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Preservative-free fixed-dose combination of tafluprost 0.0015% / timolol 0.5% in patients with open-angle glaucoma or ocular hypertension: Clinical effectiveness, tolerability and safety in a real world setting

Protocol

Version 2.0

04 November 2016

Health Economics and Epidemiology



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Prepared for:

Feride Sahin
Santen
La Voie Creuse 14,
1202 Geneva
Switzerland
feride.sahin@santen.com

Prepared by:

Richard Pitman
ICON Plc
100 Park Drive
Milton Park
Abingdon
Oxfordshire
OX14 4RY

+44 1865 324 930
richard.pitman@iconplc.com

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Abbreviations

| Abbreviation | Full description |
|--------------|---|
| ADR | Adverse drug reaction |
| CAIs | Carbonic anhydrase inhibitors |
| CI | Confidence interval |
| EAS | Effectiveness analysis set |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| FAS | Full analysis set |
| CFS | Corneal fluorescein staining |
| GPP | Good Pharmacoepidemiological Practice |
| IEC | Independent Ethics Committee |
| IOP | Intra-ocular pressure |
| IRB | Institutional Review Board |
| ISPE | International Society for Pharmacoeconomics |
| OAG | Open angle glaucoma |
| OHT | Ocular hypertension |
| PGAs | Prostaglandin analogues |
| SD | Standard deviation |
| SPC | Summary of product characteristics |
| TBUT | Tear break up time |
| VA | Visual acuity test |

1. Abstract

1.1. Title

Preservative-free fixed-dose combination of tafluprost 0.0015% / timolol 0.5% in patients with open-angle glaucoma or ocular hypertension: Clinical effectiveness, tolerability and safety in a real world setting.

1.2. Description of the medicinal product

Tafluprost 0.0015% / Timolol 0.5% eye drops in single-dose containers, commercialised by Santen, hereafter referred to as Tafluprost / Timolol. Tafluprost / Timolol is administered once daily: one drop Tafluprost / Timolol in conjunctival sac of the affected eye(s) according to the summary of product characteristics (SPC). Concomitant medication according to SPC.

1.3. Rationale and background

This is a prospective, non-interventional study of the efficacy, tolerability and safety of Tafluprost / Timolol in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to topical monotherapy with beta-blockers or prostaglandin analogues and require a combination therapy, and who would benefit from preservative free eye drops.

1.4. Research objectives

The primary objective of this study is to assess the effectiveness of Tafluprost / Timolol in controlling ocular hypertension, as measured by mean change in intra-ocular pressure (IOP) from baseline to after 6 months of treatment from initiation, in patients with open angle glaucoma (OAG) or ocular hypertension (OHT), who do not respond sufficiently to initial topical treatment, in routine clinical practice.

Secondary objectives are:

- Assess the effectiveness of Tafluprost / Timolol in controlling ocular hypertension, as measured by mean change in intra-ocular pressure (IOP) from baseline to after 4 and 12 weeks of treatment from initiation, in patients with open angle glaucoma (OAG) or ocular hypertension (OHT), who do not respond sufficiently to initial topical treatment, in routine clinical practice
- Assessing the effectiveness of Tafluprost / Timolol in reducing clinical signs and subjective symptoms after 4 weeks, 12 weeks and 6 months of treatment in routine clinical practice
- Assess the tolerability of Tafluprost / Timolol after 4 weeks, 12 weeks and 6 months of treatment in routine clinical practice
- Assess the safety of Tafluprost / Timolol after 4 weeks, 12 weeks and 6 months of treatment in routine clinical practice

1.4.1. Primary endpoint

The primary endpoint is mean absolute change (mmHg) in intraocular pressure (IOP) from baseline to 6 months after Tafluprost / Timolol initiation.

The baseline value shall be measured after obtaining informed consent and within 7 days before the start of Tafluprost / Timolol treatment.

Endpoint data will be collected 6 months (± 45 days) from the initiation of Tafluprost / Timolol treatment.

1.4.2. Key secondary endpoints

- Mean change in intra-ocular pressure (IOP) from baseline to after 4 and 12 weeks of treatment from initiation (± 7 days)
- Proportion of responders at 12 weeks, defined as change from baseline IOP of 20% or more
- Evaluation of clinical signs with Tafluprost / Timolol
- Evaluation of subjective symptoms with Tafluprost / Timolol
- Evaluation of the efficacy (IOP-development) of Tafluprost / Timolol by the physician
- Evaluation of clinical signs during therapy with Tafluprost / Timolol by the physician
- Evaluation of tolerability of Tafluprost / Timolol by the patient
- Physician assessment of patient compliance compared to previous therapy
- Concomitant therapy for glaucoma

1.5. Study design

- Non-interventional prospective study
- No washout period for prior medication
- Decision to treat to be made according to routine clinical practice and by the treating physician
- 4 Visits:
 - Visit 1: Baseline visit with 7 days before the start of first Tafluprost / Timolol prescription
 - Visit 2: Examination at 4 weeks (± 7 days) from the first Tafluprost / Timolol prescription
 - Visit 3: Examination at 12 weeks (± 7 days) from the first Tafluprost / Timolol prescription
 - Visit 4: Examination at 6 months (± 45 days) from the first Tafluprost / Timolol prescription

1.6. Population

This study will include adults with open angle glaucoma or ocular hypertension, who received their first Tafluprost / Timolol prescription at baseline, even if Tafluprost / Timolol was not continued after the first prescription. In addition, patients must have their IOP recorded within 7 days before their first prescription of Tafluprost / Timolol, in order to be eligible for this study. Only those who provide informed consent will be included.

At the time of a scheduled clinic visit, eligible patients will be invited to participate in the study and willing patients will be requested to sign an informed consent form. Once informed consent is obtained, the

patient is included in the study and relevant data will be recorded during routine clinical visits. Participation in this study is entirely voluntary; any patient may withdraw consent to participate in this study at any time. The withdrawn patient's data will not be analysed in this study and the number of patients who withdrew consent will appear in the final study report.

