A phase III, randomized, double-masked 6-month clinical study to compare the efficacy and safety of the preservative-free fixed-dose combination of tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given as individual monotherapies in patients with open angle glaucoma or ocular hypertension

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glaucoma and ocular hypertension
Study type	Interventional

Summary

ID

NL-OMON36690

Source
ToetsingOnline

Brief title
201050

Condition

- Glaucoma and ocular hypertension

Synonym
Green star/increased eye pressure

Research involving
Human

Sponsors and support

Primary sponsor: Santen Oy
Source(s) of monetary or material Support: Santen Oy

Intervention

Keyword: angle-glaucoma, ocular hypertension, tafluprost, timolol

Outcome measures

Primary outcome

Change from baseline in the average diurnal IOP at 3 months

Secondary outcome

o Proportion of responders (e.g. a decrease of IOP of 20% or more or an IOP

level of 16 mmHg or less) at 3 months

o Change from baseline in the average diurnal IOP at 2 weeks, 6 weeks and 6

months

o Change from baseline in timewise IOPs (at 8:00, 10:00, 16:00,20:00) at 2

weeks, 6 weeks, 3 months and 6 months

Study description

Background summary

Glaucoma is a family of related diseases that is frequently associated with

elevated intraocular pressure (IOP), leading to optic nerve damage and loss of vision. Glaucoma is the second leading cause of blindness worldwide (WHO, 2004). Although there is currently no cure for glaucoma, evidence from several studies indicate that achieving low levels of IOP can reduce the progression of visual field deterioration in patients with glaucoma.
Medical treatment is predominantly used as first line therapy. There are a number of topical hypotensive medications available to reduce IOP, including prostaglandin (PG) analogues. The main advantage of the prostaglandin analogue is a good IOP reducing effect, long duration of action, and low incidence of systemic side-effects. Tafluprost (referred to as AFP-168 in initial studies) is a new synthetic prostaglandin and its marketing authorization has been granted in 2008 by several European countries as well as in Japan.

In several studies, the combination of Tafluprost and Timolol showed good results on IOP lowering and that Tafluprost is generally well tolerated. Concurrently with the preserved formulation, a preservative-free formulation of tafluprost 0.0015% eye drops (available in single doses) has been developed. Especially in patients who are sensitive to the preservative, benzalkonium chloride (BAK), the new unpreserved formulation will be of benefit.

Study objective

The objective of this study is to compare the efficacy and safety of the preservative-free fixed-dose combination of tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given as individual monotherapies.
The primary objectives of the study are to demonstrate that after a 3-month treatment period the IOP-lowering effect of preservative-free fixed dose combination of tafluprost 0.0015% and timolol0.5% eye drops is superior to
o tafluprost 0.0015% eye drops in patients with open-angle glaucoma or ocular hypertension insufficiently controlled by tafluprost alone
o timolol 0.5% eye drops in patients with open-angle glaucoma or ocular hypertension insufficiently controlled by timolol alone.

Study design

This is a randomized, double-masked, active-controlled, stratified, parallel-group, multinational and multicenter phase III study.
The patients are divided in two stratums as follows:

Former timolol 0.5% users (stratum 1) are randomized to be treated with either
o Preservative-free timolol 0.5% administered twice daily at 8:00 and 20:00 in the affected eye(s)
OR
o Preservative-free fixed combination of tafluprost 0.0015% and timolol 0.5% administered once daily at 8:00 and vehicle eye drops at 20:00 in the affected

eye(s)

Former prostaglandin users (stratum 2) are randomized to be treated with either
o Preservative-free tafluprost 0.001 5 % administered once daily at 8:00 in the affected eye(s)
OR
o Preservative-free fixed combination of tafluprost 0.0015% and timolol 0.5% administered once daily at 8:00 in the affected eyes

Within the prior timolol and PG user stratums, randomization will be stratified by ocular diagnosis (ocular hypertension or glaucoma) and average diurnal baseline IOP (24 mmHg or higher/22 mmHg or higher respectively).
The duration of the study is 6 months.

Intervention

The patients will be asked to administer eye drops once or twice daily at 8:00 and 20:00 in the affected eye(s)
Patients will also underg a gonioscopy, a pachymetry and 8 biomicroscopies.

Study burden and risks

Patients are asked to come for 8 all day long visits. Side effects of tafluprost and timolol are : redness of the eye; eye irritation; pain in the eye; dry eyes; sensitivity to light; decreased sharpness of vision; change in the length, thickness and number of eye lashes; change of color of the eye lashes; feeling of having a speck in the eye; increased tear production; eye discharge; swollen eye lids; red eye lids; change of color of the skin around the eyes; change of iris pigmentation; the color of the eyes (may be permanent); decreased ability of the eye to see details; tired eyes; eye discomfort; abnormal feeling in the eye; swelling of the eye membrane surface; follicles in the eye membrane surface; allergic swelling of small spots on the eye surface; signs of a swelling in the eye; pigmentation of the eye membrane surface; unusual hair growth on eye lids; headache; numbness of the eyes; swelling spots on the cornea; reduced heart rate; depression; shortness of breath; fatigue; swelling of the eye lid and conjunctiva; visual disturbances; double vision; drooping eyelid; heart failure; irregular heartbeat; hypotension; decrease in circulation of fingers and brains; hallucinations; nightmares; weakness; dizziness; confusion; difficulty breathing (especially in patients with asthma or heart failure); blocked nose; hypersensitivity reactions (such as skin rash, hives or hair loss).

