen alone is non-inferior to 0.5 mg ranibizumab alone given PRN

*To demonstrate a stabilizing effect of adjunctive laser reflected in a lower number of study visits scheduled for treatment between Months 12 and 24, comparing 0.5mg ranibizumab TE dosing regimen with adjunctive laser with 0.5mg ranibizumab TE dosing regimen alone. The conditions for the interpretation of this result are:

1) established non-inferiority for 0.5mg ranibizumab TE dosing regimen with adjunctive laser compared to 0.5 ranibizumab alone given PRN and

2) similarity of the results with respect to the mean number of visits scheduled for treatment for the two TE treatment groups up to Month 12.

*To investigate the efficacy of 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, 0.5 mg ranibizumab TE dosing regimen alone and 0.5 mg ranibizumab alone given PRN on vision-related functioning and well-being assessed during a period of 12 months, as measured by the overall score assessed by the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25) and EuroQol EQ-5D.

*To evaluate the time course of mean BCVA change from baseline to Month 12, and up to Month 24 obtained with either a 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, or with 0.5 mg ranibizumab TE dosing regimen alone compared to 0.5 mg ranibizumab alone given PRN.

*To compare the changes in development of central retinal thickness and central subfield thickness of 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, 0.5 mg ranibizumab TE dosing regimen alone and 0.5 mg ranibizumab alone given PRN over time.

*To evaluate a reduced need for monitoring visits using TE by assessing the

average interval (months) between visits scheduled for treatment.

Study description

Background summary

Please see page 11-13 of the study protocol.

Study objective

Primary objective:
To demonstrate that the mean change from baseline in Best Corrected Visual Acuity (BCVA) over a 12 month treatment period obtained with either a 0.5 mg ranibizumab *Treat and Extend* (TE) dosing regimen with adjunctive laser, and/or with 0.5 mg ranibizumab TE dosing regimen alone is at least non-inferior to 0.5 mg ranibizumab alone given PRN in patients with visual impairment due to DME to cover a potential superiority claim. The condition for the interpretation of these results is the assessment of the extent to which the TE dosing regimens could be maintained during the study duration.

Secondary objectives:
* To evaluate whether the mean change from baseline in BCVA over a 24-month period in patients with visual impairment due to DME obtained with either a 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, or with 0.5 mg ranibizumab TE dosing regimen alone is non-inferior to 0.5 mg ranibizumab alone given PRN
* To demonstrate a stabilizing effect of adjunctive laser reflected in a lower number of study visits scheduled for treatment between Months 12 and 24, comparing 0.5mg ranibizumab TE dosing regimen with adjunctive laser with 0.5mg ranibizumab TE dosing regimen alone. The conditions for the interpretation of this result are:
1) established non-inferiority for 0.5mg ranibizumab TE dosing regimen with adjunctive laser compared to 0.5 ranibizumab alone given PRN and
2) similarity of the results with respect to the mean number of visits scheduled for treatment for the two TE treatment groups up to Month 12.
* To investigate the efficacy of 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, 0.5 mg ranibizumab TE dosing regimen alone and 0.5 mg ranibizumab alone given PRN on vision-related functioning and well-being assessed during a period of 12 months, as measured by the overall score assessed by the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25) and EuroQol EQ-5D.
* To evaluate the time course of mean BCVA change from baseline to Month 12, and up to Month 24 obtained with either a 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, or with 0.5 mg ranibizumab TE dosing regimen alone

compared to 0.5 mg ranibizumab alone given PRN.
* To compare the changes in development of central retinal thickness and central subfield thickness of 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, 0.5 mg ranibizumab TE dosing regimen alone and 0.5 mg ranibizumab alone given PRN over time.
*To evaluate a reduced need for monitoring visits using TE by assessing the average interval (months) between visits scheduled for treatment.

Exploratory objectives:
* To evaluate the effect of 0.5 mg ranibizumab TE dosing regimen with adjunctive laser, and 0.5 mg ranibizumab TE dosing regimen alone on the Early Treatment Diabetic Retinopathy Severity Score compared to 0.5 mg ranibizumab alone given PRN at baseline, at Months 6,12,18 and 24

Study design

This study is a 24 month single-masked, three arm parallel group, randomized, multicenter, controlled study comprising four periods:
*Screening period: Day -14 to Day -1
Upon signing the Informed Consent patients will be enrolled at Visit 1. Study procedures enabling assessment of eligibility will be performed.
* Treatment period I: Day 1 * Day 360
Upon confirmation of eligibility, patients will be randomized in a 1:1:1 ratio to the three treatment arms (see Figure 3-1):
* Group I: Combination of 0.5 mg ranibizumab *Treat and Extend* + laser.
* Group II: 0.5 mg ranibizumab *Treat and Extend* alone.
* Group III (control): 0.5 mg ranibizumab alone PRN.
Study treatment will be started as described in (Section 4.4).

Antimicrobial medication will be dispensed at each study visit (Group III) or before visits with scheduled injections (Groups I and II).
The last study treatment of this period is to be given at Month 11. Month 12 is the primary endpoint for analysis.
* Treatment period II: Day 360 (after assessment of efficacy) * Day 690
This period starts with the possible treatment given as a result of the Month 12 study assessment.
Antimicrobial medication will be dispensed at each study visit (Group III) or before visits with scheduled injections (Groups I and II).
The last study treatment in this period is given at Month 23. Treatment period II is the extension period of the study.
* Follow-up period: Day 691 * Day 720
After the Month 23 visit, patients will be followed for 1 month and will return for final efficacy and safety assessments at Month 24.