1.6.1. Inclusion criteria

- Signed informed consent obtained before any study-related activities (study-related activities are any procedure related to extraction of data according to the protocol)
- According to the approved indications of Tafluprost / Timolol as indicated in the SPC
 - Male or female patients ≥ 18 years of age at time of informed consent
 - Diagnosis of open angle glaucoma or ocular hypertension
 - Insufficient IOP control with a monotherapy utilising topical beta blockers or prostaglandin analogues, necessitating the use of a combination therapy according to the judgement of the treating ophthalmologist
 - Patient judged by their physician to benefit from preservative free eye drops

1.6.2. Exclusion criteria

- Patient pregnant or nursing
- Pregnancy planned in the following 6 months
- Presence of contraindications as listed in the SPC
- Any ophthalmologic surgery within 6 months prior to the study
- Participation in any other investigational study within 30 days prior to enrolment

1.6.3. Minimum available data

- IOP value within 7 days prior to date of first Tafluprost / Timolol prescription
- IOP value at 6 months (± 45 days) after the date of first Tafluprost / Timolol prescription

1.7. Variables

Where appropriate, variables will be recorded for each eye separately.

1.7.1. Baseline visit

- Demographic data
- Diagnosis (specifying affected eye)
- Type and duration of prior treatment
- IOP at baseline: value and time of day measured
- Evaluation of clinical signs under prior treatment
- Evaluation of subjective symptoms under prior treatment

- Reason(s) for change of medical therapy (efficacy evaluation of prior treatment)
- Any concomitant therapy

1.7.2. Visits at 4 weeks, 12 weeks and 6 months

- Tafluprost / Timolol time of use (morning/evening)
- IOP: value and time of day it was measured
- Evaluation of clinical signs with Tafluprost / Timolol
- Evaluation of subjective symptoms with Tafluprost / Timolol
- Evaluation of the efficacy (IOP-development) of Tafluprost / Timolol by the physician
- Evaluation of clinical signs during therapy with Tafluprost / Timolol by the physician
- Evaluation of tolerability of Tafluprost / Timolol by the patient
- Physician assessment of patient compliance compared to previous therapy
- Reason(s) for discontinuation of Tafluprost / Timolol, if applicable (efficacy evaluation)
- Documentation of adverse events during the study

1.8. Data sources

Once an informed consent form is signed by the patient, the patient is enrolled in the study and site staff may enter data into the electronic case report form (eCRF) covering the first visit. The date of Tafluprost / Timolol initiation must subsequently be recorded in the eCRF.

During routine visits at 4 weeks (± 7 days), 12 weeks (± 7 days) and 6 months (± 45 days) post first Tafluprost / Timolol prescription, site staff will enter data into the eCRF covering these visits. Only data elicited as part of standard care will be entered into the eCRF.

1.9. Study size

Approximately 1083 patients will be enrolled from study sites in thirteen countries.

1.10. Data analysis

The primary analysis will be a comparison of IOP values at baseline with values at 6 months after Tafluprost / Timolol initiation. Where data on both eyes is available, both will be recorded and the IOP value for the worst eye at baseline used in the analysis. As such, the full analysis set will include all patients who received at least one prescription of Tafluprost / Timolol. Analysis of secondary endpoints and sub-group analysis will be conducted and presented as outlined in section 5.7. All analyses will be further described in the statistical analysis plan.

A complete-case analysis approach will be undertaken for all analyses. The amount of missing information will be summarised and assessed; if more than 15% of patients have missing data for a particular outcome, patient characteristics will be compared for those with and those without missing information to

assess generalizability of the findings. All tests of statistical significance will be two-sided and will be assessed at a significance level of 5%.

2. Rationale and background

An increased intraocular pressure (IOP) represents a major risk factor for glaucoma and therefore should be sustainably lowered in patients with glaucoma or ocular hypertension in order to reduce the risk of progression to glaucomatous optic neuropathy or the conversion of ocular hypertension to glaucoma.¹

Today numerous mono preparations for the lowering of IOP are available including prostaglandin analogues (PGAs), beta-blockers, selective alpha-2-agonists, carbonic anhydrase inhibitors (CAIs) and miotics. In certain cases mono therapies are not sufficiently effective at lowering IOP and in these cases a combination therapy is required.¹

2.1. Advantages and disadvantages of fixed combinations

In patients who require a combination therapy, fixed combinations are usually favoured over non-fixed combinations as they offer numerous advantages (e.g. number of daily drop applications, no danger of confusion of vials, better compliance, possible wash out effects of non-fixed combinations, amount of preservatives) and are particularly preferred in 2nd line therapy.^{1, 2}

2.2. Fixed combination of Tafluprost 0.0015% and Timolol 0.5%

The fixed combination of the prostaglandin analogue Tafluprost 0.0015% and the nonselective beta blocker Timolol 0.5% (Tafluprost / Timolol) is available as a preservative-free formulation and as a new therapeutic option may be beneficial especially for patients who require a preservative-free fixed combination.

2.3. Pharmacology

Tafluprost / Timolol contains a combination of Tafluprost, a prostaglandin, and Timolol, a beta blocker. The prostaglandin Tafluprost is a fluorinated synthetic analogue of PGF_{2α}.³ This so called prodrug is the inactive form of the active ingredient and becomes converted to the active form Tafluprost acid once it penetrates the cornea.³ Tafluprost acid is a highly selective agonist of the prostaglandin FP-receptor and is produced from its inactive form by hydrolysis of the isopropyl ester with the help esterases naturally present in the cornea.^{3 4} Tafluprost increases the uveoscleral outflow of the aqueous humour from the eye.^{3 4}

The non-selective beta receptor-antagonist Timolol decreases the production of aqueous humour especially by blocking the β₂-receptors in the area of the ciliary body.⁵ The different pharmacologic mechanisms of Tafluprost and Timolol have synergistic effects in lowering IOP.

