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Changes in ocular signs and symptoms in patients switching from bimatoprost–timolol to tafluprost–timolol eye drops: an open-label phase IV study

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ABSTRACT (292/300 words)

Objectives

Bimatoprost–timolol (bimatoprost 0.03%–timolol 0.5% fixed-dose combination [FDC]) and tafluprost–timolol (tafluprost 0.0015%–timolol 0.5% FDC) eye drops are currently the only topical intraocular pressure (IOP)-reducing therapies available as preservative-free (PF) prostaglandin and timolol FDC. The aim of this study was to investigate changes to ocular signs and symptoms when patients with ocular hypertension (OH) or open-angle glaucoma (OAG) switched from PF or benzalkonium chloride (BAK)-preserved bimatoprost–timolol to PF tafluprost–timolol eye drops.

Methods

This 12-week, open-label, phase IV study enrolled patients with OH or OAG (IOP on medication ≤21 mmHg), treated with PF or BAK-preserved bimatoprost–timolol for ≥4 weeks before screening, and presenting with conjunctival hyperaemia and ≥1 ocular symptom. Patients were switched to PF tafluprost–timolol once daily in the treated eye(s). The primary endpoints were change from screening to Week 12 in conjunctival hyperaemia and worst ocular symptom. The secondary outcome measures were changes from screening in ocular signs (other than conjunctival hyperaemia) and symptoms at Week 12.

Results

Of 123 patients enrolled from 16 centres in Finland, Germany, Italy and the United Kingdom, 121 were included in the intention-to-treat dataset of which all were Caucasian and 54.5% were female; 76 patients used BAK-preserved bimatoprost–timolol and 45 used PF drops. Conjunctival hyperaemia and severity of worst ocular symptom following switch to PF tafluprost–timolol significantly reduced from screening to Week 12 in all patients ($p<0.001$). The percentage of patients with ocular signs and symptoms was significantly reduced at Week 12 compared with screening ($p<0.001$). IOP was not affected by the change of treatment.

Conclusions

Switching from BAK-preserved or PF bimatoprost–timolol to tafluprost–timolol reduced both signs and symptoms of ocular surface disease with no clinically relevant effect on IOP.

Trial registration: EudraCT 2014-005273-37

Strengths and limitations of this study

- The study allows for comparison between the effects of PF tafluprost–timolol and both BAK-preserved and PF bimatoprost–timolol formulations
- The study was conducted across 16 centres limiting bias
- As this was not a randomised-controlled trial, there was a potential for selection bias; however, a randomised design would have been unethical as patients would have been required to adhere to medication that caused them notable ocular intolerance
- An open-label design could not be avoided for this study because the packages of BAK-preserved and PF bimatoprost–timolol and PF tafluprost–timolol were not identical
- Regression to the mean should be considered when interpreting the results

INTRODUCTION

Glaucoma is a disorder often associated with elevated intraocular pressure (IOP) which, if left untreated, leads to retinal ganglion cell death, thinning of the retinal nerve fibre layer, optic nerve damage and cupping of the optic disc.[1] In 2013, approximately 64.3 million people were affected by glaucoma, and the number is expected to grow to 111.8 million by 2040.[2]

Medical treatment of ocular hypertension (OH) and open-angle glaucoma (OAG) focuses on the long-term control of IOP.[3, 4] Several categories of IOP-lowering topical drugs are available including prostaglandin analogues (PGA) (generally the first-line treatment), β-adrenergic blockers, carbonic anhydrase inhibitors, α-adrenergic agonists and miotics.[1] The greatest reduction of IOP is obtained with PGAs (25%–35%) followed by non-selective β-blockers (20%–25%), such as timolol; however, when patients fail to achieve IOP targets with monotherapy, fixed-dose combinations (FDCs) should be considered.[5]

There are only two available PGA–timolol preservative-free (PF) FDCs; PF bimatoprost 0.03%–timolol 0.5% (bimatoprost–timolol) and PF tafluprost 0.0015%–timolol 0.5% (tafluprost–timolol).[6] Despite numerous comparative efficacy studies to date, few have compared different PF PGA therapies.[7] While non-selective β-blockers, such as timolol, can cause bradycardia, arrhythmias, and reductions in blood pressure, PGAs lack systemic side effects[1] but may be associated with distinctive ocular adverse events (AEs), such as conjunctival hyperaemia.[6] Preservatives such as benzalkonium chloride (BAK) are toxic to the ocular surface and may aggravate the signs and symptoms of ocular surface disease (OSD).[8] In a recent study, conjunctival hyperaemia occurred at similar rates in BAK-preserved and PF bimatoprost–timolol-treated patients, suggesting that bimatoprost may have caused these AEs rather than the preservative.[9] The objective of the present study was to evaluate the changes in ocular signs and symptoms in patients diagnosed with

OH or OAG who were switched from BAK-preserved (0.005%) or PF bimatoprost–timolol eye drops (bimatoprost 0.03%–timolol 0.5%; Allergan, Irvine, CA, USA) to PF tafluprost–timolol eye drops (tafluprost 0.0015%–timolol 0.5%; Santen Pharmaceutical Co., Ltd, Osaka, Japan).

MATERIALS AND METHODS

Study design

This was an open-label, phase IV clinical study (EudraCT registration number: 2014-005273-37) conducted at 16 centres in Finland, Germany, Italy and the United Kingdom (UK) from June 2015 through to May 2016. The study was reviewed and approved by the appropriate Independent Ethics Committees in the participating countries and conducted in accordance with the Good Clinical Practice guidelines of the International Council on Harmonisation and the ethical principles of the Declaration of Helsinki.

Patient population

Patients included in this study were aged ≥18 years, diagnosed with OH or OAG, inclusive of both primary OAG and pseudoexfoliation glaucoma, and treated with bimatoprost–timolol in the evening (BAK-preserved or PF single-dose formulation) in one or both eyes for ≥4 weeks before screening. Patients presented at screening with conjunctival redness/hyperaemia of at least moderate severity (grade ≥2) in at least one treated eye and ≥one ocular symptom of at least mild severity (grade ≥2) in either eye. Exclusion criteria included: use of more than two active medicinal agents to treat OH or OAG in the 6 months prior to screening; anterior chamber angle grade <2 (Shaffer classification) in either treated eye; and any corneal abnormality or other condition preventing applanation tonometry, including prior refractive eye surgery and IOP >21 mmHg in the treated eye(s) at screening. A full list of inclusion and exclusion criteria is presented in supplementary table S1.

Treatments and assessments

Eligible patients had used BAK-preserved or PF bimatoprost–timolol (bimatoprost 0.03%–timolol 0.5%) eye drops in the evening for ≥4 weeks prior to screening. Study treatment kits, containing PF tafluprost–timolol eye drops (tafluprost 0.0015%–timolol 0.5%) in unit-dose containers, were dispensed to patients at the screening visit. Patients were not blinded to treatment because an open-label design could not be avoided owing to differences in packaging between BAK-preserved and PF bimatoprost–timolol and PF tafluprost–timolol. Each patient instilled one drop of tafluprost–timolol once daily at 21:00 (±1 hour) in the affected eye(s) for 12 weeks. Drug accountability documentation and dosing data from case report forms were used to assess treatment compliance. Patients were assessed at screening, and at 2, 6 and 12 weeks post screening. After Week 12, a post-study visit was scheduled, and the investigator was free to prescribe any IOP-lowering medication.

Ocular signs and symptoms

Ocular signs and symptoms were assessed at each visit (supplementary table S2). The co-primary endpoints were changes from screening in conjunctival hyperaemia and worst ocular symptom at Week 12. The severity of conjunctival hyperaemia was assessed from screening through to Week 12. Use of the Ora Calibra™ Redness Scale #6.0 (0–4 scale) was made under licence from Ora, Inc. Patients indicated their perceived worst ocular symptom at screening.

Secondary endpoints were changes from screening in ocular signs and symptoms, other than conjunctival hyperaemia, at Week 12. The patient was asked about each symptom by a leading question, with symptoms graded 0 (none), 1 (trace), 2 (mild), 3 (moderate) or 4 (severe). A total symptom score (0–20) was calculated. Fluorescein tear break-up time was assessed by examination of tear film under a slit lamp following instillation of 2 µL of non-preserved 2% sodium fluorescein dye to the eyes. The time taken (in seconds) to form micelles or for dry spots to develop was recorded as the break-up time. Corneal and

conjunctival fluorescein staining were also evaluated. Using reference pictures (Oxford Grading scale) the corneal fluorescein staining and nasal and temporal conjunctival fluorescein stainings were scored from 0 to V each. The presence of blepharitis was also evaluated, and the severity was graded 0 (none), 1 (mild), 2 (moderate) or 3 (severe). Tear production was assessed using the Schirmer-I test for 5 minutes without anaesthesia.

AEs

Treatment-emergent ocular and non-ocular AEs were reported at each post-screening visit. The information obtained included event term, report source, the seriousness of the event, onset and resolution date, frequency, severity, relation to study drop instillation, location (left/right eye, both or not applicable), study drug treatment action, and the investigator's causality assessment of the study treatment and outcome. All AEs were coded using the latest Medical Dictionary for Regulatory Activities.

Ocular safety and quality of life

At each visit, IOP was measured in both eyes using Goldmann applanation tonometry; the right eye was measured first. Two consecutive measurements were taken to determine the mean IOP. If the initial two measurements differed by ≥3 mmHg, then a third measurement was taken and the median IOP was determined. Other measures of ocular safety and quality of life (QOL) are described in the supplementary information.

Sample size

The paired t-test was used in sample size calculations. A power of 90% was achieved for conjunctival hyperaemia with 100 patients and a cautious mean change estimate of 0.37 units (standard deviation 1.12). A power of >99% was achieved for the worst ocular symptom using the same number of patients. The calculations were done using the nQuery Advisor (version 6.0). The Wilcoxon signed rank test performs better than the paired t-test for heavy-tailed distributions.

Statistical methods

The intention-to-treat (ITT) dataset included all enrolled patients who received at least one dose of tafluprost–timolol and had at least one post-screening primary outcome measurement available. The safety set included all enrolled patients who had at least one dose of study treatment and had a subsequent safety measurement. The primary outcome measures for ocular signs and symptoms were assessed using the Wilcoxon signed rank test. The analyses of secondary outcome and IOP measures were completed using standard statistical methods for paired data (e.g. McNemar's test for binary data, Wilcoxon signed rank test for ordinal data and the paired t-test for continuous data). For AEs, both patient and event counts were calculated, and events leading to discontinuations were summarised. Best corrected visual acuity, biomicroscopy, ophthalmoscopy, visual field test, drop discomfort and Comparison of Ophthalmic Medications for Tolerability (COMTol) were analysed descriptively.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of this study. There are no plans to involve patients in the dissemination of results as the open-label nature of the study meant that patients were aware of which medication they received.

RESULTS

Patient demographics and baseline characteristics

A total of 126 patients were screened. Of the 123 patients enrolled, two had no post-screening data and were excluded; therefore, 121 (98.4%) patients were included in the ITT analysis, of which 114 (94.2%) patients completed the study (BAK-preserved, n=71; PF, n=43) (figure 1). The safety set comprised of 123 patients. The mean (range) age was 66

(36–86) years, and more than half of the patients were female (54.5%) (table 1). Of the patients, ~70% in both BAK-preserved and PF subgroups had used bimatoprost–timolol for at least 6 months; 76 patients had used BAK-preserved (62.8%) and 45 had used PF (37.2%) bimatoprost–timolol. Approximately 20% of patients were diagnosed with OH and 75% with OAG. Most patients (91.7%) required treatment in both eyes.

Table 1 Demographics and baseline characteristics of enrolled patients

Variable	Bimatoprost–timolol		Total (n=121)
	BAK-preserved (n=76)	PF (n=45)	
Mean age, years	66.14	67.02	66.47
SD	10.17	10.71	10.34
Sex, n (%)			
Male	34 (44.7)	21 (46.7)	55 (45.5)
Female	42 (55.3)	24 (53.3)	66 (54.5)
Race, n (%)			
Caucasian	76 (100)	45 (100)	121 (100)
Hyperaemia, n (%)	76 (100)	45 (100)	121 (100)
Worst ocular symptom, n (%)	76 (100)	45 (100)	121 (100)
Severity of worst ocular symptom, n (%)			
Mild	30 (39.5)	17 (37.8)	47 (38.8)
Moderate	39 (51.3)	23 (51.1)	62 (51.2)
Severe	7 (9.2)	5 (11.1)	12 (9.9)
Abnormal ocular signs, n (%)			
Fluorescein tear break-up time	52 (68.4)	32 (71.1)	84 (69.4)
Corneal fluorescein staining	63 (82.9)	42 (93.3)	105 (86.8)
Conjunctival fluorescein staining	55 (72.4)	36 (80.0)	91 (75.2)
Blepharitis	32 (42.1)	22 (48.9)	54 (44.6)
Tear secretion/Schirmer test	47 (61.8)	29 (64.4)	76 (62.8)

Abnormal ocular symptoms, n (%)			
Irritation/burning/stinging	55 (72.4)	32 (71.1)	87 (71.9)
Foreign body sensation	41 (53.9)	19 (42.2)	60 (49.6)
Tearing	31 (40.8)	25 (55.6)	56 (46.3)
Itching	36 (47.4)	26 (57.8)	62 (51.2)
Dry eye sensation	49 (64.5)	28 (62.2)	77 (63.6)

Please refer to supplementary table S2 for criteria of abnormal signs and symptoms.

BAK, benzalkonium chloride; PF, preservative-free; SD, standard deviation.

Changes to signs and symptoms

A significant improvement was observed in the severity of both conjunctival hyperaemia and worst ocular symptom compared with screening after switching from bimatoprost–timolol to tafluprost–timolol (p<0.001 at Weeks 2, 6 and 12). The mean ± standard deviation grade of conjunctival hyperaemia for all patients decreased from 2.26±0.04 at screening to 0.94±0.06 at Week 12 (a mean reduction of 58.5%) (figure 2A). The percentage of patients with conjunctival hyperaemia significantly reduced from 76 (100%) and 45 (100%) patients at screening in BAK-preserved and PF bimatoprost–timolol groups, respectively, to 47 (66.2%) and 31 (72.1%) at Week 12 (figure 2B). All patients identified a worst ocular symptom at screening, which was at least mild in severity; the number of patients with the identified symptom was reduced to 47 (41.2%) at Week 12. The number of patients with moderate and severe worst ocular symptom decreased from 62 (51.2%) and 12 (9.9%) at screening, to 11 (9.6%) and one (0.9%) at Week 12, respectively (figure 2C). In the BAK-preserved and PF bimatoprost–timolol subgroups, the number of patients with moderate and severe worst ocular symptom decreased from 46 (60.5%) to five (7.0%) patients and from 28 (62.2%) to seven (16.3%) patients, respectively (figure 2D).

The frequencies of abnormal ocular signs and symptoms were significantly reduced at Week 12 after switching from bimatoprost–timolol to tafluprost–timolol (p<0.012 for signs and

p<0.001 for symptoms) (figures 3A, B, C and D). For ocular signs, the greatest relative reductions from screening were observed in tear secretion (screening, 62.8%; Week 12, 37.7%) and blepharitis (screening, 44.6%; Week 12, 27.2%). For ocular symptoms, all relative reductions were over 50%, and the greatest were observed in foreign body sensation (screening, 49.6%; Week 12, 20.2%) and itching (screening 51.2%; Week 12, 21.9%).

AEs

Overall, 70 treatment-emergent AEs based on the safety dataset (n=123) were reported by 41 (33.3%) patients during the study, of which 15 events in 12 (9.8%) patients were ocular and 55 events in 34 (27.6%) patients were non-ocular (table 2). Only 12 AEs in ten (8.1%) patients were classified as being related to tafluprost–timolol. Two patients had serious AEs: worsening of arterial branch occlusion (resolved after 4 weeks) and paroxysmal atrial flutter with high-grade atrioventricular block (resolved in 2 days); both of which were adjudicated by the investigator and sponsor to be unrelated to tafluprost–timolol treatment. A total of five patients discontinued the study because of AEs, which were: two cases of moderate increase in IOP; moderate pruritus and eye pruritus, a moderate urticaria; and a severe increase in lacrimation. There were no deaths during the study.