Intervention

Investigational and reference therapy:

*Ranibizumab (Lucentis®) will be supplied in vials containing a dose of 0.5 mg/0.05 ml in an aqueous solution (pH 5.5) with histidine, trehalose, and polysorbate 20. The vial contains no preservative and is suitable for single use only.

* The laser treatment technique to be applied following ETDRS guidelines to a particular patient is at the discretion of the Treatment Investigator.

Study burden and risks

The most common side effects of the study drug include: Inflammation of the eye, blurred vision, bleeding in the back of the eye (retinal bleeding), visual disturbances, eye pain, small particles or spots in your vision (floaters), bloodshot eye, eye irritation, a feeling of having something in the eye, increased tear production, inflammation or infection of the eyelid margins, dry eye, redness or itching of the eye. Increased eye pressure has been observed very commonly.

The most common non-visual side effects reported include: Sore throat, headache and joint pain.

Other common side effects include: Seeing flashes of light with floaters progressing to a loss of sight, decreased sharpness of vision, swelling of a section of the eye (uvea, cornea), clouding of the lens, small marks on the surface of the eye, bleeding in the eye, discharge from the eye with itching, redness and swelling (conjunctivitis), light sensitivity, eye discomfort, swelling of the eyelid, eyelid pain.

Other common non-visual side effects include: Fatigue, general feeling of being unwell, anxiety, cough, nausea, allergic reactions like rash, itching, skin reddening.

Uncommon side effects include: Blindness, infection of the eye globe (endophthalmitis), inflammation and bleeding in the front part of the eye, sac of pus on the eye, changes of the central part of the eye surface, pain or irritation at the site of injection, abnormal sensation in the eye, irritation of the eyelid.

The risks of drawing blood may include fainting, pain and/or bruising from the needle in the patients arm.

Contacts

Public
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CH
Scientific
Novartis

Lichtstrasse 35
4002 Basel
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patient
1. Male or female patients > 18 years of age who have signed an Informed Consent.
2. Patients with Type 1 or Type 2 diabetes mellitus (according to American Diabetes Association or World Health Organization [WHO] guidelines) with glycosylated hemoglobin (HbA1c) * 12.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes. Treatment for diabetes must have been stable for at least 3 month.;Ocular
3. Patients with visual impairment due to 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 by the investigator as the study eye.
4. BCVA * 39 and <<= 78 letters in the study eye and, inclusively, using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts at a testing distance of 4

meters (approximate Snellen equivalent of 20/32 to 20/160) at screening.
5. Concomitant conditions in the study eye which, in the opinion of the investigator, do not prevent improvement of visual acuity on study treatment.

Exclusion criteria

Patient Compliance/ Administrative
1.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.
2.Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum pregnancy test (human chorionic gonadotropin > 5 mIU/mL).
3.Inability to comply with study procedures.;Ocular medical history
4. Active intraocular inflammation (grade trace or above) in either eye at enrollment.
5. Any active infection (e.g. conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) in either eye at the time of enrollment.
6. History of uveitis in either eye at any time.
7. Structural damage within 0.5 disc diameter of the center of the macular 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.
8. Uncontrolled glaucoma in either eye at screening (IOP > 24 mmHg on medication or according to investigator*s judgment).
9. Neovascularization of the iris in either eye.
10. Evidence of vitreomacular traction in either eye.
11. Active proliferative diabetic retinopathy in the study eye.
12. Patients who are monocular or have a BCVA score in the non-study eye (fellow eye) * 24 letters (approximate Snellen equivalent of 20/320) at Visit 1.;Prior Ocular treatments
13. Any intraocular surgery in the study eye within 3 months prior to randomization.
14. History of vitrectomy in study eye regardless of time prior to randomization.
15. Planned medical or surgical intervention during the 24-months study period.
16. Panretinal laser photocoagulation in the study eye within 6 months prior to randomization.
17. Focal/grid laser photocoagulation in the study eye within 3 months prior to randomization.
18. Treatment with anti-angiogenic drugs in the study eye (pegaptanib sodium, anecortave ace tate, bevacizumab, ranibizumab, VEGF-Trap, etc.) within 3 months prior to randomization.
19. Use of other investigational drugs at the time of enrollment, or within 3 month or 5 half-lives from enrollment, whichever is longer.
20. History of intravitreal corticosteroid treatment in phakic study eye.
21. Intravitreal corticosteroids in post-cataract surgery study eye (aphakic or pseudophakic, without damaged posterior capsule) within 3 months prior to randomization.

22. Ocular conditions in the study eye that require chronic concomitant therapy with topical ocular or systemically administered corticosteroids.;Systemic conditions or treatments
23. History of stroke within 6 months prior to enrollment.
24. Renal failure requiring dialysis or renal transplant or renal insufficiency with creatinine levels > 2.0 mg/dl at screening.
25. Untreated diabetes mellitus.
26. Blood pressure systolic > 160 mmHg or diastolic > 100 mmHg at screening and randomization.
27. Untreated hypertension or change in antihypertensive treatment within 3 months preceding randomization.
28. 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.
29. Known hypersensitivity to fluorescein or ranibizumab or any component thereof or drugs of similar chemical classes.
30. Any type of advanced, severe or unstable disease or its 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 clinical status of the patient to a significant degree or put the patient at special risk.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-09-2010
Enrollment:	25
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	28-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2012
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	EUCTR2010-019795-74-NL
ClinicalTrials.gov	NCT00687804
CCMO	NL32717.018.10