2.4. Clinical profile of Tafluprost / Timolol

In a 6-month double masked, randomized, multi-center study efficacy, safety and tolerability of the preservative-free fixed combination Tafluprost / Timolol were compared with its preservative-free components (Tafluprost 0.0015% and Timolol 0.5%) applied within a non-fixed combination. In one stratum 95 patients were treated with the preservative-free fixed combination of Tafluprost and Timolol and 94 patients with preservative-free Timolol 0.5%. In the arm treated with the fixed combination, the mean IOP decreased by 32% (-8.55 mmHg) after 3 months, while in the Timolol treatment arm the IOP was lowered only by 28% (-7.35 mmHg). Therefore this study demonstrated that the IOP lowering effect of the preservative free fixed combination is superior to a mono therapy with Timolol 0.5%.

In a second stratum 188 patients were treated with the preservative free fixed combination of Tafluprost 0.0015% and Timolol 0.5% and another 187 patients were treated with preservative- free Tafluprost 0.0015%. In this stratum the IOP-lowering effect of the fixed combination (Decrease of IOP at month 3: - 8.61 mmHg; -33%) was also shown to be superior versus a monotherapy with Tafluprost 0.0015% (Decrease of IOP at month 3: -7.23 mmHg; -28%).⁶

In another clinical registration study efficacy, safety and tolerability of the fixed combination of Tafluprost 0.0015% and Timolol 0.5% with a non-fixed combination of both active ingredients was evaluated. In this study 400 patients with primary open angle glaucoma, pseudo exfoliative glaucoma, pigmentary glaucoma or ocular hypertension were included. 201 patients were treated once daily with the preservative-free fixed combination. In the second treatment arm 199 patients were treated with the preservative free non-fixed combination of Tafluprost 0.0015% and Timolol 0.5%. The IOP was lowered by the treatment with the fixed and non-fix combination by up to 34.6% (-9.13 mmHg) to 36.0% (-9.43 mmHg) respectively. The differences were found not be statistically significant, which means the fixed combination was non inferior to the non-fixed combination.⁷ In total 484 patients were treated with the new preservative-free fixed combination of Tafluprost 0.0015% and Timolol 0.5% in these 2 clinical studies.

This non-interventional prospective study will evaluate the effectiveness, tolerability and safety of Tafluprost / Timolol in routine clinical practice. As such, the study will recruit a substantially more heterogeneous patient population than would be seen in a clinical trial.

3. Research question and background

3.1. Primary objective

The primary objective of this non-interventional study with Tafluprost / Timolol is to evaluate the effectiveness of Tafluprost / Timolol in routine clinical practice, as measured by the mean change in intraocular pressure 6 months post initiation of Tafluprost / Timolol therapy, in patients with open angle glaucoma or ocular hypertension.

3.2. Secondary objectives

- Mean change in intra-ocular pressure (IOP) from baseline to after 4 and 12 weeks of treatment from initiation (± 7 days)
- Proportion of responders at 12 weeks, defined as change from baseline IOP of 20% or more
- Assessing the effectiveness of Tafluprost / Timolol in reducing clinical signs and subjective symptoms after 6 months of treatment in routine clinical practice
- Assess the tolerability of Tafluprost / Timolol after 6 months of treatment in routine clinical practice
- Assess the safety of Tafluprost / Timolol after 6 months of treatment in routine clinical practice
- Description of the profile of patient groups treated with Tafluprost / Timolol:
 - Demographics (age, gender)
 - Reasons for changing therapy

4. Workflow and data collection

After confirming a centre's participation by signing the agreement to participate in this non-interventional study, all participating centres will receive the required documents from Santen. The collection of patient data is possible as soon as the participants have received the documents of the non-interventional study.

Each participating centre takes sole responsibility for the correct and complete documentation of all data collected at their own centre.

5. Research methods

5.1. Study design

This is a non-interventional prospective study collecting data during routine clinical visits by patients with open angle glaucoma or ocular hypertension who have not responded sufficiently to monotherapy with topical beta blockers or prostaglandin analogues and therefore are in need of a combination therapy, and who their physician judge would benefit from preservative free eye drops.

Baseline data would be collected at the point the patient consents to participate in the study and before the initiation of Tafluprost / Timolol therapy. For inclusion in the analysis, Tafluprost / Timolol therapy should have been initiated within 7 days after the collection of baseline data.

Intraocular pressures measured at baseline and after 4 and 12 weeks (± 7 days) and after 6 months (± 45 days) post initiation of Tafluprost / Timolol therapy will be recorded, irrespective of whether or not the patient was still on Tafluprost / Timolol treatment at the time of the visit. Each patient's IOP data at each follow up visit will be compared with the same patient's data at baseline, thereby having each patient act as their own control.

The objective of this study is to understand the effectiveness of Tafluprost / Timolol in routine clinical practice. To achieve this objective, it is important to collect real-world data from patients, not from within a controlled environment as is typically the case in randomised clinical trials. A prospective non-interventional study was selected as the appropriate study design.

Data on each patient will be entered directly into an electronic case report form at each consultation to capture information within 7 days before the initiation of Tafluprost / Timolol therapy and after 6 months (± 45 days) of the initiation of Tafluprost / Timolol therapy.

5.1.1. Primary endpoint

The primary endpoint is mean absolute change (mmHg) in intraocular pressure (IOP) from baseline to 6 months after Tafluprost / Timolol initiation.

The baseline value shall be measured after obtaining informed consent and within 7 days before the start of Tafluprost / Timolol treatment.

Endpoint data will be collected 6 months (± 45 days) from the initiation of Tafluprost / Timolol treatment.