Table 2 The occurrence of related and unrelated ocular and non-ocular AEs in patients (n=123) after switching from bimatoprost–timolol to tafluprost–timolol

MedDRA preferred term	Mild/moderate	Severe
Related ocular AEs		
Lacrimation increased	0	1
IOP increased	3	0
Eye pruritus	1	0
Pruritus	1	0
Eyelid irritation	1	0
Related non-ocular AEs		
Urticaria	1	0
Abdominal pain upper	1	0
Dysgeusia	1	0
Headache	1	0
Somnolence	1	0
Unrelated ocular AEs in ≥2 patients		
Ocular hyperaemia	1	1
Unrelated non-ocular AEs in ≥2 patients		
Headache	10	0
Nasopharyngitis	4	0
Pyrexia	3	0
Rhinitis	3	0
Cough	3	0
Arthralgia	2	0
Back pain	2	0

AE, adverse event; IOP, intraocular pressure; MedDRA, Medical Dictionary for Regulatory Activities.

Ocular safety and QOL

At screening, IOP was well controlled with bimatoprost–timolol treatment (n=123; mean IOP 15.9±2.1 mmHg); this was sustained at Week 12 (n=114 (figure 1); mean IOP 16.3±2.3 mmHg) and was clinically insignificant and statistically non-inferior compared with screening (0.34 mmHg; 95% upper limit 0.86 mmHg). IOP was maintained at ≤21 mmHg for >97% of patients and ≤18 mmHg for >80% of patients. Other results for ocular safety and QOL are described in the supplementary information (table S3).

DISCUSSION

Medical treatment of glaucoma aims to maintain patients' visual function and QOL; however, nearly all patients with glaucoma will require a combined therapy to attain a greater than 30% 24-hour IOP reduction.[10, 11] Currently there are only two PF prostaglandin–timolol formulations available: PF bimatoprost–timolol and tafluprost–timolol. In this study, the effects of switching from bimatoprost–timolol to tafluprost–timolol on signs and symptoms of OSD and the effect of these changes in QOL were evaluated.

The study met both co-primary endpoints showing significant improvements in conjunctival hyperaemia and worst ocular symptom from screening to Week 12. No statistical evidence of heterogeneity in the occurrence of ocular signs and symptoms was found between prior BAK-preserved and PF bimatoprost–timolol. This study has shown that patients receiving bimatoprost–timolol who present with signs and symptoms of OSD benefit from switching to tafluprost–timolol. Control of IOP was maintained, and there were no reports of unexpected AEs related to tafluprost–timolol or significant findings in ocular safety during the study. These results agree with a previous double-blind phase III study where no significant differences in safety and tolerability between BAK-preserved and PF bimatoprost–timolol were observed except for more frequent skin pigmentation with PF bimatoprost–timolol.[9] The observed ocular surface abnormalities and improved tolerability may thus be related to the prostamide-mimetic properties of bimatoprost. Timolol treatment has been shown to

induce only minimal hyperaemia or irritation in the eye.[6] In this study, the percentage of symptom-free patients increased by Week 12 concomitantly with improved ocular tolerability as reported in the COMTol questionnaire after switching from bimatoprost–timolol to tafluprost–timolol. This agrees with a previous study that found an association between advanced OSD and poorer glaucoma-related QOL than in patients without OSD.[12] The aforementioned study also reported that OSD was associated with higher daily doses of BAK.

This study had several limitations. This was not a randomised controlled trial, and there was a potential for selection bias; however, a parallel-group (randomised) design with bimatoprost–timolol was considered unethical, because the patients would have continued using medication that caused them notable ocular intolerance. An open-label design could not be avoided for this study because the packages of BAK-preserved and PF bimatoprost–timolol and PF tafluprost–timolol were not identical. IOP readings were unmasked and may also have been subject to bias. 'Regression toward the mean' is the observation that if a variable is extreme on the first measurement, it will tend to be closer to the average on its second measurement. This may have introduced reduction in some ocular signs and should also be considered in the interpretation of these results. Compliance is likely to be higher in a study setting, and so these results may not be reflective of a real-world setting. Treatment persistence could not be investigated thoroughly because PF tafluprost–timolol was only commercially available for 26 patients in two of the participating countries (UK and Finland) at the time of the study.

In conclusion, switching from bimatoprost–timolol to tafluprost–timolol yielded clinical benefits in the presence of signs and symptoms of OSD in patients with OH and OAG over 12 weeks. Tafluprost–timolol provides a potential alternative treatment option for patients with OH or OAG.

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Author Contributions

RRAB, KK, KL and CET contributed to the conduction of the study. JV contributed to the study design, statistical analyses and regulatory writing of the study. AR contributed to the study design, direction and monitoring. All authors contributed towards the writing of this publication.

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Competing interests

RRAB has received travel expenses from Santen. KK has received a Consultant fee from Santen for an advisory board. KL has no conflicts of interest to report. CET has received department funding, personal fees, and non-financial support from Santen, and department funding from Novartis and Allergan. JV has received fees for statistical services from Santen. AR is an employee at Santen Oy.

Patient consent

Each patient received verbal and written communication regarding the objectives and procedures and the possible risks involved prior to inclusion in the study. The investigator obtained written informed consent prior to any study procedures being undertaken.

Data sharing statement

Data are available. Please contact corresponding author.

Ethics approval

The study protocol was reviewed and approved by Independent Ethics Committees and national competent authorities in each participating country. The study adhered to the International Council on Harmonisation Good Clinical Practice guidelines and provisions of the Declaration of Helsinki.

Provenance and peer review

Not commissioned; externally peer reviewed.

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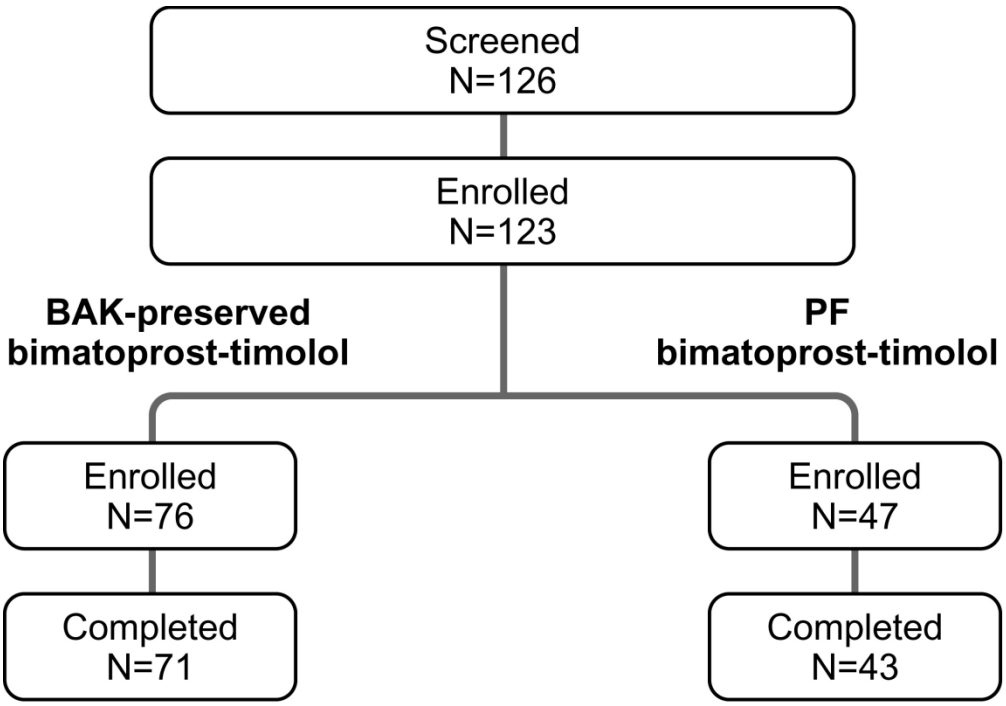
Figure 1 Patient disposition by previous bimatoprost–timolol treatment. After initial screening, three patients did not meet the inclusion criteria. A total of nine (7.4%) patients discontinued the study; five discontinued because of AEs and four withdrew from the study. BAK, benzalkonium chloride; PF, preservative-free.

Figure 2 Comparison of Week 12 outcomes with screening in conjunctival hyperaemia and worst ocular symptom after switching from bimatoprost–timolol to tafluprost–timolol (A) change in conjunctival hyperaemia from screening (n=121) to Week 12 (n=114); (B) breakdown of changes in conjunctival hyperaemia severity by subgroup at Week 12 compared with screening. One patient in the ITT dataset violated inclusion criterion 2 and only had mild conjunctival hyperaemia at screening; (C) severity of worst ocular symptom at screening and Week 12 in all patients; and (D) changes in severity of worst ocular symptom by subgroup at Week 12 compared with screening. BAK, benzalkonium chloride; ITT, intention-to-treat; PF, preservative-free.

Figure 3 Secondary endpoints (A) abnormal ocular signs at screening (n=121); (B) abnormal ocular signs at Week 12 (n=114); (C) abnormal ocular symptoms at screening; (D) abnormal ocular symptoms at Week 12. BAK, benzalkonium chloride; PF, preservative-free.



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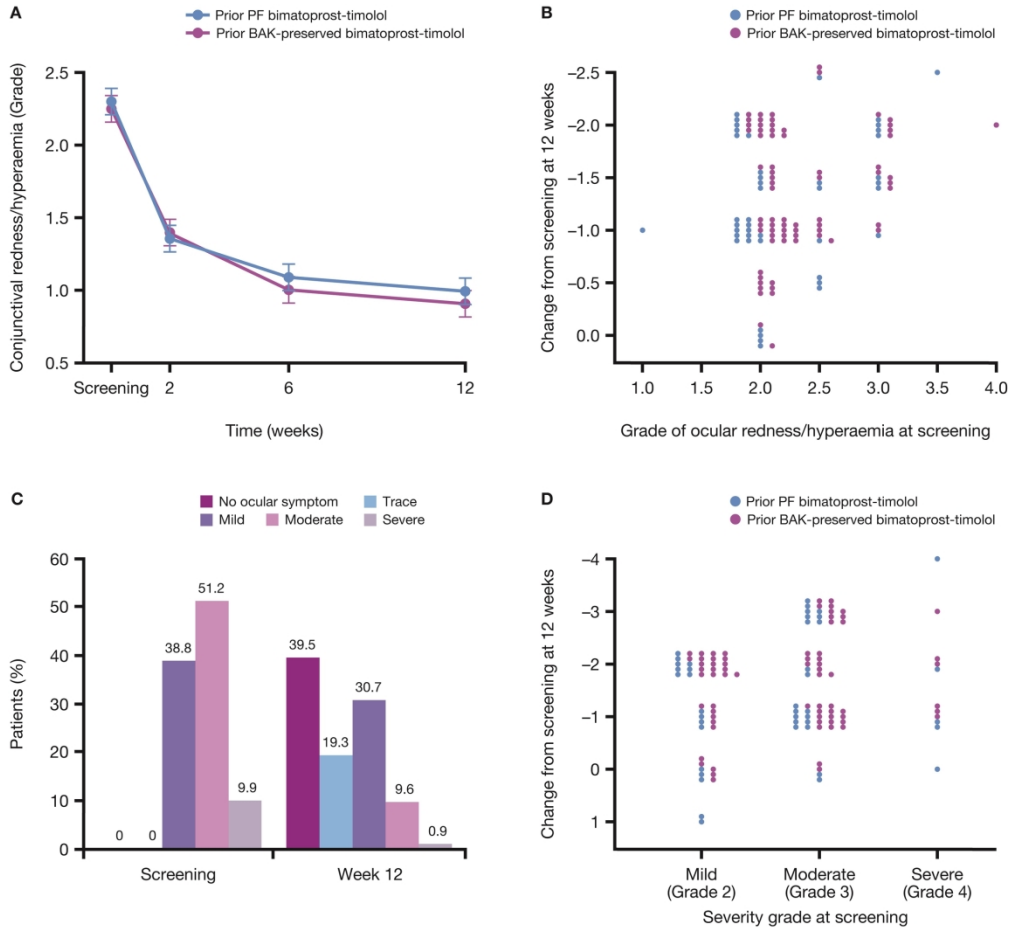

Figure 2 Comparison of Week 12 outcomes with screening in conjunctival hyperaemia and worst ocular symptom after switching from bimatoprost–timolol to tafluprost–timolol (A) change in conjunctival hyperaemia from screening (n=121) to Week 12 (n=114); (B) breakdown of changes in conjunctival hyperaemia severity by subgroup at Week 12 compared with screening. One patient in the ITT dataset violated inclusion criterion 2 and only had mild conjunctival hyperaemia at screening; (C) severity of worst ocular symptom at screening and Week 12 in all patients; and (D) changes in severity of worst ocular symptom by subgroup at Week 12 compared with screening. BAK, benzalkonium chloride; ITT, intention-to-treat; PF, preservative-free.

204x189mm (300 x 300 DPI)

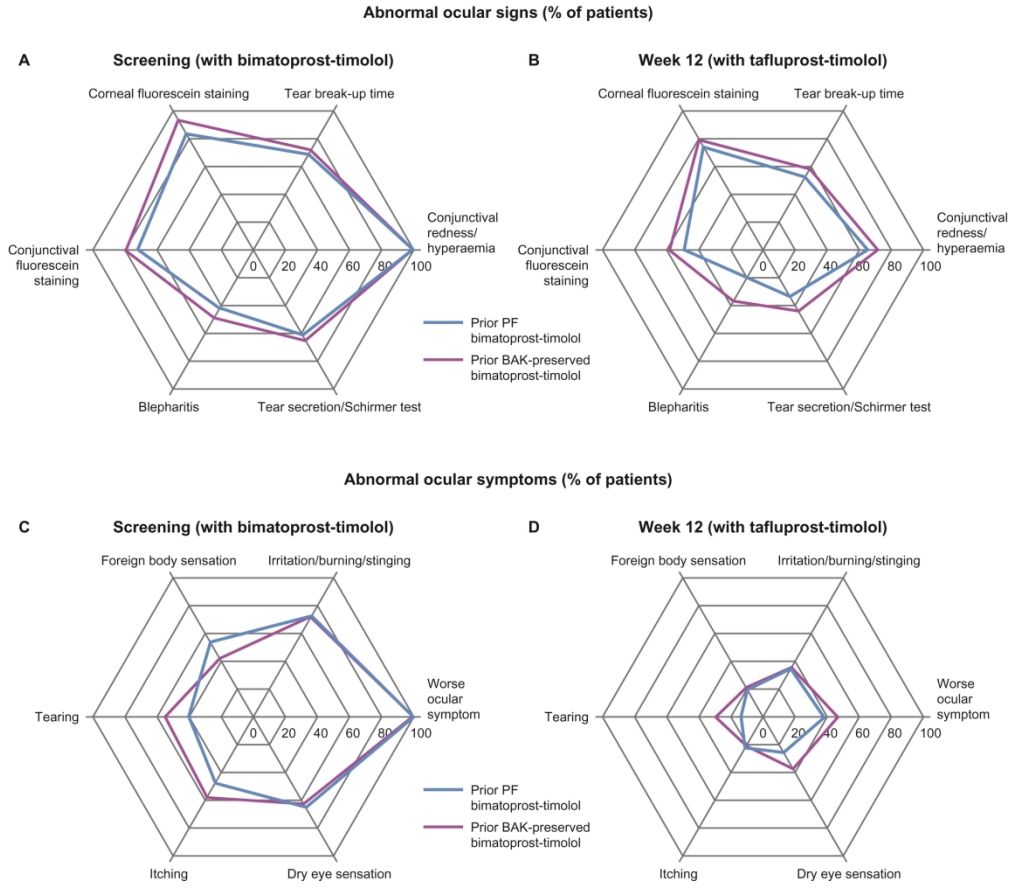

Figure 3 Secondary endpoints (A) abnormal ocular signs at screening (n=121); (B) abnormal ocular signs at Week 12 (n=114); (C) abnormal ocular symptoms at screening; (D) abnormal ocular symptoms at Week 12. BAK, benzalkonium chloride; PF, preservative-free.