The eye examination may cause some discomfort. Dilation of the pupil during ophthalmoscopy causes light sensitivity and a slight blurring of vision.

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

1. Aged 18 years or more
2. A diagnosis of ocular hypertension or open-angle glaucoma (either POAG, capsular glaucoma or pigmentary glaucoma) in one or both eyes, for which the patient has been regularly using prostaglandin (e.g. Xalatan®, Lumigan®, Travatan®, Taflotan®) or timolol 0.5% (several brand names) monotherapy for at least two weeks before Screening (confirmed in anamnesis).
3. Clinical need for additional IOP lowering medication as judged by the investigator and at the Screening visit evaluation in either treated eye:
o IOP measurement of >= 22 mmHg at any time of the day for prior timolol users (stratum 1) OR
o IOP measurement of >= 20 mmHg at any time of the day for prior prostaglandin users (stratum 2)

4. At the End-of-run-in visit after 2-week treatment with preservative-free timolol 0.5% (stratum 1) or with preservative-free tafluprost 0.0015% (stratum 2) in either treated eye:
o IOP measurement of >= 22 mmHg at 8:00 for prior timolol users (stratum 1)
OR
o IOP measurement of >= 20 mmHg at 8:00 for prior prostaglandin users (stratum 2)
5. At the Baseline visit after a washout period of at least 4 weeks in either eye:
o An increase of at least 2 mmHg in the average diurnal IOP (measured at 8:00, 10:00, 16:00 and 20:00) as compared to the average diurnal IOP at the End-of-run-in visit
6. A best corrected ETDRS visual acuity score of +0.6 logMAR or better in both eyes (i.e. monocular patients are not eligible)
7. Are willing to follow instructions
8. Have provided a written informed consent

Exclusion criteria

1. Females who are pregnant, nursing or planning pregnancy, or females of childbearing potential who are not using a reliable method of contraception
2. Anterior chamber angle in either eye to be treated less than grade 2 according to Schaffer classification as measured by gonioscopy
3. Any corneal abnormality or other condition preventing reliable applanation tonometry in the treated eyes, including prior refractive eye surgery
4. IOP of 35 mmHg or greater at any time point in either eye at Screening or End-of-run-in visits
5. Diagnosis of angle-closure glaucoma or secondary glaucoma other than capsular or pigmentary glaucoma in either eye
6. Suspected contraindication to tafluprost or timolol therapy;
a. hypersensitivity to tafluprost/timolol or any of the excipients
b. low heart rate of <50 bpm (at Screening visit) or clinically relevant low blood pressure for age, chronic obstructive pulmonary disease, bronchial asthma, strong tendency to bronchospasm, certain cardiac arrhythmias, the most common of which are second or third degree AV block and bradycardia, or uncontrolled congestive heart failure
c. also for washout medication Azopt® (use of which is judged by the investigator): hypersensitivity to brinzolamide or any of the excipients, known hypersensitivity to sulphonamide, severe renal insufficiency or hyperchloraemic acidosis
7. Glaucoma filtration surgery or any other ocular surgery (including ocular laser procedures) within 6 months prior to Screening in eye(s) to be treated with study medication
8. Use of contact lenses at Screening or during the study
9. Advanced visual field defect in either eye or anticipated progression during the study as judged by the investigator
10. Inability to safely discontinue the use of ocular hypotensive medications during the washout period
11. Any ocular (e.g. aphakia, pseudophakia with torn posterior lens capsule or anterior chamber lenses, known risk factors for cystoid macular oedema or iritis/uveitis), systemic or psychiatric disease/condition (e.g. uncontrolled arterial hypertension, diabetes) that may put the patient at a significant risk or may confound the study results or may interfere

significantly with the patient*s participation in the study as judged by the investigator
12. Change of an existing chronic therapy that could substantially affect the IOP or the study outcomes within 30 days prior to Visit 1, or anticipated change in such therapy during the study
13. Current alcohol or drug abuse
14. Current participation in another clinical trial involving an investigational drug/device, or participation in such a trial within the last 30 days

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):	21-06-2011
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Preservative-free fixed dose combination of tafluprost 0.0015% and timolol 0.5% eye drops
Product type:	Medicine
Brand name:	OFTAN® TIMOLOL 5 mg/ml
Generic name:	timolol

Product type:	Medicine
Brand name:	TAFLOTAN 15µg/ml
Generic name:	Tafluprost
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	31-01-2011
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-02-2011
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-12-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2010-022965-82-NL
ClinicalTrials.gov	NCT01292460
CCMO	NL34789.028.10