The primary endpoint will be assessed for the whole patient group and separately in specific subgroups according to their last glaucoma treatments before initiating Tafluprost / Timolol. Classification of prior therapy will be based on classes of glaucoma treatment: Prostaglandin analogues or beta blockers.

5.1.2. Secondary endpoints

- Mean change in intra-ocular pressure (IOP) from baseline to after 4 and 12 weeks of treatment from initiation (± 7 days)
- Proportion of responders at 12 weeks, defined as change from baseline IOP of 20% or more
- Evaluation of clinical signs with Tafluprost / Timolol
 - Change in conjunctival hyperaemia distribution by severity
 - Change in corneal fluorescein staining (CFS) distribution by severity. Optional
 - Mean change in Visual acuity test (VA)
 - Mean change in Schirmer's test. Optional
 - Mean change in tear break up time (TBUT). Optional
- Change in the evaluation of subjective symptoms with Tafluprost / Timolol. Difference in distribution by severity. Severity categorised as none, mild, moderate, severe.
 - Dry eye
 - Irritation
 - Itching eyes
 - Foreign body sensation
 - Eye pain
 - Other
- Evaluation of the efficacy (IOP-development) of Tafluprost / Timolol by the physician as measured by change in distribution by severity
 - Better than prior medication
 - Same as prior medication
 - Worse than prior medication
- Evaluation of clinical signs during therapy with Tafluprost / Timolol by the physician as measured by change in distribution by severity
 - Better than prior medication
 - Same as prior medication
 - Worse than prior medication
- Evaluation of tolerability of Tafluprost / Timolol by the Patient as measured by change in distribution by severity
 - Very good
 - Good
 - Satisfactorily
 - Poor
- Physician assessment of patient compliance compared to previous therapy
 - Better
 - Equal
 - Worse
- Concomitant therapy for glaucoma

All secondary endpoints will be assessed for the whole patient group and separately in specific subgroups according to their last glaucoma treatments before initiating Tafluprost / Timolol. Classification of prior therapy will be based on classes of glaucoma treatment: Prostaglandin analogues or beta blockers.

5.1.3. Treatment of patients

The patient's physician is solely responsible for the initiation of treatment, following the specifications set out in the SPC for Tafluprost / Timolol, and for the consideration of precautions, contraindications and all other details of the treatment.

Participation in this non-interventional study does not have any influence on the prescription or number of prescriptions of Tafluprost / Timolol nor on those of any other glaucoma related treatment.

5.1.3.1. Dosage

One drop of Tafluprost / Timolol per day is applied into the lower conjunctival sac of the affected eye(s). If other topical medicinal products are applied at the same time, a time lag of at least 5 minutes between single administrations should be considered.

Contact lenses should be removed before the administration of Tafluprost / Timolol and may be reinserted 15 minutes after administering the eye drops.

5.1.3.2. Duration of use

Open-angle glaucoma and ocular hypertension usually require chronic treatment. The duration of use for an individual patient is determined by their therapeutic requirements as assessed by their attending physician.

5.1.3.3. Concomitant medications

During this non-interventional study it is possible that other concomitant medications may be prescribed by a patient's physician, according to the specifications of the SPC. If concomitant medications are needed these should be recorded in the eCRF.

5.1.3.4. Documentation of medication

The following details must be specified in the eCRF:

- Starting date of medical treatment with Tafluprost / Timolol
- Prior medication and duration
- Details of any combination therapy in addition to the use of Tafluprost / Timolol

5.2. Setting

Data will be recorded during routine consultations by adults with open angle glaucoma or ocular hypertension, who received their first Tafluprost / Timolol prescription, at clinics in the United Kingdom, Ireland, Spain, Portugal, Netherlands, Sweden, Denmark, Norway, Italy, Russia, Austria, Latvia and Hungary.

In this prospective study, patient eligibility will be determined by their attending physician, according to the inclusion and exclusion criteria set out in this protocol. Eligible patients attending an appointment at a participating clinic will be informed of the study. Patients who provide informed consent will be included in the study. During routine consultations with their physician clinical information will be recorded in the eCRF. The target population for the current study is all eligible patients who received at least one prescription of Tafluprost / Timolol in the United Kingdom, Ireland, Spain, Portugal, Netherlands, Sweden, Denmark, Norway, Italy, Russia, Austria, Latvia and Hungary; however the sample population will be limited to eligible patients in the clinics included in the study.

5.2.1. Study population

Planned number of patients to be included: 1083

Planned number of patients to be included in the primary analysis: 1083

5.2.2. Inclusion criteria

- Signed informed consent obtained before any study-related activities (study-related activities are any procedure related to the recording of data according to the protocol)

According to the approved indications of Tafluprost / Timolol as indicated in the SPC:

- Male or female patients ≥ 18 years of age at time of informed consent
- Diagnosis of open angle glaucoma or ocular hypertension
- Insufficient response to treatment with a monotherapy utilising topical beta blockers or prostaglandin analogues, necessitating the use of a combination therapy
- Patient judged by their physician to benefit from preservative free eye drops

5.2.3. Exclusion criteria

- Patient pregnant or nursing
- Pregnancy planned in the following 6 months
- Presence of contraindications as listed in the SPC
 - Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 of the SPC
 - Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease
 - Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock
- Any ophthalmologic surgery within 6 months prior to the study
- Participation in any other investigational study within 30 days prior to enrolment

5.2.4. Minimum available data

- IOP value within 7 days prior to date of first Tafluprost / Timolol prescription
- IOP value at 6 months (± 45 days) after the date of first Tafluprost / Timolol prescription

5.2.5. Withdrawal criteria

The patient may withdraw consent at any time. If a patient decides to withdraw consent, no additional data will be recorded. The withdrawn patient's data will not be analysed in this study and the number of patients who withdrew consent will appear in the final study report.