201x176mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

Contents

METHODS

Inclusion and exclusion criteria

The full inclusion and exclusion criteria are summarised in table S1.

Supplementary table S1 Inclusion and exclusion criteria

Inclusion	Exclusion
OH or OAG diagnosis (IOP ≤21 mmHg on medication)	≥2 OH or OAG treatments or ocular surgery within 6 months prior to screening
Prior treatment with preserved or PF bimatoprost–timolol FDC eye drops for ≥4 weeks before screening and grade ≥2 (moderate) conjunctival hyperaemia in one treated eye	Grade <2 anterior chamber angle, angle closure glaucoma or secondary glaucoma other than PEX
≥1 grade 2 (mild) ocular symptom	Use of other preserved drops within 2 weeks prior to screening
Best corrected ETDRS visual acuity score of +0.6 logMAR or better in both eyes	Corneal abnormality or prior refractive surgery
Aged 18 years or over	Females who are pregnant, nursing or planning a pregnancy, or females of childbearing potential who are not using a reliable method of contraception
Provided written informed consent	Anterior chamber angle in either eye to be treated less than grade 2 according to Schaffer classification as measured by gonioscopy
	IOP greater than 21 mmHg in treated eye(s) at screening
	Use of preserved eye drops (other than bimatoprost–timolol) including artificial tears at screening or within 2 weeks prior to screening visit

ETDRS, early treatment diabetic retinopathy study; FDC, fixed-dose combination; IOP, intraocular pressure; logMAR, Logarithm of the Minimum Angle of Resolution; OAG, open-angle glaucoma; OH, ocular hypertension; PEX, pseudoexfoliation; PF, preservative-free.

Assessment of abnormal ocular signs and symptoms

Abnormal signs and symptoms were defined by the criteria shown in table S2.

Supplementary table S2 Grading criteria of abnormal ocular signs and symptoms investigated in this study

Ocular sign	Units/grades	Abnormal
Fluorescein tear break-up time	Seconds*	<10 seconds
Corneal fluorescein staining	0–V†	≥I
Conjunctival fluorescein staining	0–X‡	≥II
Blepharitis	0–3§	≥1
Conjunctival hyperaemia	0–4¶	≥1
Tear production	mm‖	≤10 mm
Ocular symptom	**Grades**	**Abnormal**
Irritation/burning/stinging	0–4**	≥2
Foreign body sensation	0–4**	≥2
Tearing	0–4**	≥2
Itching	0–4**	≥2
Dry eye sensation	0–4**	≥2

Treated eyes were considered together for ocular symptoms whereas ocular signs were evaluated by eye; the eye with the worse grade at screening was analysed.

*Slit-lamp microscope. †Oxford grading scale (0–V). ‡Combined nasal (0–V) and temporal (0–V) score by Oxford grading scale. §0=none, 1=mild, 2=moderate and 3=severe. ¶Ocular redness scale; used under license from Ora, Inc., Andover, MA, USA; 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe; half grades were allowed. ‖Schirmer's test; **0=none, 1=trace, 2=mild, 3=moderate and 4=severe.

Ocular safety and quality of life

Best corrected visual acuity was measured at each visit using an Early Treatment Diabetic Retinopathy Study chart, and the Logarithm of the Minimum Angle of Resolution (logMAR) scores were calculated. The base logMAR value is the value of the last line in which a letter was read correctly (>0.2 logMAR score was considered abnormal). A biomicroscopic assessment of the lids, conjunctiva, cornea, anterior chamber and iris was performed at all visits. Evaluations were graded as mild, moderate, severe or not applicable. The biomicroscopic assessment of the lens was performed at screening, Week 12 and post study. Ophthalmoscopy examinations of the vitreous, retina and the optic nerve with the pupil dilated were performed at screening and Week 12. The findings were graded for severity as 1 (mild), 2 (moderate) and 3 (severe). This was repeated at the post-study visit for treatment-related abnormalities at Week 12. Visual field testing was performed using the Humphrey 24-2/30-2 (full threshold or Swedish interactive threshold algorithm standard) or Octopus G2 program (normal or dynamic strategy) with one test used consistently in each patient. Visual field testing was assessed for changes between screening and the post-study visit and was graded for severity as 1 (mild), 2 (moderate) and 3 (severe). Drop discomfort was assessed using a four-point scale as 1 (mild), 2 (moderate) and 3 (severe). Quality of life (QOL) was evaluated using the Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire[1] at all visits up to Week 12. The questionnaire consisted of 11 questions, which scored discomfort from 0 to 5–6, and was divided into five side-effect domains (ocular symptoms, taste, vision, accommodation and brow ache), three activity-limitation domains (driving, reading and moderate activities) and five global assessments (preference, effect of side effects on QOL, effect of activity limitations on QOL, compliance and satisfaction).

RESULTS

Ocular safety and QOL

At Week 12, there were no clinically relevant changes in visual acuity or visual fields attributable to tafluprost–timolol treatment and no severe biomicroscopy or ophthalmoscopy findings. The number of patients that did not report drop discomfort increased from 28 (22.8%) patients at screening (n=123) to 61 (53.5%) at Week 12 (n=114). Worsening of drop discomfort at Week 12 was observed in 6 (5.3%) patients and improvement was observed in 65 (57.0%) patients ($p<0.001$).

By Week 12, the COMTol questionnaire indicated that more patients were symptom-free for common ocular side effects and activity limitations compared with screening (supplementary table S3). Overall, 62.0% of the patients whose QOL was affected by the side effects that were prevalent at screening (n=123) reported improved QOL at Week 12 (n=114) because of alleviated side effects. Accordingly, 66.7% of patients reported improved QOL owing to decreased activity limitations. Approximately 66% of patients in the prior benzalkonium chloride (BAK) bimatoprost–timolol and 51% of patients in the prior preservative-free (PF) bimatoprost–timolol group preferred tafluprost–timolol. Only 12% and 13% preferred BAK and PF bimatoprost–timolol, respectively. The remaining patients had no preference. Satisfaction with medication increased after switching from bimatoprost–timolol to tafluprost–timolol. The number of patients who were totally or very satisfied increased from 41 (33.3%) at screening to 84 (73.7%) at Week 12. Fewer patients in the BAK bimatoprost–timolol group were totally or very satisfied with medication than in the PF bimatoprost–timolol group at screening (25.0% and 46.8%, respectively). By Week 12, satisfaction in both groups had improved substantially compared with screening (77.5% and 67.4%, respectively). Compliance during the final 2 weeks of the study improved after switching from bimatoprost–timolol to tafluprost–timolol. The number of patients who claimed not to miss a dose increased from 89.4% at screening to 94.7% at Week 12.

Supplementary table S3 The percentage of patients without symptoms or limitations after switching from bimatoprost–timolol to tafluprost–timolol

Symptom-free patients, n (%)	Screening	Week 12
Burning/stinging	24 (19.5)	56 (49.1)
Redness	16 (13.0)	51 (44.7)
Itchy eyes	45 (36.6)	57 (50.0)
Discharge from eyes	76 (61.8)	96 (84.2)
Swelling of eyelids	95 (77.2)	104 (91.2)
Dry eyes	36 (29.3)	55 (48.2)
Tearing	55 (44.7)	74 (64.9)
Bitter taste	105 (85.4)	108 (94.7)
Unusual taste	113 (91.9)	111 (97.4)
Blurred vision	61 (49.6)	84 (73.7)
Dimming of vision	101 (82.1)	105 (92.1)
Trouble seeing at night	81 (65.9)	101 (88.6)
Difficulty in focusing	81 (65.9)	95 (83.3)
Trouble in reading	82 (66.7)	95 (83.3)
Brow ache	112 (91.1)	109 (95.6)
Limitation-free patients		
Day driving	65 (73.0)	73 (90.1)
Night driving	46 (68.7)	58 (92.1)
Reading newspaper	89 (74.2)	105 (93.8)
Reading other	87 (75.0)	102 (94.4)
Carrying groceries	109 (92.4)	110 (99.1)
Climbing stairs	108 (90.0)	112 (100.0)
Walking blocks	103 (88.8)	108 (99.1)

References

1. Barber BL, Strahlman ER, Laibovitz R, *et al*. Validation of a questionnaire for comparing the tolerability of ophthalmic medications. *Ophthalmology* 1997;104:334–42.

CLINICAL STUDY PROTOCOL

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Date: 05 January, 2015

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(including appendices)

Phase: IV

EudraCT no: 2014-005273-37

Title: A phase IV study on the changes in ocular signs and symptoms in patients with ocular hypertension or open-angle glaucoma switched from Ganfort® eye drops (bimatoprost 0.03%/timolol 0.5%) to Taptiqom® eye drops (tafluprost 0.0015%/timolol 0.5%).

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1 CONTACT INFORMATION AND SIGNATURES

This study will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, the applicable regulatory requirements and the Declaration of Helsinki.

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Date

Signature

OTHER RELEVANT PARTIES

Contact information and principal investigator signatures from all study centres will be incorporated in the study protocol with Appendix 1. Detailed contact information of study teams, institutions and CROs/ clinical laboratories/ medical/ technical departments involved in the study are maintained in trial- and investigator study files.

2 PROTOCOL SUMMARY AND SCHEDULE OF ASSESSMENTS

2.1 Summary

Objectives:	The objective of this study is to investigate whether changes in ocular signs or symptoms occur when patients are switched from Ganfort® eye drops (fixed dose combination [FDC] of bimatoprost 0.03% and timolol 0.5%) to Taptiqom® eye drops (FDC of tafluprost 0.0015% and timolol 0.5%).
Type and design:	This will be an open-label, multicenter, phase IV study (country specifically depending on marketing authorization status). Only patients who (i) have been using Ganfort® (preserved formulation or preservative-free single-dose formulation) as their only prior glaucoma medication, (ii) have intraocular pressure (IOP) of 21 mmHg or less on treatment, and (iii) fulfil all the eligibility criteria (including the presence of conjunctival redness/hyperemia and at the minimum one of the ocular symptoms listed below) will be assigned to receive the following treatment: • Taptiqom®: preservative-free FDC of tafluprost 0.0015% and timolol 0.5% (single-dose) eye drops once daily at 21:00 (±1h) into the treated eye(s) Duration of the treatment period will be twelve (12) weeks; a post-study follow-up period of 1-3 weeks will succeed the treatment period.
Methods:	Evaluation of ocular signs: o Conjunctival redness/hyperemia (ORA scale) o fBUT o Corneal and conjunctival fluorescein staining (scale 0-V) o Blepharitis (severity scale 0-3) o Schirmer test Evaluation of ocular symptoms upon non-instillation (severity scale 0-4): o Irritation/burning/stinging o Foreign body sensation o Tearing o Itching o Dry eye sensation Evaluation of ocular safety and quality of life (QoL): o IOP o Adverse events (AE) o Best corrected visual acuity o Biomicroscopy o Ophthalmoscopy o Visual field test o Drop discomfort (upon instillation) o QoL questionnaire (including medication preference)

Number of patients:	Approximately 120 patients will be enrolled to this study to ensure at least 100 evaluable patients. Assuming a mean change from baseline of 0.37 units in conjunctival redness/ hyperemia and a standard deviation of 1.12 units (conservative estimates from tafluprost switch studies), a power of 90% is achieved for a paired t-test with 100 patients.

Patient characteristics:	Patients diagnosed with ocular hypertension (OHT) or open-angle glaucoma (OAG) (primary open-angle glaucoma [POAG] or pseudoexfoliative glaucoma [PEX]) and with prior Ganfort® treatment for at least 4 weeks (in the evening) before the study screening visit can be enrolled to the study. In addition, at screening eligible patients are required to have at least grade 2 conjunctival redness/ hyperemia AND one ocular symptom of at least mild severity (grade 2) upon non-instillation.

Criteria for evaluation:	
Primary outcome measures:	o Change from screening in conjunctival redness/hyperemia at week 12 o Change from screening in worst ocular symptom upon non-instillation at week 12
Secondary outcome measures:	o Change from screening in ocular signs at week 12 (other than conjunctival redness/hyperemia) o Change from screening in ocular symptoms upon non-instillation at week 12
Ocular safety and QoL variables:	o Descriptive statistics, identification of change(s) from screening

Statistical analysis of primary outcome measure(s):	Standard statistical methods appropriate for the underlying design will used in the analyses of primary outcome measures (e.g. McNemar's test for binary data, Wilcoxon signed rank test for ordinal data, and paired t-test for continuous data.).

Duration of treatment:	The duration of the treatment period with the preservative free Taptiqom® study medication will be 12 weeks; a post-study follow-up period of 1-3 weeks will succeed the treatment period.

General schedule:	The clinical phase of the study is scheduled to be started in the first half of 2015 and completed in 2016.

2.2 Schedule of assessments

Table 1 Schedule of assessments

Procedure	**Screening / Baseline**[1]	**Week 2** (Day 14 ±2 days)	**Week 6** (Day 42 ±5 days)	**Week 12** (Day 84 ±7 days)	**Post-study** (V4 + 1-3 weeks)
Visits	**V1**	**V2**	**V3**	**V4**	**V5**
Informed consent	**X**				
Inclusion & exclusion criteria	**X**				
Demographics	**X**				
Current ocular condition(s) and medical history/ concomitant diseases	**X**				
Prior IOP lowering medication	**X**				
Urine pregnancy test	**X**[2]		**X**[2]	**X**[2]	
Gonioscopy	**X**				
Concomitant medication	**X**	**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**	**X**
Visual acuity	**X**	**X**	**X**	**X**	**X**
Biomicroscopy	**X**	**X**[9]	**X**[9]	**X**	**X**
IOP	**X**[1,3]	**X**[3]	**X**[3]	**X**[3]	**X**
Ophthalmoscopy (dilated)	**X**			**X**	**X**[4]
Visual field test	**X**[5]				**X**[6]
Ocular signs[7]	**X**[1,3]	**X**[3]	**X**[3]	**X**[3]	**X**
Ocular symptoms[8]	**X**[1,3]	**X**[3]	**X**[3]	**X**[3]	**X**
Drop discomfort and QoL	**X**	**X**	**X**	**X**	
Study medication dispense	**X**[1]		**X**		
Study medication return			**X**	**X**	
Patient compliance		**X**	**X**	**X**	

[1] For patients screened outside the time window for evaluation of ocular signs and symptoms (12 ±1 h after Ganfort® instillation in the evening before), a separate Baseline visit within 3 days after Screening may be performed. Baseline visit activities thereby include ocular signs and symptoms, measurement of IOP and dispense of study medication. The patient is advised to start study medication instillation in the evening of the Baseline visit.
[2] for females of childbearing potential only
[3] 12 hours after instillation of glaucoma medication (around 9:00 ±1h)
[4] If necessary/ study treatment related abnormalities at V4
[5] Test may be omitted if a reliable visual field test result taken within 3 months from Screening is available
[6] Test may be performed prior to visit day so that results are available for evaluation at V5
[7] Includes: conjunctival redness/hyperemia, fBUT, corneal and conjunctival fluorescein staining, evaluation of blepharitis, Schirmer test
[8] Includes: patient's assessment of irritation/burning/stinging, foreign body sensation, tearing, itching and dry eye sensation
[9] Except lens

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical (classification)
BAK	Benzalkonium chloride
COMToL	Comparison of Ophthalmic Medications for Tolerability
CRF	Case report form (electronic: eCRF)
CRO	Contract research organization
CSI	Case of special interest
DDD	Defined Daily Dose
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
fBUT	Fluorescein Tear Break-up Time
FDC	Fixed dose combination
GCP	Good clinical practice
GMP	Good manufacturing practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IOP	Intraocular pressure
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
OAG	Open-angle glaucoma
OHT	Ocular hypertension
OTC	Over the counter
PEX	Pseudoexfoliative glaucoma (also known as exfoliative or capsular glaucoma)
PG	Prostaglandin
POAG	Primary open-angle glaucoma
PP	Per protocol
PVU	Pharmacovigilance unit
QA	Quality assurance
QC	Quality control
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of product characteristics

5 INTRODUCTION

Glaucoma is a family of related diseases that is frequently associated with elevated intra-ocular pressure (IOP), leading to optic nerve damage and loss of vision. Glaucoma is the second leading cause of blindness worldwide (WHO, 2004). Globally primary open-angle glaucoma affects approximately 13.5 million people over the age of 40 (Thylefors and Négrel, 1994). Although there is currently no cure for glaucoma, evidence from several studies, including results from the Advanced Glaucoma Intervention Study (The AGIS Investigators, 2000, Leske et al., 2003) indicate that achieving low levels of IOP can reduce the progression of visual field deterioration in patients with glaucoma. In addition, results reported from the Ocular Hypertension Treatment Study show that treating ocular hypertension patients with topical ocular hypotensive medications was effective in delaying or preventing the onset of primary open-angle glaucoma (Kass et al., 2002).

