The Efficacy and Safety of Bimatoprost SR in Patients With Open-angle Glaucoma or Ocular Hypertension

Published: 27-03-2015
Last updated: 14-04-2024

To evaluate the intraocular pressure (IOP)-lowering efficacy and safety of 2 dose strengths of Bimatoprost SR in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) after initial and repeated administrations

Ethical review	Approved WMO
Status	Will not start
Health condition type	Glaucoma and ocular hypertension
Study type	Interventional

Summary

ID

NL-OMON45083

Source
ToetsingOnline

Brief title
ARTEMIS II

Condition

- Glaucoma and ocular hypertension

Synonym
glaucoma and increased pressure inside the eye

Research involving
Human

Sponsors and support

Primary sponsor: Allergan Limited
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Bimatoprost SR, Ocular Hypertension, Open-angle Glaucoma

Outcome measures

Primary outcome

Response Measures

Efficacy: Intraocular pressure (IOP) measured by Goldmann applanation tonometry

Safety: Adverse events; ocular parameters as determined through assessment of visual acuity and visual field; evaluation of macroscopic bulbar conjunctival hyperemia and iris color; assessment of endothelial cell density and corneal thickness; IOP measurement, biomicroscopic and ophthalmoscopic examinations (including gonioscopy with Bimatoprost SR implant assessment, optic disc examination and dilated fundus examination); and optical coherence tomography (OCT) of the macula.

Secondary outcome

NA

Study description

Background summary

In the ongoing 192024-041D phase 1/2 clinical study, preliminary results suggest that Bimatoprost SR provides IOP-lowering efficacy similar to topical prostaglandin analogs in the dose strengths proposed for this phase 3 investigation. Additionally, the safety profile of Bimatoprost SR at dose strengths of 20 µg (2 x 10 µg) or less in the phase 1/2 study has been acceptable, and supports additional clinical study in man. The current study 192024-092 is a randomized, patient and efficacy evaluator-masked, parallel-group comparison to evaluate the safety and IOP-lowering effects of

repeated administrations of 10 µg or 15 µg Bimatoprost SR in patients with OAG or OHT and open iridocorneal angles inferiorly in the
study eye by clinical gonioscopy. The 2 dose strengths of Bimatoprost SR will be compared versus a control group treated with the active comparator, topically applied timolol 0.5%. Timolol is a well-established treatment for IOP lowering in glaucoma and ocular hypertension, and has been used as a comparator in other IOP-lowering studies.

Study objective

To evaluate the intraocular pressure (IOP)-lowering efficacy and safety of 2 dose strengths of Bimatoprost SR in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) after initial and repeated administrations

Study design

Study Design
Structure: Phase 3 multicenter, randomized, masked, parallel-group comparison (2 dose strengths of Bimatoprost SR versus active control), repeat administration.
Duration: Approximately 22 months, consisting of screening of up to 28 days before washout, washout period of up to 42 days before initial administration of study medication, 52-week treatment period, plus 8 months extended follow up.
Study Treatment Groups: Bimatoprost SR dose groups: 10 µg and 15 µg
Control: Timolol eye drops plus Sham needleless procedure (that involves touching the eye at the area of insertion with a needleless applicator).
Dosage/Dose Regimen: Patients will receive one of 2 dose strengths of Bimatoprost SR or Control treatment in the study eye on Day 1 (with repeat administration of the same dose strength or Sham at Week 16 and Week 32). Bimatoprost SR-treated patients will receive intracameral administration of Bimatoprost SR in the study eye using a prefilled applicator. Timolol vehicle eye drops will be used twice daily (BID; in the morning and evening) to mask the treatment of patients receiving Bimatoprost SR in the study eye. The fellow eye will receive a Sham needleless procedure (hereafter called *Sham administration* or *Sham administration procedure*) plus topical timolol eye drops, BID. Control group patients will receive a Sham administration plus timolol in both eyes.
The patients will begin self-administration of the study-provided eye drops (vehicle or timolol) in both eyes, starting with the evening dose on the first administration (Bimatoprost SR or Sham Administration) day visit. Patients will continue self-administration of the study-provided eye drops in the morning (08:00 ± 1 hour) and in the evening (20:00 ± 1 hour) approximately 12 hours apart throughout the study, with the exception of the morning of a subsequent visit, on which the morning eye drop administration will be performed at the study site.