5.2.6. Rationale for selection criteria

The present study population constitutes a broader real-world glaucoma/ocular hypertension patient population than is typically included in randomised controlled trials. This study seeks to represent the current patient population treated with Tafluprost / Timolol in the real-world setting, and their associated treatment patterns.

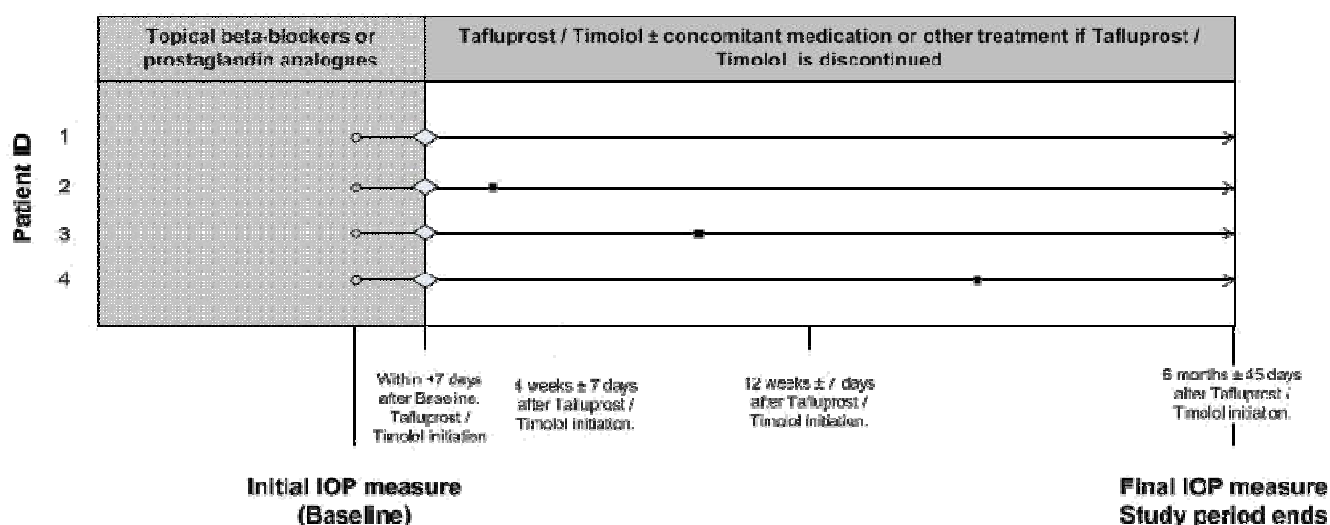
5.2.7. Visit procedure

The study accrual period will be determined based on the number of clinics recruited to achieve the current study goals. Collection of data for eligible patients will be undertaken between approximately February 2017 and February 2018, assuming a sufficient number of clinics to provide data for 1083 patients. During the recruitment period all eligible patients attending participating clinics will be invited to participate in the study, and if patients provide informed consent, relevant data will be recorded during routine clinical visits.

The flow chart below shows the time points at which data will be collected.

Legend

| | |
|---|----------------------------------|
| ◇ | Tafuprost / Timolol initiation |
| ○ | Start of data collection |
| ■ | Tafuprost / Timolol discontinued |
| → | End of follow-up |



For definitions of 'baseline' refer to section 5.1.1. The variables to be collected at each time point are outlined in section 5.3. Country and site information will be collected for all participants.

5.3. Variables

Country and site information will be collected for all participants. Where appropriate, variables will be recorded for each eye separately. Intraocular pressure to be measured by Goldmann applanation tonometry

5.3.1. Baseline visit

- Demographic data
 - Gender
 - Date of birth
- Diagnosis (specifying affected eye)
 - Ocular Hypertension
 - Primary Open-Angle-Glaucoma
 - Normal Tension Glaucoma
 - Pseudoexfoliative Glaucoma
 - Pigmentary Glaucoma
 - Other Glaucoma
- Type of prior treatment and duration of use

- IOP at baseline: value and time of day at which it was measured
- Evaluation of clinical signs under prior treatment
 - Conjunctival hyperaemia
 - None
 - Mild
 - Moderate
 - Severe
 - CFS (Oxford scale grade) Optional
 - 0
 - I
 - II
 - III
 - IV
 - V
 - Visual acuity test (VA)
 - Schirmer's test Optional
 - Tear break up time (TBUT) Optional
- Evaluation of subjective symptoms under prior treatment.
Severity categorised as none, mild, moderate, severe
 - Dry eye
 - Irritation
 - Itching eyes
 - Foreign body sensation
 - Eye pain
 - Other
- Reason(s) for change of medical therapy (efficacy evaluation of prior treatment)
 - Insufficient IOP control within prior medication
 - Progression of glaucoma
 - Conversion of ocular hypertension – first glaucomatous damages
 - Poor local tolerance
 - Poor compliance
 - Other reasons
- Any concomitant therapy

5.3.2. Visits at 4 weeks (± 7 days), 12 weeks (± 7 days) and 6 months (± 45 days) post initial Tafluprost / Timolol prescription

- Tafluprost / Timolol time of use (morning/evening)
- IOP : value and time of day it was measured
- Evaluation of clinical signs with Tafluprost / Timolol
 - Conjunctival hyperaemia
 - None
 - Mild
 - Moderate