Medical treatment is predominantly used as first line therapy and therefore the majority of patients receive several decades of treatment. There are a number of topical hypotensive medications available to reduce IOP. These include miotics, β-adrenergic receptor antagonists (β-blockers), carbonic anhydrase inhibitors, α-adrenergic receptor agonists (α-agonists), and prostaglandin (PG) analogues.

Tafluprost (referred to as AFP-168 in initial studies) is a synthetic PG analogue and selective FP prostanoid receptor agonist like bimatoprost (Lumigan®). Tafluprost is an analogue of $PGF_{2\alpha}$ that is rapidly hydrolyzed by corneal esterases to become the biologically active metabolite, tafluprost acid (referred to as AFP-172 in initial studies).

Pivotal Phase III studies comparing tafluprost to timolol (Chabi et al., 2012, Study 15-003) and latanoprost (Uusitalo et al., 2010a) have demonstrated safety and efficacy of tafluprost 0.0015% in treatment of glaucoma and OHT. First marketing authorization for Tafluprost 0.0015% eye drops was granted in 2008 and currently tafluprost is commercially available in several European, Middle-Eastern, East-Asian and South American countries as well as in the US and Australia (Taflotan®, Saflutan®, Tapros®, Taflotan sine®, Zioptan®, Taflotan-S®).

Tafluprost ophthalmic solution has been developed in both a benzalkonium chloride (BAK) containing formulation and a preservative-free formulation. BAK has been shown to have direct toxicity to a variety of tissues of the ocular surface and may play a role in the tolerability of these compounds over time, especially in those patients with ocular surface disease such as dry eye (Baudouin et al., 1999; Broadway et al., 1993; Broadway et al., 1994; Schwab et al., 1992; Steuhl et al., 1991; Pisella et al., 2002). It has also been demonstrated that the incidence of ocular signs and symptoms was higher in patients receiving preserved eye drops, and that the incidence of these signs/symptoms decreased significantly by switching to a preservative-free formulation or by reducing the amount of preservative-containing treatment (Jaenen et al., 2007).

The preservative-free and preservative-containing solutions of tafluprost have proven to be identical with respect to the ocular absorption, systemic bioavailability, and IOP reducing effect (Pellinen and Lokkila, 2009; Uusitalo et al., 2008; Hamacher et al., 2008). Changes in ocular signs, symptoms and conjunctival markers have been studied in patients switched from Xalatan® (latanoprost with preservative) to preservative-free tafluprost eye drops (Uusitalo et al., 2010b, Study 77553). Switching to preservative-free tafluprost significantly

reduced ocular symptoms and signs as well as abnormal levels of conjunctival markers, and improved the patients' quality of life.

The combination use of PGs and β-blockers is widely documented. Using timolol and tafluprost concomitantly is well-justified as the two medications have different mechanisms of action: timolol acts mainly by reducing the inflow (Coakes and Brubaker 1978) and tafluprost by increasing the uveoscleral outflow (Nilsson et al 1989). Additionally, the use of combination product may improve the compliance in patients requiring multiple glaucoma drugs.

An adjunctive therapy study investigating the use of tafluprost in patients already treated with timolol 0.5% has been performed (Egorov and Ropo, 2009). The group of patients receiving both tafluprost and timolol showed an additional IOP lowering effect of 2 mmHg compared to those receiving timolol and vehicle. More recently, two pivotal Taptiqom® studies have also shown, that the fixed dose combination (FDC) of tafluprost and timolol was non-inferior to the concomitant administration of tafluprost once daily and timolol twice daily (Holló et al., 2014) and superior to the individual monotherapies (Pfeiffer et al., 2014).

There are currently three PG[1] -timolol FDC products marketed in the European Union; Xalcom® (latanoprost + timolol), Duotrav® (travoprost + timolol) and Ganfort® (bimatoprost+ timolol). The Draft Assessment Report from German regulatory body BfArM for the European marketing authorization application of Taptiqom® (alternative brand name Loyada®) was received in September 2014 with the conclusion, that the product is approvable. Thereafter, the first national marketing authorization for Taptiqom® was issued in the UK in October 2014.

At present, Taptiqom® and Ganfort® are the only FDC products of PG and timolol which will be available in a completely preservative-free formulation.

6 OBJECTIVES AND DESIGN OF THE STUDY

6.1 Study objective

The objective of this study is to investigate whether changes in ocular signs or symptoms occur when patients with OHT or OAG (POAG or PEX) are switched from Ganfort® eye drops (FDC of bimatoprost 0.03% and timolol 0.5%) to Taptiqom® eye drops (FDC of tafluprost 0.0015% and timolol 0.5%).

The primary outcome variables will measure the change from screening in conjunctival redness/hyperemia and worst ocular symptom after 12 weeks of treatment with Taptiqom®.

[1] Therapeutical class of PG analogues include latanoprost, travoprost and tafluprost as well as bimatoprost which is a prostamide.

6.2 Study type and overall design

This will be an open-label, multicenter, phase IV study enrolling 120 patients diagnosed with OHT or OAG (POAG or PEX).

Patients who have been regularly using preserved/unpreserved Ganfort® eye drops in the evening for at least 4 weeks before Screening will be switched to unpreserved Taptiqom® eye drops given once daily in the evening for a period of 12 weeks. The Taptiqom® treatment period includes visits at Weeks 2, 6 and 12 and is followed by a post-study visit.

The schedule of assessments is presented in section 2.2.

6.3 Discussion on study design

The rationale of this study is to investigate whether ocular symptoms and signs of patients using Ganfort® eye drops can be improved by switching treatment to unpreserved Taptiqom® eye drops.

The study design is open-label, because due to the different size and look of the preservative-free Ganfort® and Taptiqom® primary single-dose containers, a double-masked comparison study would not have been feasible. Also, as the study will include only patients who are suspected of having Ganfort®-related signs and symptoms at entry, investigator masked study parallel-group study design was considered unethical (keeping intolerant patients on the same medication).

Some changes caused by PG containing eye drops, e.g. conjunctival hyperemia, appear in hours after dosing, whereas other PG-mediated inflammatory signs may take some time to evolve. Thus selecting patients, who have been using Ganfort® for at least 4 weeks prior to study, is justified. For PGs, the maximal IOP lowering is usually achieved 3 to 5 weeks from commencement of the treatment (EGS 2014). Therefore the 12 weeks' treatment period employed in this study is expected to provide ample time for showing full efficacy profile of Taptiqom® as well as changes in ocular symptoms and signs, which are the primary outcome measures of the study.

Currently registered PG-timolol combinations including Ganfort® are dosed once daily in the morning or evening. The dose and once daily dosing frequency of Taptiqom® eye drops is based on the summary of product characteristics (SmPC, dated 2-Oct-2014) approved in the European Union decentralised procedure. The SmPC (appended also to Investigator's Brochure) includes summary of the known and potential risks and benefits of Taptiqom®.

The IOP is measured at each study visit to monitor the IOP lowering effect after the switch to Taptiqom® treatment. The peak effect of PGs occurs 8 to12 hours after instillation in contrast to timolol with peak effect at 2 hours (EGS 2014). Since timolol component is the same in both products, the IOP measurement time point at 12 hours after instillation was chosen. The same standardized timing is applied also to the evaluation of ocular signs and symptoms. For practical reasons, only patients using Ganfort® in the evening are enrolled, to enable evaluation of ocular signs and symptoms and IOP measurement during the morning office hours.

6.4 Selection of study population

Approximately 120 patients with OHT or OAG will be enrolled to this study to achieve at least 100 evaluable patients. Of these patients, one third is expected to be prior users of preservative-free Ganfort®. Patients of any race and either sex who meet all of the inclusion criteria and none of the exclusion criteria listed below will be considered eligible for this study:

6.4.1 Inclusion criteria

1. Aged 18 years or more
2. A diagnosis of ocular hypertension or open-angle glaucoma (either POAG or PEX) in one or both eyes, for which the patient has been regularly using Ganfort® in the evening (preserved formulation or preservative-free single-dose formulation) for at least 4 weeks before Screening (confirmed in anamnesis).
3. In the Screening visit evaluation, the presence of:
   - Conjunctival redness/hyperemia of at least grade 2 severity at least in one treated eye
     AND
   - At least one ocular symptom considered for the two eyes together (irritation/burning/stinging, foreign body sensation, tearing, itching or dry eye sensation) of at least mild severity (grade ≥ 2) upon non-instillation
4. A best corrected ETDRS visual acuity score of +0.6 logMAR or better in both eyes
5. Have provided a written informed consent and are willing to follow instructions

6.4.2 Exclusion criteria

1. Females who are pregnant, nursing or planning a pregnancy, or females of childbearing potential who are not using a reliable method of contraception[2]
2. Use of more than two active medicinal agents to treat glaucoma/OH during the past six months prior to Screening
3. Anterior chamber angle in either eye to be treated less than grade 2 according to Schaffer classification as measured by gonioscopy
4. Any corneal abnormality or other condition preventing reliable applanation tonometry, including prior refractive eye surgery
5. IOP greater than 21 mmHg in treated eye(s) at Screening/Baseline visit
6. Use of preserved eye drops (other than Ganfort®) including artificial tears at screening or within two weeks prior to screening visit
7. Diagnosis of angle-closure glaucoma or secondary glaucoma other than PEX in either eye

[2] A reliable method of contraception is defined as sterilization or those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.

8. Suspected contraindication to tafluprost or timolol therapy
    a. hypersensitivity to tafluprost/timolol or any of the excipients
    b. low heart rate or clinically relevant low blood pressure for age, chronic obstructive pulmonary disease, bronchial asthma, strong tendency to bronchospasm, certain cardiac arrhythmias or uncontrolled congestive heart failure
9. 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
10. Use of contact lenses at Screening or during the study
11. Any ocular (e.g. aphakia, pseudophakia with torn posterior lens capsule[3] 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. Current alcohol or drug abuse
13. Current participation in another clinical trial involving an investigational drug/device, or participation in such a trial within the last 30 days prior to Screening

7 TREATMENT OF PATIENTS

7.1 Prior medication

Qualified patients will be required to have used Ganfort® eye drops (preserved or preservative-free formulation of bimatoprost 0.03% and timolol 0.5% FDC) in the evening for at least four weeks before the study screening.

7.2 Study treatment

At the Screening visit, or separate Baseline visit if applicable (see Section 8.3.1), all eligible patients will be assigned to receive the following treatment:

- Taptiqom®: preservative-free FDC of tafluprost 0.0015% and timolol 0.5% (single-dose) eye drops once daily at 21:00 (±1h) into the treated eye(s)

The duration of the study treatment period will be 12 weeks.

The study medication, Taptiqom® eye drops, is formulated as follows and will be available in single use containers:

[3] Excluding laser capsulotomy (LCT)

FDC of tafluprost 0.0015% and timolol 0.5%		
Tafluprost		0.015 mg
Timolol		5.0 mg
Polysorbate 80		q.s.
Disodium phosphate dodecahydrate		q.s.
Disodium edetate		q.s.
Glycerol		q.s.
Sodium hydroxide diluted and /or Hydrochlorid acid diluted		q.s.
Water for injection	to	1 ml

7.3 Administration

Each patient will receive a 12-week treatment of Taptiqom® eye drops administered once daily. If only one eye satisfies the inclusion criteria for the study, but the other eye also needs to be treated as judged by the investigator, then both eyes need to be treated with the study medication only. There should be no exclusion criteria for the eye(s) treated with the study medication. Unilateral dosing of the study medication is allowed, if the other eye does not need medication as judged by the investigator.

Study medication is started in the evening of the Baseline visit day. One drop of the study medication will be administered once daily at 21:00 in the affected eye(s) for 12 weeks. The drops will be administered in the temporal lower conjunctival cul de sac of the eyes. Every effort is made to administer the study drops at the given time, but a deviation up to one hour is allowed in the timing of administration. One single-dose container can be used for single administration time only, i.e. one drop is instilled in both eyes from one container.

At Visits 2-4, the study team should make sure, that the patient has administered the medication in the evening before the visit.

7.4 Assignment of patient number

Patients who have given written informed consent will be assigned a unique patient number. This number will be used to identify the patients throughout the trial. Should the patient subsequently fail to qualify for the study, his/her patient number must not be re-used for any other patient. A patient may be re-screened one additional time for a total of two screenings.

The patient number consists of a center number predefined by sponsor for each site, as well as an ascending number for each patient.

7.5 Handling and management of investigational medicinal products

7.5.1 Labelling

Taptiqom® study medication is manufactured by Laboratoire Unither, France, and labelled by Santen Oy, Finland. Manufacturing and labeling will be done according to good manufacturing practice (GMP) regulations (EU GMP Guideline, Annex 13).

The label texts on outer packages will be in local language of the country. The immediate package is a laminated pouch, which includes a set of ten single-dose containers. This pouch will be labeled according to the requirements in paragraph 26 of Annex 13 as well as applicable country-specific requirements.

Pouches are collected into cartons (treatment kits) including medication for dispense at Baseline and Week 6 visits. Each kit has a unique code which is used in investigational medicinal product (IMP) accountability records and which allows identification of the IMP used by any specific patient. The pouches in the kit have the same number.

7.5.2 Storage

Unopened pouches must be stored in a refrigerator at 2 to 8ºC. Opened pouches can be stored at room temperature (not above 25°C) and the single-dose containers must be used within 4 weeks of opening the pouch (unused single-dose containers must be kept inside the pouch to protect from evaporation).

7.5.3 Supply accountability

The investigator or a designated person (e.g. study nurse or pharmacist) in the center will keep a record of the inventory and dispensing of the IMP on study medication accountability forms. These records will be made available to the monitor for the purpose of verifying the IMP inventory. Any significant discrepancy and/or deficiency will be recorded, with an explanation. All supplies sent to the study center must be accounted for and in no case should the IMP be used in any unauthorized situation.

After administering the eye drops, the used single-dose containers may be discarded by the patients. All unused supplies, pouches and packages, may be returned from the study center to the sponsor who will arrange for their destruction. If the IMP destruction is outsourced (e.g. to site pharmacy) the procedure should be agreed in advance and documented stating where, when, how and by whom the IMP was destroyed.

7.6 Masking

Not applicable as this study is open-label; the patient, investigators' site personnel and the sponsor are not blinded to treatment.