Randomization/Stratification: Randomization to treatment groups will use a 1:1:1 ratio (Bimatoprost SR 10 µg:Bimatoprost SR 15 µg:Control). Randomization will be stratified by baseline study eye Hour 0 IOP (<= 25 mm Hg or > 25 mm Hg).
Visit Schedule: Patients who complete the entire study without receiving nonstudy IOP-lowering medication in both eyes will have a minimum of 25 visits and 6 phone calls. The schedule includes:
• Screening (up to 28 days); Washout period of up to 42 days for both eyes (which may begin once screening procedures have been completed and the site has obtained confirmation of anterior segment optical coherence tomography [AS-OCT] iridocorneal angle qualification from the Reading Center); Baseline (Days 3 to 1)
• Treatment Period
o Cycle 1: Day 1 Administration Day; Day 2; phone call on Days 4 and 8; and visits at Weeks 2, 6, 12, and 15
o Cycle 2: Week 16 Administration Day; Cycle 2 Day 2; phone call on Cycle 2 Days 4 and 8; and visits at Weeks 18, 22, 28, and 31
o Cycle 3: Week 32 Administration Day; Cycle 3 Day 2; phone call on Cycle 3 Days 4 and 8; and visits at Weeks 34, 38, 44, 48, and 52
• Extended Follow Up
o Visits at Months 14, 16, 18, and 20/Exit
IOP evaluations will occur at 2 timepoints: Hour 0 (08:00 ± 1 hour) and Hour 2 (Hour 0 + 2 hours [± 30 min]).
Patients who have not received nonstudy IOP-lowering medication (prohibited prior to Week 52) in both eyes will receive a repeat administration of Bimatoprost SR (or Sham administration in Control group study eyes and all fellow eyes) at the Week 16 and Week 32 visits as indicated. Administration should not occur if the investigator believes that there are any safety concerns. Patients who have received nonstudy IOP-lowering medication in both eyes will be followed for at least 12 months following the last administration of Bimatoprost SR or Sham, at which time they may exit early at the investigator*s discretion.

Intervention

Dosage/Dose Regimen: Patients will receive one of 2 dose strengths of Bimatoprost SR or Control treatment in the study eye on Day 1 (with repeat administration of the same dose strength or Sham at Week 16 and Week 32).

Study burden and risks

Burden and risks

There are possible side effects and discomforts associated with the procedures and study treatment. The subject may experience some, all, or none of these effects.

Side effects from the study drug

Bimatoprost SR Risks:
Bimatoprost SR has the same active ingredient as the commercially approved bimatoprost eye drops (LUMIGAN®) for lowering the pressure inside the eye in patients with glaucoma and ocular hypertension. Side effects and discomforts reported by patients using the eye drops include: eye redness, growth of eye lashes, eye itchiness, dryness, burning/stinging, grittiness (foreign body sensation in the eye), visual disturbance (blurred eye sight), darkening of the iris (eye color). Less than 1% of patients using the eye drops experience difficulties breathing, asthma, worsening of asthma, and changes in blood pressure or heart rate. Bimatoprost will not be given in eye drop form in this study.

Timolol Eye Drop Risks:
Side effects or discomforts to the eyes associated with the eye drops are inflammation of the surface of the eye, fluid accumulation in the central area of the retina, skin allergies around eyes, eyelid drooping, eye redness, eye irritation or itchiness, eyes feeling dry or less sensitive, loss of the surface layer of cornea, blurred or double vision. Other possible side effects are asthma, worsening of asthma or other lung disease, difficulties breathing, slow or irregular heartbeat, low or high blood pressure, stroke, insufficient blood flow to brain, worsening of heart failure, worsening of angina, sudden stop of heart beat, fluid accumulation in lung and body, or other heart conditions, poor blood circulation, allergic reactions, dizziness, fainting, sleepiness or sleeplessness, psychic disturbances, fatigue, headache, nausea, diarrhoea, indigestion, dry mouth, distortion of sense of taste, muscle pain, masking of symptoms from low blood sugar or from thyroid gland overactivity, tissue fibrosis in lower abdomen, decreased libido, impotence, systemic lupus erythematosus.

Eye Dilation Drop Risks:
Side effects and discomforts associated with the drops used to enlarge the pupils of the
eyes include: stinging, sensitivity to lights, and blurring of vision. When the pupils are enlarged, the eyes will be sensitive to light (because more light is getting into the eye) and the subject may also have trouble focusing on close objects. These effects can last for several hours, depending on the strength of the drop used. The subject should bring sunglasses with you at these visits. The subject should not operate a motor vehicle until the vision returns to normal.

Side effects from study procedures
Study Drug Administration Procedure:

Local Anaesthesia Risks
Side effects and discomforts from local anesthesia (numbing medicine) may

include: swelling, redness and allergic reaction to the anesthesia.

Bimatoprost SR Administration Risks
Side effects and discomforts associated with the Bimatoprost SR procedure may include:

- possible loss of corneal endothelial cells (the layer of cells lining the inner side of the cornea) due to the Bimatoprost SR touching the inner layer of the cornea - seen in less than 1% of patients.