- Severe
 - CFS (Oxford scale grade) Optional
 - 0
 - I
 - II
 - III
 - IV
 - V
 - Visual acuity test (VA)
 - Schirmer's test Optional
 - Tear break up time (TBUT) Optional
- Evaluation of subjective symptoms with Tafluprost / Timolol.
Severity categorised as none, mild, moderate, severe
 - Dry eye
 - Irritation
 - Itching eyes
 - Foreign body sensation
 - Eye pain
 - Other
- Evaluation of the efficacy (IOP-development) of Tafluprost / Timolol by the physician
 - Better than prior medication
 - Same as prior medication
 - Worse than prior medication
- Evaluation of clinical signs during therapy with Tafluprost / Timolol by the physician
 - Better than prior medication
 - Same as prior medication
 - Worse than prior medication
- Evaluation of tolerability of Tafluprost / Timolol by the patient
 - Very good
 - Good
 - Satisfactorily
 - Poor
- Physician assessment of patient compliance compared to previous therapy
 - Better
 - Equal
 - Worse
- Reason(s) for discontinuation of Tafluprost / Timolol, if applicable (efficacy evaluation)
 - Insufficient IOP control
 - Progression of glaucoma
 - Conversion of ocular hypertension – first glaucomatous damages
 - Poor local tolerance
 - Poor compliance
 - Other reasons
- Documentation of adverse events during the study

5.4. Data sources

Once an informed consent form is signed by the patient, the patient is enrolled in the study and site staff may enter data into the electronic case report form (eCRF) covering the first visit. The date of Tafluprost / Timolol initiation must subsequently be recorded in the eCRF.

During routine visits at 4 weeks (± 7 days), 12 weeks (± 7 days) and 6 months (± 45 days) post first Tafluprost / Timolol prescription, site staff will enter data into the eCRF covering these visits. Only data elicited as part of standard care will be entered into the eCRF.

5.5. Study size

This study aims to evaluate IOP at 6 months after Tafluprost / Timolol initiation in routine clinical practice. Results can be presented by specific subgroups (e.g. according to the treatment immediately preceding Tafluprost / Timolol start). For each patient group/subgroup, the sample size is based on the expected values of IOP at the time of treatment start and the expected mean change over time after the initial prescription of Tafluprost / Timolol.

Table 1 below describes the potential sample sizes required to detect a mean decrease of IOP of 0.885, tested by a 2-sided paired-test and considering a significance level of 0.05, with a range of possible standard deviations (SD) of the difference (σ_d) (ranging from 2.75 to 3.5) and power (ranging from 80% to 95%). Mean decrease of IOP of 0.885 was chosen because this is the magnitude of IOP change from baseline that could be expected in the real-world.⁶

| Power (%) | σ_d | | | |
|-----------|------------|-----|------|-----|
| | 2.75 | 3.0 | 3.25 | 3.5 |
| 80 | 76 | 91 | 106 | 123 |
| 85 | 87 | 104 | 122 | 141 |
| 90 | 102 | 121 | 142 | 165 |
| 95 | 126 | 150 | 176 | 204 |

Based on the calculations above, an assessment of the primary outcomes with a power of 80% can be achieved with a minimum of 91 patients with complete data in each group.

When considering pre-Tafluprost / Timolol treatments, it is assumed that 69% of patients would be on prostaglandin analogues versus 31% on beta blockers.⁶

To allow for an analysis in the subgroup on beta blockers as pre-Tafluprost / Timolol treatment, the number of patients with complete data will be 294 (i.e., $91/0.31$). The group expected to be observed least frequently (i.e. beta blocker group) is chosen for sample size calculation to ensure that there are enough patients in the least frequently prescribed regimen group. As it is expected that 24% of the patients

included could have inconsistent data, a minimum of 387 (i.e. 294/0.76) patients will be included to ensure a sufficient sample to detect the IOP difference separately in all patients, and by pre-Tafluprost / Timolol treatment subgroup. Therefore the total number of patients to be included is approximately 387.

5.6. Data management

The physician must keep a patient enrolment log to record eligible patients providing informed consent to participate, and a log of patients evaluated for but not included in the study. These can be combined in one document. Patient identification numbers can be assigned in a consecutive manner, with the first two digits of a patient's identification being the site identification, and the last digit(s) being the patient number (e.g., 04 – 25).

Data collected during scheduled consultations will be entered into an eCRF (DataTrak) and will be stored on their secured server. Each patient will be assigned a unique study identifier by the principal physician or designee, and there will be no direct identifiers attached to the recorded data. Only those assigned to the task of collecting data at each site will have access to the identified data. Physicians and all site staff participating in this study will be trained on study procedures prior to start of the study.

Appropriate measures such as encryption of data files must be used to assure confidentiality of patient data if it is transmitted over open networks.

ICON will provide electronic eCRFs for capture of study specific patient data. Instructions for completion and correction of eCRFs will be provided.

The physician must ensure that study specific patient data is entered in the eCRF according to agreed study specific timelines. The eCRFs data will be collected, by ICON.

The system for Electronic Data Capture (EDC), DataTrak, and support services for the system will be supplied by ICON.

An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for any correction, the original entry and the corrected entry.

By signing the affirmation statement/casebook the physician confirms that the information in the eCRF is complete and correct.

If corrections are made by the physician's authorised staff after the date of the physician's signature on the affirmation statement/casebook, this must be checked and signed again by the physician.

5.7. Data analysis

5.7.1. Definition of analysis sets

The primary dataset will be the full analysis set (FAS) i.e. all patients having signed the informed consent form and for whom Tafluprost / Timolol was prescribed at least once, irrespective of whether patients continued Tafluprost / Timolol after the first prescription.

Any one analysis will include patient records with complete data on the variables required for that analysis. To reflect real life utilisation, no patient will be excluded from the follow up and analyses will start with the full cohort (regardless of continuation/discontinuation).

A secondary effectiveness analysis set (EAS) will include all patients already included in the FAS and having continued Tafluprost / Timolol treatment for 6 months after initiation and with at least one measurement of IOP at 6 months (± 45 days) after initiation.

Safety analysis set (SAS): N /A.

5.7.2. Statistical methods

The general approach will be to test the difference in the response variable (IOP value) before and after initiation of treatment with Tafluprost / Timolol. Initial exploratory analyses will utilise the paired t-test to identify potentially significant mean changes in response. These will be augmented by the use of linear regression models that account for covariates (more important at smaller sample sizes) as well as confounding. The exact form of these models, such as the error distribution and link function of choice will be guided by the available data.