8 STUDY PROCEDURES

8.1 Patient recruitment methods

Identification of potential patients will mainly be performed by investigators by review of medical records. Open communication with colleagues in order to capture new patients is also encouraged. Study awareness may be enhanced by using direct-to-patient advertising (e.g. newspaper, internet). If used, applicable ethics committee should approve the text and content of such advertisements or web sites. The study will also be publically registered, allowing patients with OHT or glaucoma to look for ongoing studies in their country or area.

8.2 Patient information and consent

A patient shall only take part in this study after giving his/her written informed consent. Patients must be provided with adequate time to think over their possible participation in the study, to ask questions from the investigator and/or to discuss the study participation with their family or primary care physician. No measures whatsoever described in the study protocol shall be undertaken without such consent indicating that the patient has been given both verbal and written information about the study and the study treatment.

The informed consent form (ICF) shall be signed and dated by the patient and the investigator or designated person who has given the information. The original form shall be included in the investigator's study file, and a copy shall be given to the patient.

The ICF must receive approval of the applicable Independent Ethics Committee (IEC) before use. The patients must also be informed in timely manner if any new information becomes available that may be relevant to their willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised ICF signed by the patient.

8.3 Assessments

Schedule of assessments is provided in Table 1.

8.3.1 Description of study visits

The order of assessments given below is recommended to be followed. The technique for each assessment is described, when it first appears in the text.

Visit 1, (Screening/Baseline)
The purpose and details of the study will be explained to the patient and a written informed consent has to be received before any study related procedures are undertaken. A unique patient number is assigned.

Inclusion and exclusion criteria will be evaluated. Patient's demographic information, current ocular condition(s) (including diagnosis for IOP-lowering treatment) and relevant medical

history/concomitant diseases, corresponding chronic medications (up to one month prior to screening) and prior IOP-lowering medication (within 6 months) will be obtained.

Patient is asked whether (s)he has regularly used Ganfort® before the visit. Clock time of the latest eye drop instillation is recorded. The visit should be scheduled so, that evaluation of ocular signs and symptoms can be performed 12 hours ±1h after instillation of prior evening medication, i.e. in the forenoon depending on instillation time.

For females of childbearing potential, pregnancy and contraceptive status will be queried and a urine pregnancy test will be done to confirm that the patient is not pregnant.

The following assessments will be performed (see also patient eligibility criteria and instructions in Appendices 2-7):

- Ocular symptoms (upon non-instillation)
  The patient will be asked about each symptom (irritation/burning/stinging, foreign body sensation, tearing, itching, and dry eye sensation) by a leading question; the symptoms are graded in scale of 0-4 (none, trace, mild, moderate, and severe). The worst symptom is also identified by the patient. (Appendix 2)

  To qualify for the study, one symptom of at least mild severity (grade 2) needs to occur.

- The evaluation of conjunctival redness/hyperemia is done using the set of reference photographs (ORA redness scale Appendix 3). Findings are graded in scale of 0-4 (none, mild, moderate, severe, very severe). Half-grades are also allowed to refine the scale.

  To qualify for the study, at least moderate conjunctival redness/hyperemia (grade 2) needs to occur in at least one treated eye.

- Drop discomfort and QoL
  Patient will be queried about the drop discomfort during latest administration of prior eye drops. The discomfort is evaluated using the scale from 0-3 (none, mild, moderate, severe). A Comparison of Ophthalmic Medications for Tolerability COMTol QoL questionnaire (Appendix 7) will then be administered by an interviewer. Patient's answers are recorded in the questionnaire.

- Best corrected visual acuity
  Best corrected visual acuity will be measured for each eye under normal room illumination using an eye chart in ETDRS format and the logMAR scoring system, according to recommendations regarding use of the ETDRS chart. The used refraction will also be recorded.

  To qualify for the study, best corrected ETDRS visual acuity score should be +0.6 logMAR or better in both eyes.

- Biomicroscopy
  The biomicroscopy examination (excluding staining) will consist of the evaluation of the lids, conjunctiva, cornea, anterior chamber, iris and lens. The lens must be

examined in connection with the pupil dilatation for ophthalmoscopy. If any findings or abnormalities are present, they will be specified using the definitions and terms found on a separate list (Appendix 6). All findings will be graded as mild (1), moderate (2) or severe (3) or as NA if coding is not applicable (e.g. in case of pseudophakia). Signs of blepharitis, corneal/conjunctival fluorescein staining and conjunctival redness/hyperemia will not be recorded here as they are evaluated separately.

- Presence of blepharitis is graded in scale of 0-3 (none, mild, moderate, severe).

- The fluorescein tear break-up time (fBUT) measurement is performed in conjunction with corneal/conjunctival fluorescein staining. 2 µl of non-preserved 2% sodium fluorescein is instilled onto the bulbar conjunctiva of the right eye without inducing reflex tearing by using a micro-pipette. The patient is instructed to blink several times naturally without squeezing to thoroughly mix the fluorescein with the tear film. Within 10-30 seconds of fluorescein instillation, the patient is asked to look straight ahead without blinking. Under the slit lamp the tear film is then observed: the time between the last blink and first appearance of dry spots is measured in seconds using stopwatch. This procedure will then be performed for the left eye. The assessment time of fBUT is recorded as the evaluations should be performed around the same time during all consequent visits.
- Using reference pictures (Oxford Grading scale, Appendix 4) the corneal fluorescein staining and nasal and temporal conjunctival fluorescein stainings will be scored from 0 to V each.
- The tear production Schirmer test is performed without anaesthesia by placing filter paper inside the lower lids of the eyes. The eyes are closed for 5 minutes after which the papers are removed and the amount of moisture is read from the test strips (in millimeters). Patient number and visit (V1-5) will be recorded on the back of the strip. A horizontal line will be drawn across the leading edge of moisture with a ballpoint pen and the strip will be attached to the source document.
- Visual field test
  Visual field may be tested any time during the day but before IOP measurement with either Humphrey 24-2/30-2 (Full threshold or SITA standard) or Octopus G2-program (normal or dynamic strategy), but the same program must always be used for a particular patient. The visual field test result will be categorized as normal or abnormal. In case of an abnormality, it will be graded from 1 to 3 (1 = mild, 2 = moderate, 3 = severe). If a reliable visual field test result (of the same test program to be used later) is available and has been taken no more than 3 months prior to screening, this can be used as the screening visual field test.
- IOP
  Intraocular pressure will be measured by applanation tonometry after topical anaesthesia and use of fluorescein.

  The measurement procedure (Appendix 5) will be a modification of the procedure utilized in the Ocular Hypertension Treatment study (Kass et al, 2002). The IOP will be recorded in mmHg using one decimal place. The right eye is always tested first. At least two, and sometimes three, consecutive measurements are made to obtain a

determination of intraocular pressure. Each IOP measurement should be entered in the corresponding Case Report Form (CRF) section. If the two measurements differ by 2 mmHg or less, then the average of the two measurements becomes the actual IOP value to be used in analysis of efficacy. For example, if the two measurements are 22 and 23, then 22.5 is recorded as the actual IOP value. If the two measurements differ by 3 mmHg or more, then a third measurement is made, and the median of the three measurements becomes the IOP value to be used (the median is the middle measurement after arraying the measurements from low to high). For example, if the three measurements are 15, 19, and 16, then 16.0 is the value used in IOP analysis. The IOP in the left eye is then measured using the same technique.

To qualify for the study, IOP must be ≤21 mmHg in the treated eye(s)

- Gonioscopy
  The width of the anterior chamber will be evaluated using a goniolens. The Shaffer scale will be used to assess the angle width as follows:
  Grade 0. No structures visible
  Grade 1. Schwalbe line visible
  Grade 2. Schwalbe line and trabecular meshwork visible, but scleral spur not visible
  Grade 3. Scleral spur visible
  Grade 4. All the structures visible from the Schwalbe line to the ciliary band

  To qualify for the study, a patient's Shaffer classification must be grade 2 or more in the treated eye(s).

- Ophthalmoscopy
  The vitreous, retina and the optic nerve will be examined with the pupil dilated. Findings will be classified using the definitions and terms listed in Appendix 6 and graded for severity (1 = mild, 2 = moderate, 3 = severe). In cases where the severity cannot be defined, e.g. in case of posterior vitreous detachment, the severity can be marked as not applicable (NA).

The Taptiqom® study medication will be dispensed to the patient and dispensing will be recorded on study medication accountability forms. The patient will be given instructions to start instilling one drop in the affected eye(s) at 21:00 in the evening.

If the Screening visit is performed outside the time window given for evaluation of ocular signs and symptoms and IOP (12 hours ±1h after instillation of prior Ganfort® medication), a separate Baseline visit must be scheduled within 3 days after the screening visit. During that visit the ocular signs and symptoms are assessed, IOP is measured and thereafter the study medication is dispensed. Medication is then started in the evening of the Baseline visit.

The patient will be scheduled to return for Visit 2 (Week 2, Day 14 ± 2 days). Furthermore, if the patient has been using unpreserved artificial tears by the time of screening, he /she is advised to continue using them throughout the study period in the same manner (using the same dosing frequency per day). He/she is not allowed to start any new artificial tear medications during the study period. The use of unpreserved artificial tears is to be recorded in concomitant medications.

Visit 2 (Week 2, Day 14 ± 2 days)
The scheduled assessments will be done in following recommended order:

- Review of possible changes to concomitant medication(s)
- Adverse events
  The definition of an AE is given in section 9.1.

  Patients will be asked about their ocular and non-ocular symptoms with a non-leading question. Patients should be asked using a general, non-direct question if there has been any change in how they feel from the previous visit. If they report new symptoms or symptoms that have clinically significantly deteriorated from screening/baseline, these will be recorded on the AE form. Any signs considered being clinically significant by the investigator also need to be recorded as AEs, including significant worsening of biomicroscopy or ophthalmoscopy findings (see section 9.1.1).
- Inquiry of patient compliance
  With respect to the previous evening study medication instillation time: if the patient dropped the medication for more than two hours outside the time window at 21:00, the visit should be rescheduled
- Ocular symptoms*
- Conjunctival redness/ hyperemia evaluation*
- Drop discomfort and QoL
- Best corrected visual acuity
- Biomicroscopy (except lens)
- Presence of blepharitis*
- fBUT*
- Corneal and conjunctival fluorescein staining*
- Schirmer test *
- Measurement of IOP*

* 12 hours after instillation of medication – around 9:00±1h

Patient is advised to continue instilling the study medication into treated eye(s) in the evening at 21:00 (within ± 1 h). The patient will be scheduled to return for Visit 3 (Week 6, Day 42± 5 days) and reminded then to take all the unused study medications, pouches and packages with her/him to the clinic.

Visit 3 (Week 6, Day 42±5d)

Same assessments as for Visit 2 will be performed. Additionally for females of childbearing potential, a urine pregnancy test is taken. New Taptiqom® study medication is dispensed to the patient and he/she is scheduled to return for Visit 4 (Week 12, Day 84± 7 days).

Visit 4 (Week 12, Day 84±7d)

The scheduled assessments will be performed in following recommended order:

- Review of possible changes to concomitant medication
- Adverse events
- Inquiry of patient compliance
  With respect to the previous evening study medication instillation time: if the patient dropped the medication for more than two hours outside the time window at 21:00, the visit should be rescheduled
- Ocular symptoms *
- Conjunctival redness/ hyperemia evaluation*
- Drop discomfort and QoL
- Best corrected visual acuity
- Biomicroscopy (including lens)
- Presence of blepharitis*
- fBUT*
- Corneal and conjunctival fluorescein staining*
- Schirmer test*
- Measurement of IOP*
- Ophthalmoscopy (dilated, after the IOP measurement)

* 12 hours after instillation of medication – around 9:00±1h

For females of childbearing potential, urine pregnancy test is taken at any time during the visit.

Unused study medications, pouches and packages will be returned and recorded on study medication accountability forms.

The further treatment of the patient will be determined and recorded in source data by the investigator (until next visit to the treating doctor of that patient). The patient is scheduled to return to the final post study visit (Visit 5) in 1–3 weeks.

Visit 5 (post-study, 1-3 weeks after Visit 4 or discontinuation of study medication)

Following assessments will be done:

- Follow up of any adverse events persisting from previous visit/discontinuation of study medication
- Follow up of changes in concomitant medications continuing from previous visit
- Ocular symptoms

- Conjunctival redness/ hyperemia evaluation
- Best corrected visual acuity
- Biomicroscopy (including lens if pupil dilation because of ophthalmoscopy is done)
- Presence of blepharitis
- fBUT
- Corneal and conjunctival fluorescein staining
- Schirmer test
- Visual field test
- IOP (single measurement at any time of the day)

Visual field test is taken during or just before the visit, so that the results are available latest at the post-study visit. The visual field test results are compared against the screening test and possible changes are confirmed by the investigator.

Ophthalmoscopy is performed if considered necessary by the investigator and in case of study treatment related abnormalities persisting from the previous visit.

The patient is exited from the study. However, in case of ongoing serious adverse events (SAEs, see 9.1.2) or cases of special interests (CSI, see 9.1.3), the patient will be followed up until the event has resolved or stabilized.

8.4 Patient compliance

It is critical that each study patient complies with the dosing schedule specified in the protocol. Patients will receive verbal and written instructions regarding the proper instillation of study medication and the dosing regimen. The drug accountability documentation, will also be used to document and follow up the patient compliance in this study.

In addition, at each post-baseline visit, the time point of administration of the study medication (at Visit 5 of the applicable further treatment started) on the previous evening will be recorded. If it is noted at Visits 2-4 that a patient has completely missed the previous evening dose or dosing time has been out of window for more than two hours (of the scheduled time at 21:00), the visit should be rescheduled to next day (if possible).

8.5 Concomitant treatment

Concomitant treatment is any treatment or medication given concurrently with the study treatment and that is mentioned in the local Medicines Compendium.

The use of any concomitant prescription or over-the-counter (OTC) medication must be recorded in the patient's source document and on the appropriate CRF along with the reason for the medication taken.

Prior IOP-lowering medication information (within 6 months) is collected as well as any chronic medication or treatment taken during the last month prior to the study Screening visit.

8.5.1 Prohibited medications or treatments

Use of any ocular or systemic IOP-lowering medications during the study treatment period with Taptiqom®, is prohibited. Also use of any topical eye medications with preservative (e.g. artificial tears, ocular antibiotics, antihistamines and corticosteroids) is prohibited during study treatment. Additionally, if a patient has used e.g. preserved dry eye medication until the time of Screening visit, stopping its use at Screening does not make the patient eligible for the study.

Any changes to dosing of e.g. unpreserved artificial tears during the study period is prohibited.

The decision to administer a prohibited medication or treatment should be done with the safety of the patient as the primary consideration. Whenever possible, Santen Oy should be notified before any prohibited medication or treatment is administered. There may be prohibited therapies not mentioned above. Santen Oy should be contacted if the permissibility of a specific medication or treatment is in question.

8.5.2 Permitted medications or treatment

Patients are allowed to continue using unpreserved artificial tears, which they have used prior to screening (Visit 1). The same dosing frequency has to be maintained and no new artificial tear medications should be started during the study period. There should be at least 30 minutes between the administrations of the study medication and concomitant ocular medications. Therapy considered necessary for the patient's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the investigators. Whenever possible, medications should be administered in dosages that remain constant throughout the study period.

8.6 Conditions for premature patient discontinuation

For each patient the study is considered completed, when *all assessments and examinations have been undertaken in accordance with the study protocol*. Each patient is, however, free to discontinue his/her participation in the study at any time. The investigator may also withdraw a patient prematurely from the study and the investigator may be advised by a representative of Santen Oy to withdraw a patient. Possible reasons for withdrawal include the following:

- AE(s) necessitating discontinuation from the study
- Lack of efficacy as judged by the investigator
- New concomitant medication or dose change of ongoing prior medication that has an effect on the study outcome parameters. In this case sponsor should always be consulted before withdrawal decision. The type of medication, duration of its use and timing in relation to study visits are considered.
- The patient is unwilling or not able to follow the dosing schedule of the study treatment or is otherwise non-compliant
- Improper entry
- Patient request
- Pregnancy (patient has become pregnant during the study)
- Other reason (e.g. loss to follow up)

If a patient is discontinued from the study before completing the 12-week study treatment period, then to the extent possible, all follow-up assessments that are scheduled for Week 12 (Visit 4) as well as obtaining the visual field should be performed on the day of discontinuation. Further treatment of patient's condition is determined by the investigator.