- pain or abnormal sensation in the eye, bleeding at the injection site, tearing, sensitive to light - seen in more than 10% of patients.

- blurry vision, eye inflammation and small amount of fluid leak from the injection site - seen in more than 1% but less than 10% of patients.

- In rare cases, partial or total loss of vision due to infection, bleeding, retinal detachment, or cataract may occur following injections inside the eye - seen in less than 1% of patients.

A small amount of blood in the anterior chamber of the eye (the area between the cornea [clear outer part of the eye] and the inner iris [colored part of the eye]) causing an increased eye pressure has been reported in patients with a blood disorder called sickle cell following Bimatoprost SR placement - seen in more than 1% but less than 10% of patients..

Bimatoprost SR is not attached to any tissues and typically falls to the lowest position in the eye. However, there is a small chance that the Bimatoprost SR might move from the lower position. If this happens, the subject may see the Bimatoprost SR in the eye in front of the iris [the colored part of the eye].

In the rare event that the Bimatoprost SR must be removed for safety reasons, the study doctor will do so by making an incision similar to that made in a cataract surgical procedure. Although the incision is similar to that of a cataract surgery, the Bimatoprost SR removal procedure will not involve the removal or replacement of the eye*s lens and will not provide any cataract treatment. Significant risks associated with the removal of the Bimatoprost SR that could affect vision (if Bimatoprost SR implant removal is required for any reason in the future, there might be an impact on vision depending on the reason for implant removal. The rate of potential vision impact is unknown.) include cataract formation, and postoperative events including irritation at the site of surgery where the stitches are, swelling of the cornea (the clear part of the eye), astigmatism (an eye condition that causes blurred vision), and swelling in the inner back part of the eye that can blur a person's central vision. There is a very small chance (significantly less than 1% risk) of endophthalmitis, an eye infection that has the potential to permanently reduce vision.

Antibiotic Used Before and After The Procedure
Side effects and discomforts associated with the antibiotic used to treat the eyes that the subject may experience include: burning, stinging, redness, and itching.

Eye Exam Risks
The subject may feel temporary discomfort during the eye examinations and photographs due to the bright lights. When the study doctor is examining the inside of the eye, sometimes there is a need to put mild pressure on the eye. This causes mild to moderate discomfort that goes away quickly. The subject may possibly experience eye swelling from the mild pressure put on the eye from these exams.

Blood Sample Risks
The subject may feel a slight needle prick when blood is drawn. Some patients may have a slight bruise that will go away within a few days. Sometimes, patients feel light headed or feel dizzy. Other rare complications associated with the blood sample collection include: infections, nerve lesions, accidental arterial puncture (when the needle pierces an artery instead of a vein).

Benefits

The subject may not receive any direct medical benefit from participating in this study. The participation may help others with the same condition as a result of the knowledge gained from this research for future treatments.

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

Key Inclusion Criteria:
• Written informed consent has been obtained
• In the opinion of the investigator, based on prior use or on IOP rebound (elevation) during the washout period, patient is a responder to IOP lowering by topical prostamides, prostaglandins, or prostaglandin analogs
• The iridocorneal angle inferiorly in the study eye must be confirmed as being qualified by Reading Center AS-OCT assessment
• By the Baseline visit, the final central endothelial cell density in both eyes must be confirmed as being qualified by Reading Center assessment
• Diagnosis of either OAG (ie, primary OAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT in each eye, and both eyes require IOPlowering treatment (Note: diagnosis does not have to be the same in both eyes)
• In the investigator's opinion, either eye can be treated adequately with topical ophthalmic beta-blocker (eg. timolol) eye drops as the sole therapy
• In both eyes, at the baseline visit: Hour 0 IOP in the study eye of >= 22 mm Hg and <= 32 mm Hg, and in the fellow eye of <= 32 mm Hg
• In both eyes at Hour 2 IOP in the study eye of >= 19 mm Hg and <= 32 mm Hg, and in the fellow eye of <= 32 mm Hg

Exclusion criteria

History of cataract surgery in the study eye resulting in anterior chamber intraocular lens implant (IOL), phakic IOL, sulcus IOL, aphakia, or complications (eg, a posterior capsular tear [with or without vitreous loss], iris trauma, etc)

• In the investigator's opinion, patient is nonresponsive to topical ophthalmic beta-blockers and/or topical prostamides, prostaglandins, or prostaglandin analogs (eg, LUMIGAN, Xalatan, Travatan)
• Contraindications to beta-blocker therapy

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Bimatoprost SR
Generic name:	Bimatoprost SR
Product type:	Medicine
Brand name:	Timolol
Generic name:	Timolol maleate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-03-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-08-2017
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014□003186□24-NL
ClinicalTrials.gov	NCT02247804
CCMO	NL52429.078.15