For all analyses, the amount of missing information will be described. In particular, if a significant degree of missing/inconsistent information is present in the data informing the primary endpoint (i.e. more than 15% of patients excluded from analysis), a comparison of patient characteristics among those with and without missing information will be conducted to assess the generalizability of the main results. Additionally, the rate of refusal per study site will be presented.

For all tests of statistical significance, formulation will be two-sided, and will be assessed at a significance level of 5%.

Primary endpoint

The primary analysis will be a comparison of the IOP value at baseline with the IOP value at 6 months after Tafluprost / Timolol treatment start.

IOP values at baseline and at 6 months post Tafluprost / Timolol initiation, as well as change in IOP after 6 months of treatment, will be summarised by their mean and SD. A 95% confidence interval (CI) will also be reported for the mean change in IOP from baseline. A paired t-test will be conducted to assess statistical significance of the mean IOP change.

The primary endpoint will also be estimated as a baseline adjusted change using a normal linear regression model. In this model, change from baseline in IOP will be modelled as a function of the baseline value and relevant covariates. Covariates may include, but not be limited to, the following variables: country, age, gender, clinical signs at baseline (conjunctival hyperaemia, corneal fluorescein staining results, Schirmer's test result, tear film breakup time), as well as change in signs from baseline to 6 months post Tafluprost / Timolol initiation.

Results will be presented overall, and according to relevant subgroups, e.g., previous treatment received, Tafluprost / Timolol discontinuation / continuation, last IOP measured before Tafluprost / Timolol prescription and country.

Secondary endpoints

Secondary endpoints will be presented descriptively. Continuous Data will be summarised with the use of means, standard deviation, minimum, maximum, median and number of valid values.

For categorical data such as gender and age categories, counts and proportions will be used to summarise the data. Categorical variables will be compared between subgroups using the Chi-squared test if the total of each class studied is greater than 5, otherwise Fisher's exact test will be used.

Several secondary outcomes are expressed as numbers or ordinal scales, these include tolerability scales and efficacy scales. A negative binomial model will be used to model these data, with subgroup included as a factor.

5.7.3. Preliminary analyses

Preliminary analyses may be performed over the course of the study.

5.7.4. Sequential safety analysis/safety monitoring

N/A

5.8. Quality control

Before beginning data collection, all sites or CRO staff members will receive training on study procedures and completion of the eCRF. Remote monitoring of recorded data will be conducted for each site throughout the study. The value of periodic monitoring will be in that records with errors can be flagged and corrected. It is anticipated that monitoring will be performed on 20% of records; this will be tracked electronically.

5.8.1. Monitoring procedures

The ICON site manager will conduct in-house monitoring activities as needed during the study.

In-house site management activities will include site contact, generation of contact reports, site status tracking, attendance at team meetings, attendance at team training, responding to site questions, maintenance of updated investigator regulatory documents, issue resolution from previous site monitoring visits/calls, assisting with data queries, planning next calls, generation of reports, assist as needed with mass distribution of information, and maintaining the investigator file. ICON will maintain telephone contact with sites on a regular basis throughout the study.

Adverse events, SAEs, their follow up and reconciliation as needed shall remain the responsibility of Santen.

5.8.2. Critical documents

Before the physician starts the study (which is when informed consent is obtained from the first patient), the following documents must be available to Santen:

- Regulatory approval and/or notification as required
- Documentation of the physician's qualifications as medically qualified (for instance a short curriculum vitae or authorisation)
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any amendment(s), if applicable
- Approval/favourable opinion from Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (or other appropriate bodies as required locally) clearly identifying the documents reviewed: the protocol, any amendments, patient information/informed consent form and any other written information to be provided to the patient, patient enrolment procedures
- Copy of IEC/IRB approved patient information/informed consent form/any other written information/advertisement
- Non-interventional study agreement
- Source document agreement

5.8.3. Retention of study documents

Santen will comply with Good Pharmacoepidemiological Practice (GPP) and relevant national legislation related to archiving of study documentation.

The physician must agree to archive the documentation pertaining to the study in an archive for at least 5 years after final report/first publication of the study, whichever comes later. The physician should not destroy any documents without prior permission from Santen.

Santen will retain the documentation pertaining to the study according to company procedures and in accordance with national regulations if they require a longer retention period.

6. Protection of human subjects

The study will be conducted in accordance with GPP, ISPE guideline for Good Pharmacoepidemiology Practices.⁸

6.1. Informed consent form for study patients

A voluntary, signed and personally dated, informed consent form will be obtained from the patient prior to any study-related activity.

The physician must give the patient information in a form that the patient can read and understand. This includes the use of an impartial witness where required.

In obtaining and documenting informed consent, the physician must comply with the applicable regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki.

The task of seeking informed consent can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must also sign and date the patient information/informed consent form.

6.2. Data handling

If a patient withdraws previously given informed consent to participate in the study, that patient's data that has already been collected will be archived but will not be used in data analyses.

6.3. Premature termination of the study

The sponsor, physician or a pertinent regulatory authority may decide to stop the study or part of the study at any time, but agreement on procedures to be followed must be obtained.

Unplanned discontinuation of the study will be characterised by permanent suspension of data collection and other study-related activities.

If a study is prematurely terminated or suspended, information must be provided to the relevant national bodies as required by national regulation and procedure.