8.7 Collection and processing of patient data

8.7.1 Case report forms (CRFs)

CRFs are records of data on each patient as defined by the study protocol. All data on the CRFs must be verifiable in the source data or patient records unless declared as source data in the monitoring plan. Any data that are directly entered into the electronic CRF (eCRF) without maintaining a paper source will be clearly defined before start of the study and documented in the monitoring plan.

Electronic data capture (EDC) compliant with all legislation relevant to electronic records and signatures (FDA 21 Part 11) will be used. The study personnel will enter and edit the data via a secure network with secure access features (username and password). A complete electronic audit trail will be maintained. The study personnel will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded.

After study completion eCRFs are archived by the sponsor. CDs/DVDs with all eCRF data in PDF format will be provided to investigator for archiving with the investigator site file.

8.7.2 Data management

A detailed data management plan for the activities described later will be prepared. The study characteristics of the protocol are entered into the EDC system and the structure of the database will be based on the eCRFs.

Edit checks will be defined and programmed in the EDC system to reveal possible discrepancies (missing, incomplete or illogical data). Edit checks will be triggered on-line according to an agreed data validation plan. Discrepancies revealed by the edit checks will be

visible and notified to the user to be corrected immediately during data entry. In addition, study monitor(s) or data management staff may create manual queries to resolve data incoherencies or discrepancies with source data. The EDC system will keep track of query forms and eventual data corrections.

The clean database will be locked after all data have been entered, detected discrepancies have been resolved and the database updated accordingly. Only authorized and well-documented updates are possible after the database lock.

There will be no special software requirements at the study centre, because the EDC application runs with standard Web-browsers. Further EDC application details will be given in separate documents.

9 REPORTING OF ADVERSE EVENTS AND OTHER SAFETY INFORMATION

9.1 Definitions

9.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation patient who has been administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP.

AEs may also occur in screened patients during any pre-allocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

In general, changes in clinical safety variables will be recorded as AEs if clinically significant changes as judged by the investigator occur during the study. These may include, but are not limited to, cases where a patient spontaneously reports a new symptom or when a change from baseline of clinical importance as judged by the investigator occurs.

Worsening of findings e.g. in biomicroscopy or ophthalmoscopy from no findings to finding graded as moderate/severe, or change in grading from mild to severe, may be an indication of an AE. By investigator's judgment, also milder changes can be recorded as AEs. Patients' answers given to study questionnaires (or changes in these) are not reviewed as basis for occurrence of AEs.

9.1.2 Serious Adverse Event (SAE)

An adverse event (any untoward medical occurrence or effect) that at any dose

- results in death,
- is life-threatening*,
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect, or
- is other medically significant condition (including sight-threatening** events and cancer of any type).

*Herein 'Life-threatening' refers to an event in which the patient was at immediate risk of death at the time of event; it does not refer to an event which hypothetically might have caused death.
**Similarly 'Sight-threatening' refers to an event in which the patient was at immediate risk of losing sight; it does not refer to an event which hypothetically might have caused losing of sight.

9.1.3 Case of Special Interest (CSI)

The following cases are considered to be of special interest by the sponsor:

- Overdose
  - Administration of a quantity of a medicinal product exceeding the dose defined in the study protocol/otherwise specify overdose
- Misuse of study product
  - Situations where the medicinal product is intentionally and inappropriately used not in accordance with the study protocol.
- Medication error
  - Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.
- Abuse of study product
  - Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.)
- Non-serious AEs requiring expedited (24h) reporting to the sponsor
  - Uveitis
  - Macular edema

9.1.4 Pregnancy report

Although not considered an AE, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Santen Oy Pharmacovigilance Unit (PVU).

The pregnancies of partners to patients with paternal drug exposure do not have to be reported or followed up.

9.2 Assessment of AEs and documentation of the safety information

All patients enrolled in the study will be evaluated for AEs from the time that the informed consent is signed until the last study visit. Even after completion of the study, the investigator shall notify Santen Oy PVU of any new SAEs that may be associated with the investigational treatments.

All non-serious AEs will be evaluated until recovery or until last post-study visit.

SAEs will be evaluated until their recovery or until the investigator determines that the patient's condition is stable. The investigator will take appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the case documentation.

9.2.1 Seriousness

The seriousness of each event must be assessed by the investigator according to the criteria set for SAEs in section 9.1.2. If the event does not meet the criteria of a SAE, it is assessed as non-serious. Serious and non-serious AEs have different reporting requirements as detailed in section 9.3.1.

Special medical judgment should be exercised in deciding whether an AE is serious as regards 'other medically significant conditions'. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or convulsions that do not result in hospitalization.

9.2.2 Severity

The investigator will 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

In rare cases when the above grading is not applicable e.g. in case of abnormal laboratory values, the severity of the finding will be determined by the investigator based on the clinical significance of the finding.

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a SAE. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs listed in section 9.1.2.

9.2.3 Causality

The investigator will assess the causal relationship between the study treatment and the AE as follows:

- Related: there is a reasonable possibility that the event is caused by the study treatment
- Not related: there is no reasonable possibility that the study treatment caused the event

9.2.4 Expectedness

AEs will be evaluated as to whether they are expected or unexpected. The assessment is performed by the sponsor and it is based on the available product information, either Investigator's Brochure for unauthorized IMPs or SmPC for authorized products.

- Expected: An AE is expected when the nature or severity of which is consistent with the applicable product information.

- Unexpected: An AE is unexpected when the nature or severity of which is not consistent with the applicable product information

The sponsor is responsible for ongoing safety evaluation of the study treatment. When there is at least a reasonable possibility that the event is related to the study treatment the AE will be categorised as Adverse Drug Reaction (ADR). If the reaction is both serious and unexpected, the sponsor shall initiate expedited reporting according to pharmacovigilance guidelines to all relevant parties, including investigators.

9.2.5 Documentation of the safety information

All AEs will be recorded by the Investigator in the source documents and AE CRF using standard medical terminology. Pregnancy reports and CSIs will be recorded in the source documents. The sponsor records all SAEs, CSIs and Pregnancy reports in the safety database of Santen Oy.

9.3 Reporting

9.3.1 Reporting of non-serious and serious AEs

All serious and non-serious AEs occurring until completion of the study must be recorded on the AE CRF. In addition, SAEs (intial and follow-up information) must be reported expeditedly to the sponsor as described in section 9.3.2.

The AE information to be collected is described in section 10.1.4.1. The following information will be included in the AE CRF:

- Adverse Event term*
- Frequency
- Seriousness (whether or not event is SAE)
- Severity
- Location (e.g. right/left eye, both eyes, or NA if non ocular event)
- Date of onset
- Action taken with study treatment
- Outcome of event
- Date of resolution
- Causality to study treatment
- Report source (how the information was received).

*Event term: a diagnosis should be given as an event term rather than individual signs and symptoms. However, if signs and/or symptoms cannot be undoubtedly medically characterized as a single diagnosis, each one of them should be recorded as an individual AE.

For example:

- Rash, dyspnea, hypotension, and laryngospasm ⇒ Anaphylactic reaction

  The event term is Anaphylactic reaction

- Orthostatic hypotension ⇒ fainting and fall to floor ⇒ head trauma ⇒ neck pain

  The event term is Orthostatic hypotension

9.3.2 Expedited reporting of SAE/Pregnancy/CSI

The Investigator must report all SAEs, CSIs and pregnancies or their follow-ups (new information related to previous reports), **within 24 hours of awareness,** to the sponsor.

Reporting must be done by completing an appropriate reporting form* and providing it with all the relevant documentation (eg. copies of related results/reports, consultant report(s)) to Santen Oy Pharmacovigilance unit. It should be noted that SAEs must be recorded also in the AE CRFs.

Santen Oy, Pharmacovigilance Unit (PVU)
Fax SAE Report Form to +358 3 318 1060 or
Email to drugsafety@santen.fi
(Phone +358 3 284 8625)

* Blank copies of the SAE, CSI and Pregnancy reporting forms are available in the investigator's study file and as well as electronically. If the form is not available, similar information shall be submitted; the minimal required information comprises study identification (such as study number), patient identification (such as patient number, age and sex), information on the case (brief description), information on study treatment and reporter identification.

All SAEs must be followed until their recovery or until the investigator determines that the patient's condition is stable. Also the outcome of the pregnancy shall be reported to Santen Oy. Follow-up reporting must be done in expedited manner as described above.

Reporting responsibilities are described in study specific safety management plan. Santen Oy is responsible for assuring that IEC and regulatory authorities are informed of SAEs, CSIs and pregnancies in accordance with national laws and regulations.

As applicable, the investigator shall follow the local IEC and authority's requirements for reporting SAEs, CSIs and pregnancies.

10 STUDY VARIABLES AND STATISTICAL ASPECTS

10.1 Study variables

In short, the study variables will include:

- Background information (section 10.1.2)
- Outcome variables (section 10.1.3)
- Safety and QoL variables (section 10.1.4)

10.1.1 Appropriateness of measurements

The assessments included in this study are consistent with standard ophthalmic procedures used to examine patients with OHT or OAG (POAG or PEX). The assessments include measurement of IOP using a standardized procedure, generally used safety measures (biomicroscopy, visual acuity, ophthalmoscopy and visual fileds) and a direct clinical assessment of ocular symptoms and signs. In addition, analysis of COMTol questionnaire provides information on the patients' QoL.

10.1.2 Background information

Patient demography (gender, age, race and iris color), current ocular condition(s), prior IOP-lowering medication, medical history/concomitant diseases, concomitant medication, gonioscopy, and pregnancy test for females of childbearing potential will be assessed at screening visit (Visit 1). The choices for iris color will be blue/gray, blue/gray–brown, green, green-brown, brown, yellow-brown and other.

Prior IOP-lowering medication (used within 6 months) and chronic medications (taken during 1 month prior to screening visit) as well as all concomitant medications will be coded using the current ATC/DDD index. Previous and concomitant diseases and ocular conditions recorded in medical history will be coded using the current MedDRA dictionary.

10.1.3 Outcome variables

Outcome variables include ocular symptoms upon non-instillation (section 10.1.3.1) and ocular signs (section 10.1.3.2). Evaluation of ocular signs and symptoms will be performed at all five visits.

The evaluation of ocular symptoms is done for treated eye(s) considered together. The change from screening/baseline will be computed by patient for each symptom. The analysis will be performed on each symptom, total ocular symptom score, and the worst ocular symptom. The worst ocular symptom will be designated by the patient at Visit 1.

The evaluation of ocular signs is based on the worse eye designated respectively for each sign, i.e. the eye with the greatest conjunctival redness/hyperemia, the greatest corneal/conjunctival fluorescein staining score, the shortest fBUT, the shortest tear fluid secretion measure, score and the greatest severity grading score for blepharitis, will be considered the worst eye. If an ocular sign has the same severity in both eyes, the right eye will be designated.

The primary outcome variables will be:

- Change from screening in conjunctival redness/hyperemia at week 12
- Change from screening in worst ocular symptom upon non-instillation at week 12

Thus, the analyses of primary outcome variables will be done using the evaluations from Screening/Baseline and Week 12 (primary analysis).

The secondary outcome variables will be:

- Change from screening in ocular signs at week 12 (other than conjunctival redness/hyperemia)
- Change from screening in ocular symptoms[4] upon non-instillation at week 12

Additionally, for ocular symptoms and signs, the evaluations from Week 2, Week 6 and post-study will be summarised.

10.1.3.1 Ocular symptoms

Ocular symptoms to be assessed include the following: irritation/burning/stinging, foreign body sensation, tearing, itching and dry eye sensation. Each symptom will be scored as none (0), trace (1), mild (2), moderate (3) or severe (4). At Screening/Baseline, patient will also indicate the symptom that is considered the worst symptom. Ocular symptom total score will be calculated by summing up the scores (i.e. the range for the total score is from 0 to 20).

[4] Except the worst symptom which is analysed as the second of the primary outcome variables

10.1.3.2 Ocular signs

Five ocular signs will be evaluated:

Conjunctival redness/hyperemia
Conjunctival redness/hyperemia will be assessed using reference photos (ORA Redness scale) and a five-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. In addition, half-grades are allowed to refine the scale.

Fluorescein Tear Break-Up Time (fBUT)
Fluorescein dye is added to the eyes and the tear film is observed under the slit lamp. The time it takes to form micelles i.e. dry spots develop is recorded as the break-up time (in seconds).

Corneal and conjunctival fluorescein staining
Fluorescein dye solution is administered and using reference pictures (Oxford Grading scale) corneal as well as nasal and temporal conjunctival fluorescein stainings will be scored from 0 to V each.

Blepharitis
Presence of blepharitis will be evaluated and severity graded from 0 (none), 1 (mild), 2 (moderate) or 3 (severe).

Tear secretion/Schirmer test
The test is performed without anaesthesia by placing filter paper inside the lower lid of the eye. The amount of moisture is read from the test strip (in millimeters). Both eyes may be tested at the same time.

10.1.4 Safety and QoL variables

Safety variables include adverse events (section 10.1.4.1) and ocular safety and QoL variables (section 10.1.4.2).

The disposition of patients (including premature discontinuations) will be summarised. The exposure to study treatment will also be presented.

The evaluation of safety will be based on the safety dataset (see section 10.2.2.3). For ocular safety and QoL variables, all eyes will be evaluated. For the untreated eyes, data will be collected and listed only.

10.1.4.1 Adverse events

The definition of an AE is given in section 9.1. AEs will be queried from the patients at each post-baseline visit. The information will include event term, report source, whether or not the event is serious, onset and resolution date, frequency, severity, relation to study drop instillation, location (left/right eye, both or NA if non-ocular event), action taken with study treatment, investigator's causality assessment as regards to the study treatment and outcome.

All adverse events will be coded using the latest MedDRA dictionary. Ocular and non-ocular events will be summarized separately.

10.1.4.2 Ocular safety and QoL variables

The ocular safety measurements will be summarized separately for the left and right eye. In addition, the results for the eye with the worse measurement may be summarized. The screening value will be the last corresponding measurement before starting the study medication (as in case of ocular signs and symptoms, at screening or separate baseline visit).

In addition to AEs, the following ocular safety variables will be evaluated:

- IOP
- Best corrected visual acuity
- Biomicroscopy
- Ophthalmoscopy
- Visual field test
- Drop discomfort
- QoL - COMTol questionnaire

IOP

Intraocular pressure will be measured from both eyes at all visits. At visits 1-4, measurement is done 12 hours after evening instillation of study medication. Measurement can be any time on Visit 5. If both eyes are treated, then the mean IOP value of the two eyes will be used. If only one eye is treated, the IOP value of this eye will be used. IOP values will be tabulated.

Best corrected visual acuity

Best corrected visual acuity will be measured at each visit using an ETDRS chart. The used refraction will also be recorded. LogMAR scores will be calculated using the following algorithm, where the Base LogMAR value is the logMAR value of the last line in which a letter was read correctly:

LogMAR score = Base LogMAR value + (0.02 x the total number of letters missed)

Deteriorations from baseline of at least 0.2 LogMAR scores (two lines of letters) will be identified.

Biomicroscopy

During each visit the biomicroscopic examination will include evaluation of the lids, conjunctiva, cornea, anterior chamber and iris. Additionally at Visits 1 and 4 the lens is examined. The findings are graded from 1 to 3 (1 = mild, 2 = moderate, 3 = severe) or as NA if grading is not applicable.

Ophthalmoscopy

Ophthalmoscopy will be performed at Screening- and Week 12 visits (Visits 1 and 4). If necessary, and in case of treatment related abnormalities at Visit 4, the assessment must be repeated at Post-study visit (Visit 5). The evaluation will include vitreous, retina and optic nerve. All findings will be graded as mild (1), moderate (2), severe (3) or NA (not applicable). Changes (deteriorations) from screening will be identified.

Visual field

Visual field test will be done at Screening and Post-study visit. All results will be categorized as normal or abnormal. If there are abnormal results, the abnormality has to be specified and graded from 1 to 3 (1 = mild, 2 = moderate, 3 = severe). Furthermore, the results at the Post-study visit will be compared with the screening results. The investigator will evaluate, whether a change from screening has occurred or not.

Drop discomfort and COMTol

Drop discomfort and quality of life using Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire will be evaluated from Screening up to Week 12 (a total of 4 evaluations). For drop discomfort a four-point scale will be used in the evaluation: none (0), mild (1), moderate (2) and severe (3). Changes from screening in drop discomfort will be identified. COMTol questionnaire will be administered by an interviewer. It consists of 11 questions mainly scoring from 0 to 5-6 and with higher score indicating the patients' increased discomfort. The questions are divided into five global assessments (preference, effect of side effects in QoL, effect of activity limitations on QoL, compliance, and satisfaction), five side effects domains (ocular symptoms, taste, vision, accommodation, and browache), and three activity limitations domains (driving, reading, and moderate activities).

10.2 Statistics

10.2.1 Sample size

The sample size calculation was made based on conservative estimates from previous tafluprost switch studies (Uusitalo et al., 2010b; Study 77553): Assuming a mean change from baseline of 0.37 units in conjunctival redness/hyperemia and a standard deviation of 1.12 units, a power of 90% is achieved for a paired t-test with 100 patients (and a power of ~80% with 70 patients). Analogously, a power of >99% is attained for the second primary outcome measure - worst ocular symptom - with 100 patients.

Thus, in order to reach the target of 100 evaluable patients, a total of approximately 120 patients need to be enrolled to this study.

It should be noted that the Wilcoxon signed rank test (i) performs better than the paired t-test for heavy-tailed distributions and (ii) has an asymptotic relative efficiency of 0.955 versus the paired t-test under the assumption of normal distribution.

10.2.2 Statistical methods

10.2.2.1 Statistical analysis plan

A detailed statistical analysis plan (SAP) will be prepared prior to database lock.

10.2.2.2 Statistical hypotheses

To show statistically significant improvement ($p<0.05$) for the primary outcome measure(s).

10.2.2.3 Datasets to be analysed

The intention-to-treat (ITT) dataset will include all enrolled patients who receive at least one dose of study treatment and have at least one post baseline primary outcome measurement available (ocular symptom or sign).

The per protocol (PP) dataset is a subset of the ITT dataset excluding patients or measurements for a given patient with major protocol violation(s) expected to alter the outcome to treatment. Detailed criteria for patient classification will be prepared before database lock.

The safety dataset will include all enrolled patients who receive at least one dose of study treatment and have a subsequent safety measurement.

The primary outcome measures will be analysed using both the ITT (primary analysis) and the PP dataset.

10.2.2.4 General statistical considerations

All background, outcome and safety variables will be summarized by visits. In addition to absolute values, changes relative to screening values will be summarized, if feasible.

Correlations among the study variables (e.g. ocular symptoms, ocular signs and QoL) may be investigated.

10.2.2.5 Background information

The disposition of patients will be summarized. All background variables (see Section 10.1.2) will be tabulated with descriptive statistics.

In addition, the prior use of Ganfort® eye drops, and the use of other ocular hypertensive medications and artificial tears (and changes in these) will be summarized.

10.2.2.6 Analysis of outcome variables

The results of ocular signs and symptoms (see Section 10.1.3) over the course of the study will be summarized descriptively

The analysis of the primary outcome measure for ocular signs (12-week change from screening in conjunctival redness/hyperemia) and the primary outcome measure for ocular symptoms (12-week change from screening in worst ocular symptom) will be done using the Wilcoxon signed rank test.

The analysis of secondary outcome measures (12-week changes from screening for the remaining ocular signs and symptoms; see Section 10.1.3) will be done using standard statistical methods for paired data (e.g. McNemar's test for binary data, Wilcoxon signed rank test for ordinal data, and paired t-test for continuous data).

In addition, (i) the 6-week changes will be analysed accordingly and (ii) generalized linear mixed models may be used to further characterize the results.

Subgroup analyses

If feasible, subgroup analyses will be conducted by (pooled) center, age, gender, ocular diagnosis (OH/ POAG/PEX), use of artificial tears, and type and length of prior Ganfort® medication.

10.2.2.7 Analysis of safety and QoL

Adverse events
Ocular and non-ocular adverse events will be tabulated by system organ class, preferred term, causality and severity, if feasible. Both patient and event counts will be calculated. In addition, SAEs and AEs leading to a discontinuation will be summarized.

Ocular safety and QoL
IOP, Best corrected visual acuity, biomicroscopy, ophthalmoscopy, visual field test, drop discomfort and COMTol (see Section 10.1.4) will be analysed descriptively. The results will be summarized separately for the left and right eye, if feasible. In addition, the results for the eye with the worse measurement may be summarized.

For COMTol, scores will also be defined and reported separately for global assessments, side effect domains and activity limitation domains following the instructions of the COMTol manual. Methods outlined for the outcome variables will be used to analyse the changes from screening in COMTol variables, if feasible.

For IOP, individual (and mean) curves will be used to characterise the IOP lowering effect during the 12-week treatment period. In addition to paired t-test, analysis of variance models may be used to further characterize the results.

10.2.3 Hardware and software

Statistical analysis, tables and patient data listings will be performed with SAS® version 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

11 ETHICAL CONSIDERATIONS AND REGULATORY COMPLIANCE

This study is to be conducted in accordance with the ICH-GCP guidelines and the Declaration of Helsinki.

11.1 Ethics committee(s)

The study protocol, the patient information and ICF will be submitted for review and approval to appropriate IEC(s) according to ICH-GCP as well as national- and any local requirements.

The study cannot begin before ethics committee approval(s) have been obtained.

11.2 Authorities

The study protocol will be submitted for approval/notification to relevant health authorities in accordance with the ICH-GCP guidelines and national laws and regulations.

The study cannot begin before the authorities' requirements have been fulfilled.

11.3 Quality Assurance (QA) and Quality Control (QC)

Review and audit processes will be carried out within the schedule of Santen Oy quality units for the clinical study protocol, for overall performance of study, for investigational medication preparing, labeling, packaging and delivering processes, and for the clinical study report.

11.4 Training

An investigator meeting (local or joint meeting for all centers) will be held prior to study start to train investigators and site staff, and to ensure clarification and standardization of procedures. Training sessions for study staff will be held also during the pre-study and initiation visits to sites. Further investigator meetings and targeted training will be held as necessary.

11.5 Monitoring

A designated study monitor will verify compliance with the study protocol, check the data entered on eCRFs and SAE/CSI/Pregnancy forms against source data and review the study medication storage and accountability. All occurred protocol deviations should be documented and listed.

The frequency and extent of monitoring schedule will be performed according to the study specific monitoring plan. Additional visits may be performed based on the enrollment rate or specific needs of the site. Patient’s answers to ocular symptoms and QoL questionnaires may be regarded as source data. Further source data and source data verification requirements will also be specified in the monitoring plan.

11.6 Amendments to the study protocol

Any changes to the signed protocol should be discussed and agreed between all those concerned. If considered necessary or by request of IEC(s) or health authorities handling the study, the protocol may be amended. An amendment is an official alteration to the study protocol, and shall be agreed upon and signed by protocol signatories or their deputies.

Need for reapproval by or notification of ethics committee(s) and health authorities must be considered, as well as the impact on study patients' safety and willingness to continue their participation. An update of the patient information and ICF is prepared when appropriate.

11.7 Responsibilities of the investigator

The investigator shall conduct the study in accordance with the ICH-GCP, study protocol and relevant local laws and regulations. The Principal Investigator at each study site has the overall responsibility with regard to the conduct of the study and the members of his/her study team.

Description of specific responsibilities of the Sub Investigator(s) or other qualified persons to whom the Principal Investigator has delegated trial related duties should be found in a detailed list in each center.

11.8 Audits

The study may be subjected to auditing by representatives of Santen Oy and/or to inspection(s) by authorized representatives of local and/or foreign health authorities. In case of an audit or inspection, the investigator will be informed in advance.

12 CONFIDENTIALITY

12.1 The patient

All data on the patients, including their identity and all personal medical data will be considered confidential and handled as such. Data verification procedures will be performed in strict confidence.

12.2 The sponsor

The investigator's study team shall keep secret all information and results related to or arising from the study, and shall not disclose such information or results to any person other than employees of Santen Oy immediately concerned with the study, if not otherwise agreed upon. The investigator's study team shall also keep secret all information relating to the trade, business or activities of Santen Oy, which they may learn having entered into this collaboration.

13 AGREEMENT AND FINANCIAL ASPECTS

The final study protocol together with the approved budget, form a part of the agreement between the relevant party (investigator, institution, hospital or university) and Santen Oy. The agreement will be finalized before initiation of the study at the site.

Alternatively trial agreements may be made between the investigator site and CRO to which Santen Oy has delegated sponsor responsibilities.

14 INSURANCES

The manufacturer will maintain a liability insurance policy sufficient to cover liabilities arising from the study product(s). If required by the applicable local regulatory requirements, the sponsor should provide additional insurance for the investigator.

15 STUDY COMPLETION/TERMINATION

15.1 Completion

The clinical phase of the study shall be considered completed when the activities described in the study protocol have been completed for all patients participating in the trial. Study completion procedures following completion of the clinical phase (whether at full-time or premature) include collection of all remaining study-related material, and review of administrative tasks, such as reporting and filing.

Essential documents should be retained by sponsor for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.

The original trial documents in investigator's file must be stored for at least 15 years from the end of the trial. The keeping of patient files is governed by the relevant general provisions and local regulations. It is the responsibility of the sponsor to inform the investigator/institution by writing as to when these documents no longer need to be retained.

15.2 Premature study termination

The sponsor reserves the right to discontinue the study conduct for any safety, ethical or administrative (force majeure) reason at any time.

If the trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IECs should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

16 STUDY REPORTS AND PUBLICATIONS

The investigator shall submit the results obtained from the study to Santen Oy. All data obtained in connection with the study shall be delivered to and become the property of Santen Oy unless written instructions to the contrary are received from Santen Oy.

The final study report will be prepared by the sponsor in collaboration with Oy 4Pharma Ltd.

Any results from this study may be used by the sponsor for the following purposes:

- submissions to health authorities and IECs
- inclusion in Santen Oy files in order to be used to inform the medical profession of the activity, dosage, therapeutic effect, safety of the treatment or of precautions to be observed during the treatment.

Scientific reports will be published based on separate mutual agreement. The sponsor respects the investigators' wish to publish results of the study, and will not unnecessarily restrict the spreading of information of scientific interest. However, the study may involve confidential information affecting the company's business, such as aspects related to patent application. Therefore, the investigators agree to allow the sponsor to review any manuscripts and to negotiate timing and forum of publication.

Trial result-related information will also be published in accordance with the applicable European regulation and guidelines.

17 GENERAL SCHEDULE

The clinical phase of the study is scheduled to start in first half of 2015 and to be completed in 2016.

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19 APPENDICES

Appendix 1	Protocol signature by principal investigators
Appendix 2	Ocular symptoms questionnaire
Appendix 3	Conjunctival redness/hyperemia evaluation – ORA scale
Appendix 4	Corneal and conjunctival fluorescein staining evaluation – Oxford grading scale
Appendix 5	Intraocular pressure measurement
Appendix 6	Terms and codes for biomicroscopy and ophthalmoscopy findings
Appendix 7	Quality of Life questionnaire – COMToL

PROTOCOL SIGNATURE BY PRINCIPAL INVESTIGATORS

In order to fulfill the ICH-GCP Guidelines the following information of the study center should be found in the Essential Documentation of the study.

By signing this document you accept to conduct the study according to the protocol and ICH-GCP guidelines.

Fill in all relevant information of responsible person (at least name and country).

Center No ___	Principal Investigator: Address: Telephone: Telefax:	NN, MD, PhD Title Department of University of Area Country +000 0 000 000 +000 0 000 000	_____ Date _____ Signature

Fill in this form for all centers involved in the study.

GCP Statement

This study will be conducted in accordance with ICH-GCP guidelines, the applicable regulatory requirements and the Declaration of Helsinki.

Assessment of Ocular Symptoms

The patient will be asked about each symptom by a leading question.

The symptoms are graded in scale of 0-4.

At Screening/Baseline visit, patient is asked to indicate the symptom that he/she considers the worst symptom.

Visit: Baseline

	0 = none	1 = trace	2 = mild	3 = moderate	4 = severe	Worst symptom at baseline*
Irritation/ burning/stinging	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐
Foreign body sensation	☐	☐	☐	☐	☐	☐
Tearing	☐	☐	☐	☐	☐	☐
Dry eye sensation	☐	☐	☐	☐	☐	☐

***Check only one**

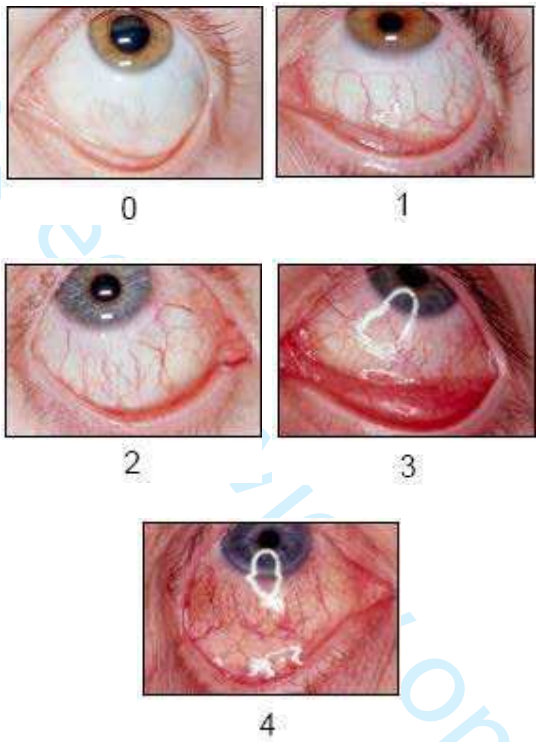
Visit: ☐ Week 2 ☐ Week 6 ☐ Week 12 ☐ Post-study

	0 = none	1 = trace	2 = mild	3 = moderate	4 = severe
Irritation/ burning/stinging	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐
Foreign body sensation	☐	☐	☐	☐	☐
Tearing	☐	☐	☐	☐	☐
Dry eye sensation	☐	☐	☐	☐	☐

Conjunctival redness/hyperemia evaluation – ORA scale

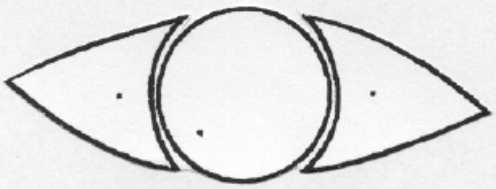
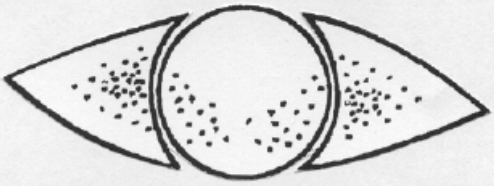
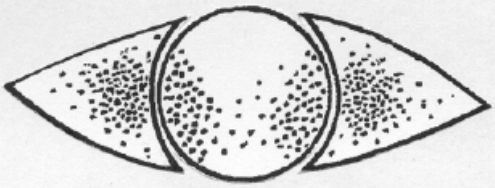
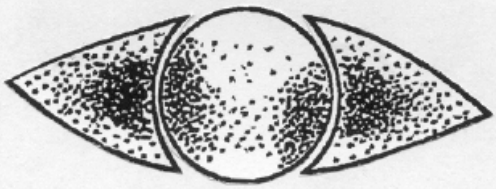
ORA Scale #6.0
Santen Protocol #201450

ORA Redness Scale



Corneal and conjunctival fluorescein staining evaluation – Oxford grading scale

MANUAL DEFINITION OF TERMS
Oxford Grading scale

		Grade		Dot Count		Log
A		0	≤ A	1		0
B	A < 	I	≤ B	10		1.0
C	B < 	II	≤ C	32		1.5
D	C < 	III	≤ D	100		2.0
E	D < 	IV	≤ E	316		2.5
	E <	V		1000		3.0

Intraocular pressure (IOP) measurement

The following IOP measurement procedure is a modification of the procedure utilized in the Ocular Hypertension Treatment Study (Kass et al, 2002, OHTS Manual of Procedures).