6.4. Responsibilities

6.4.1. Overall responsibility for the project and scientific queries related to Tafluprost / Timolol

Santen

Feride Sahin
Director, Medical Affairs Europe
Medical Affairs CH
Santen Switzerland SA
La Voie-Creuse 14, 1202 Genève, Switzerland

e-mail: feride.sahin@santen.com

Mob.: +41 79 749 23 67

6.4.2. Reports and documentation of adverse events

Santen Oy Pharmacovigilance Unit

Niittyhaankatu 20, PO Box 33
33721 Tampere
Finland

e-mail: safetyEU@santen.com

Tel.: +358 3 284 8625 (24 hour)

Fax: +358 3 318 1060

6.4.3. Planning, preparation, technical project organization, data management and analysis, reporting

ICON

Maria Luisa Mesa, PharmD
Project Manager
ICON Clinical Research
Mobile Phone: +34 600 401 606
Email: MariaLuisa.Mesa@iconplc.com

7. Managing and reporting of adverse episodes/adverse reactions

Santen has the duty to collect adverse events (AEs) that occur at the time of medical treatment **irrespective whether a causal link is assumed or not**. All participants in the non-interventional study with Tafluprost / Timolol shall be obligated to ensure that all adverse AEs observed during the study are carefully recorded.

AE reporting forms shall be used to record all non-serious and serious cases of AEs that occurred or are observed during the non-interventional study, including:

- **already known AEs (for details see SPC)**

and

- **unexpected AEs**

AEs shall be entered into the eCRF immediately at the latest within 24 hours after the physician became aware of the AE (for evaluation of Santen Pharmacovigilance Unit). All the relevant information related to the AE shall be recorded into the eCRF. It is particularly important to provide:

Causality assessment

- It shall be assessed if the AE is possibly related or not related to Tafluprost / Timolol

Seriousness assessment

- The AE is classified as **serious** when it is fatal, life-threatening or sight-threatening, requires an in-patient treatment or extension of an in-patient treatment, leads to a permanent or serious disability or invalidity or represents a congenital anomaly or a birth defect.

Severity assessment

The investigator shall evaluate the severity of all AEs as follows:

- Mild: awareness of sign/symptom, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity
- Severe: incapacitating sign/symptom with inability to work or do usual activity

Relevant concomitant conditions/medications

- All concomitant conditions/medications which may have a relation to AE shall be reported.

Any AE or SAE which occurs during this study must be recorded by the Investigator/site staff within 24 hours in the eCRF. Entry into the eCRF will trigger an e-mail alert to Santen Medical Safety with the details of the event.

Line listings of all non-serious AEs and Serious AEs will be created by Data Management and sent to Santen PVU for review and reconciliation with the safety database on a regular basis.

In addition, the Investigator will report suspected adverse reactions to regulatory authorities, as required by pharmacovigilance practice regulations for marketed drug products

All AE reports will identify patients by unique code numbers assigned to the study patients, rather than by the patients' names, personal identification numbers, or addresses.

In addition, any information on the following events, regardless whether with or without AE, constitute collectable Safety Information and shall be recorded into eCRF:

- Misuse
- Overdose
- Medication error
- Off-label use
- Exposure during pregnancy via mother or father
- Exposure during lactation
- Lack of or reduced therapeutic efficacy
- Abuse
- Occupational exposure
- Suspected or confirmed transmission of an infectious agent via a medicinal product
- Suspected or confirmed interaction with another medicinal product or other interaction
- Suspected falsified medicinal products

Santen will submit to regulatory authorities and ethic committees notification of emerging safety issues, if required. Santen will also provide annual and/or periodic safety reports to regulatory authorities.

8. Plans for dissemination and communicating study results

The information obtained during the conduct of this study is considered confidential and can be used by Santen for regulatory purposes and for safety surveillance. All information supplied by Santen in connection with this study must remain the sole property of Santen and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Santen. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with the study product, if deemed necessary by Santen.

8.1. Registration of study information

This study is eligible for registration at www.clinicaltrials.gov. If disclosure of non-interventional studies is mandatory in local study registries, the study will be registered in the appropriate registries according to local regulations.

Note: Study registration is regarded as the publication of an internationally-agreed set of information (which can be found at the World Health Organization (WHO) homepage) about the design, conduct and administration of non-interventional studies. These details are published on a publicly-accessible website managed by a registry conforming to WHO standards (also found at the WHO homepage); for example, www.clinicaltrials.gov.

In accordance with Santen standard practice, topline study results will also be provided on EUDRAT / ClinicalTrials.gov.

8.2. Communication and publication

In accordance with Santen standard practice, key data from this study will be presented at a recognised congress and/or published in a peer-reviewed journal. Santen will work with a study publication steering committee and, as required, medical writers to develop the publications.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the physician from each site will be named in the acknowledgement.

The physician must ensure submission of the results of the study (either abstracts or full study report) to IEC/IRB (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In all cases, the study results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the physicians' and Santen's opinions must be fairly and sufficiently represented in the publication.

Santen maintains the right to be informed of any physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol, to ensure the scientific accuracy of the data. Any such communication must be submitted in writing to the Santen study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

9. References

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4. Ishida N, Odani-Kawabata N, Shimazaki A, et al. Prostanoids in the therapy of glaucoma. *Cardiovasc Drug Rev* 2006;**24**(1):1-10.
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7. Hollo G, Hommer A, Anton Lopez A, et al. Efficacy, safety, and tolerability of preservative-free fixed combination of tafluprost 0.0015%/timolol 0.5% versus concomitant use of the ingredients. *J Ocul Pharmacol Ther* 2014;**30**(6):468-75.
8. International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). Initially issued in 1996. Revision 2, April 2007. 2007.

10. Final protocol sign off

Title: Preservative-free fixed-dose combination of tafluprost 0.0015% / timolol 0.5% in patients with open-angle glaucoma or ocular hypertension: Clinical effectiveness, tolerability and safety in a real world setting.

Version: 2.0

Date : 04 November 2016

| Santen representative | ICON representative |
|-----------------------|--|
| Name (Please print): | Name (Please print): Richard Pitman |
| Position: | Position: Lead Epidemiologist |
| Signature: | Signature: |
| Date: | Date: 04 November 2016 |