The right eye is always tested first. At least two, and sometimes three, consecutive measurements are made to obtain a determination of IOP. Each IOP measurement should be recorded on the CRFs.

A single measurement is made as follows:
The force on the tonometer dial is adjusted to an initial setting corresponding to 10 mmHg. The slit lamp magnification is set at 10X. The light source is positioned at an angle of approximately 45º, and the aperture is maximally opened. A cobalt blue filter is employed.

After instillation of a topical anesthetic, additional preservative-free fluorescein may be instilled if necessary (see study visit descriptions and assessment of ocular signs). Alternatively a fluorescein paper strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid is sufficiently colored, the paper strip is removed.

The patient and slit lamp are adjusted so that the patient's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight-fitting neckwear is loosened. The patient is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the eyelids are held against the orbit rim, taking care not to apply any pressure to the globe. The patient is cautioned not to hold his/her breath.

The examiner looks through the slit lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well-focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately 1/10 their diameter, additional fluorescein is instilled.

The measuring drum is adjusted until the inner borders of the two mires just touch each other or, if pulsation is present, until the mires separate a given distance during systole and overlap the same distance during diastole.

The tip is removed from the cornea and the reading on the dial is recorded, rounded to the next highest integer. For example, if the measurement indicated is between 16 and 17, then 17.0 is recorded as the measurement.

If corneal astigmatism is greater than 3.0 D, the prism is rotated so that the red line corresponds to the orientation of the longer axis of the elliptical applanated area.

The above procedure is then repeated for the same eye.

If the two measurements differ by 2 mmHg or less, then the average of the two measurements becomes the actual IOP value to be used for analysis of efficacy. For example, if the two measurements are 22 and 23, then 22.5 is the value to be used.

If the two measurements differ by 3 mmHg or more, then a third measurement is made, and the median of the three measurements becomes the actual IOP value to be used for analysis of efficacy (the median is the middle measurement after arraying the measurements from low to high). For example, if the three measurements are 15, 19, and 16, then 16.0 is thevalue to be used in IOP analysis.

The IOP in the left eye is then measured using the same technique.

TERMS AND CODES FOR BIOMICROSCOPY AND OPHTHALMOSCOPY FINDINGS

Biomicroscopy

	Code			Code	
Lids Grading: 1= mild 2= moderate 3= severe	1	Chalazion	**Cornea** Grading: 1= mild 2= moderate 3= severe	36	Arcus senilis
	2	Discharge		37	Dystrophy (specify)
	3	Dryness of the skin		38	Endothelial pigment
	4	Edema		39	Endothelial precipitate
	5	Eczema		40	Epithelial edema
	6	Erythema (Hyperemia)		41	Epithelial erosion
	7	Exudate		42	Filaments
	8	Eyelash growth		43	Guttata
	9	Eyelash thickening		44	Keratitis (specify), other than SPK (code 50)
	10	Eyelash darkening		45	Krukenberg's spindle
	11	Eyelid skin darkening		46	Pannus
	12	Hordeolum (Stye)		47	Scar
	13	Ptosis		48	Stromal edema
	14	Retraction (lower lid)		49	Stromal opacity
	15	Trichiasis		50	Superficial punctate keratitis (SPK)
	16	Other (state)		51	Other (state)
	17	Other (state)		52	Other (state)
	18	Other (state)		53	Other (state)
	19	Other (state)		54	Other (state)
	20	Other (state)		55	Other (state)

	Code			Code	
Conjunctiva Grading: 1= mild 2= moderate 3= severe	21	Chemosis	**Anterior Chamber (AC)** Grading: **Cells**: 1: <10 cells 2: 10-30 cells 3: >30 cells **Flare**: 1 = + 2 = ++ 3 = +++ **Other:** 1= mild 2= moderate 3= severe	56	Cells
	22	Conjunctivitis (specify)		57	Flare
	23	Discharge		58	Other (state)
	24	Edema		59	Other (state)
	25	Follicles		60	Other (state)
	26	Nevus		61	Other (state)
	27	Papillae			
	28	Pinguecula			
	29	Pigment			
	30	Pterygium			
	31	Subconjunctival hemorrhage			
	32	Other (state)			
	33	Other (state)			
	34	Other (state)			
	35	Other (state)			

Biomicroscopy cont.

Code			Code		
Iris Grading: 1= mild 2= moderate 3= severe	62	Atrophy	**Lens** Grading: 1= mild 2= moderate 3= severe *NA= grading not applicable	73	Anterior subcapsular cataract
	63	Cysts		74	Aphakia*
	64	Increased pigmentation		75	Combined cortical+ posterior subcapsular cataract
	65	Neovascularization		76	Combined nuclear sclerosis+cortical cataract
	66	Peripheral anterior synechiae			
	67	Posterior synechiae		77	Combined nuclear sclerosis+ posterior subcapsular cataract
	68	Transillumination defect			
	69	Other (state)		78	Combined nuclear sclerosis+cortical cataract+posterior subcapsular cataract
	70	Other (state)			
	71	Other (state)			
	72	Other (state)		79	Cortical cataract
				80	Nuclear sclerosis
				81	Pseudoexfoliation
				82	Pseudophakia*
				83	Posterior subcapsular cataract
				84	Secondary cataract
				85	Vacuoles
				86	Other (state)
				87	Other (state)
				88	Other (state)
				89	Other (state)

Ophthalmoscopy

Code			Code		
Vitreous Grading: 1= mild 2= moderate 3= severe *NA= grading not applicable	90	Degeneration	**Retina** Grading: 1= mild 2= moderate 3= severe	98	Age related macular degeneration (dry,specify)
	91	Posterior Detachment (PVD)*		99	Age related macular degeneration (wet, specify)
	92	Hemorrhage		100	Cystoid macular edema (CME)
	93	Opacity		101	Detachment
	94	Other (state)		102	Diabetic retinopathy (specify)
	95	Other (state)		103	Drusen
	96	Other (state)		104	Hemorrhage
	97	Other (state)		105	Macular edema
				106	Pigment alteration
				107	Schisis
				108	Other (state)
				109	Other (state)
				110	Other (state)
				111	Other (state)
			Optic nerve Grading: 1= mild 2= moderate 3= severe	112	Atrophy
				113	Disc hemorrhage
				114	Drusen
				115	Edema
				116	Glaucomatous cupping (specify)
				117	Ischemia
				118	Other (state)
				119	Other (state)
				120	Other (state)
				121	Other (state)

Comparison of Ophthalmic Medications for Tolerability Questionnaire (COMTol)

Manual

Administration
Scoring
COMTol Questionnaire

Administration of the COMTol

The purpose of this disease-specific questionnaire is to assess the tolerability of ophthalmic medications and their effect on health-related quality of life. The development and validation of the COMTol is described in Barber BL, Strahlman ER, Laibovitz R, Guess HA, Reines SA. "Validation of a questionnaire for comparing the tolerability of ophthalmic medications." Ophthalmology 1997;104:334-342.

Please review these guidelines carefully and adhere to them during the study.

The COMTol is interviewer administered (i.e., the patient completes the questionnaire with the assistance of an interviewer). The interview should take approximately 15 minutes or less to complete. If possible, the patient should complete the questionnaire in a quiet and private setting (in the absence of family or friends).

COMTol Tips and Traps

1. Questions #1 and #2
   a) Asked **only** after the conclusion of a cross-over trial.
   b) Make sure the patient understands what "Period 1" and "Period 2" are and does not confuse "Period 1" with the run-in period.
2. Question #3
   a) Read each side effect slowly enough to make sure the patient comprehends and has time to give a thoughtful response.
   b) Make sure the patient responds "yes" or "no" to **each** side effect.
   c) Make sure you circle the affirmative responses in the spaces provided on **both** Questions #4 and #5.
   d) If the patient experienced **none** of the side effects, check the appropriate box at the end of Question #4 and then skip to Question #7.
3. Questions #4 and #5
   a) There should be one and only one check on each line of Questions #4 and #5, unless the patient experienced **none** of the side effects.
   b) Make sure that the list of side effects circled on these two questions match.
   c) Make sure you check the response on the correct line for the side effect.
4. Question #7
   a) Asked **only** at baseline. This question is used as a benchmark for all visits to determine which activities the patient performs routinely. The activity item(s) to which the patient responded affirmatively should be circled on Card "B" to be used for Questions #8 and #9. (See instruction for Questions #8 and #9)
   b) If a patient stops performing an activity **because of their eyedrops** then this should be reported as an "extreme" activity limitation. If a patient stops performing an activity **for any reason other than their eyedrops** then this should be reported as not being limited at all.
   c) If a patient does not perform any of the activities listed

i) **Note this on the COMTol form** to make sure that it was clear that this item was completed.

ii) Skip to Question #10.

iii) *Please note that this questionnaire has not been validated in a patient population with activity limitations which are that severe.* The Activity Limitations domains and Question #9 would be severely limited by a floor effect if there were a significant number of patients that did not perform any of the activities listed in Question #7 at baseline.

5. Questions # 8 and #9

a) Refer to the Question #7 Card "B" items **from the baseline visit** (i.e., Question 7 should not have been asked at later visits). It is important to compare the activity limitations in Question #8 and #9 throughout the study to this baseline set of activities because it is possible that some medications could have side effects that are so severe that they would stop the patient from performing the activity during one of the study periods. If you don't ask about the activities reported at baseline then you may miss some of the most severe activity limitations.

i) Example: At baseline, the patient reported "driving during the day" and "reading the newspaper" on Question #7. Therefore, for Question #8 you should only ask about the limitations of "driving during the day" and "reading the newspaper" at baseline **and all subsequent visits**. Don't ask about the other activities. Don't record limitations for any activities which weren't reported at baseline.

Required Instructions to Patient

1. Emphasize that we are interested in **the patient's own opinions** about the questions on the questionnaire, not the opinions of his or her doctor, family or friends.
2. Make sure that the patient understands that the questions refer to experiences during the time period specified in the questions.
3. Tell the patient that all answers will remain confidential.
4. Emphasize the importance of collecting this information about their quality of life. The results may help in the development of treatments that improve the quality of life for patients in the future.

General Interviewing Techniques

1. Tasks of the interviewer.

a) Increase the number of patients who agree to participate by explaining the importance of the questionnaire and the importance of getting information from as many patients as possible.

b) Motivate the patient to answer questions thoughtfully.

c) Communicate questions accurately.

d) Record responses accurately.

e) Listen actively to determine what is relevant.

f) For open-ended questions, probe to increase the validity, clarity, and completeness of the response.

g) Before the patient leaves, quickly review the form to make sure that all of the questions have been answered.

h) Thank the patient for their cooperation.

i) Sign and date the form.

2. Maintain a neutral role as interviewer. The interviewer should be a neutral instrument through which questions and answers are transmitted.
   a) Do not express your own opinions.
   b) Avoid "clever" remarks.
   c) Do not give any unnecessary or overly enthusiastic reinforcement.
   d) **Never** suggest an answer.
3. Be careful what information you give to the patient.
   a) Read questions precisely as written. Do not rephrase, interpret, or "explain" the question.
   b) I repeat, read each question **exactly** as written. It is extremely important that everyone be asked the same question in the same way. Changing even one word could change the meaning and thus the response.
   c) If asked, you may explain or define **words**.
   d) Do not interpret the question or the patient's response. Have the patient interpret the question or choose their response. Some phrases you might use are:
      i) "We would like you to answer the question in terms of the way it is stated. Let me read it again for you."
      ii) "Please choose the response that is closest to the way you feel."
      iii) "If you are not sure how to answer the question, please answer to the best of your understanding."
      iv) "Please choose the response that is closest to the way you feel. Then I will write the additional comments that you just mentioned on the questionnaire."
      v) If the patient insists that he or she cannot, or will not, answer a question, tell him or her that it can be left blank (after encouraging him or her to try to answer). If the question is left blank, make a notation of the reason the question wasn't answered and date and initial the remark.
4. Accept only the patient's opinion.
   a) All responses should reflect what the PATIENT thinks--not the patient's children, spouse, parents, nurse, doctor, friends, etc. Therefore, you might need to say, "I see. Now, what is **your** opinion?"
5. Keep all information strictly confidential. We are **extremely** strict about confidentiality. The success of this study depends on our ability to develop and maintain a reputation for keeping strict confidentiality. Remember, word spreads even if other people promise not to repeat the story. This can be damaging to a person's reputation and can be damaging to the success of the study.
   a) Do not tell anyone the names or any identifying information about the patients.
   b) Do not tell anyone about any of the content of an interview, even fascinating or humorous parts.
6. As an interviewer, you should **NEVER**...
   a) Try to give long explanations of the study
   b) Change the order of questions or question wording
   c) Try to justify or defend what you are doing
   d) Suggest an answer or disagree with an answer
   e) Interpret the meaning of a question or an answer

f) Give an example
g) Ask questions from memory
h) Rush the patient
i) Patronize patients
j) Let anyone else answer for the patient
k) Interview someone you know
l) Falsify an interview or an answer
m) Improvise
n) Add response categories
o) Ask a question without providing the response options
p) Leave a question blank (if absolutely necessary, it must be documented why it is blank)
q) Finish an interview without reviewing the form to make sure all questions have been answered
r) Forget to sign and date the form

7. Interview tips.
   a) Show neutral signs of interest. A neutral expression of interest and understanding (e.g., nodding, "uh-huh", "I see") shows that you are listening.
   b) Pause. Silence can show that you are waiting to hear more.
   c) Repeat the question. Repeating the question helps a patient if they have not understood or have gotten off track.
   d) Repeat the reply. This shows that you are listening actively and can allow the patient to recognize a mistake.
   e) Ask a neutral question to clarify or expand.
      i) "I see. So, which of these choices would be closest to the way you feel?"
      ii) "What do you mean exactly by that?"
      iii) "Could you please explain that?"
      iv) "Could you please be more specific about that?"
      v) "Anything else?"
   f) Ask a neutral question to make sure you get the patient's opinion.
      i) "I see. Now, what is **your** opinion about that?"
      ii) "Uh-huh. And how do **you** feel about that?"

Scoring the COMTol

Standardization

As with all scored questionnaires, it is important that the administration and scoring of the COMTol be as standardized as possible across all participants. The administration guidelines and scoring rules presented in this manual are meant to help ensure the reliability and validity of scores reported above and in future studies using the COMTol. The standardization also enables researchers to make meaningful comparisons between study populations.

COMTol Scores

The COMTol Questionnaire consists of eleven questions. The questions are divided into five global assessments (preference, effect of side effects in QoL, effect of activity limitations on QoL, compliance, and satisfaction), five side effects domains (ocular symptoms, taste, vision, accommodation, and browache), and three activity limitations domains (driving, reading, and moderate activities). With all questions, higher scores are worse.

Step 1. Coding the Questions

Question	Original Response Choices	Code	Special Instructions
#1: Medication preference	Period 1 Period 2 Neither	Period 1 Period 2 Neither	Asked only at end of a cross-over trial.
#2: Reason for preference	Free field text	Free field text	Asked only at end of a cross-over trial. If you wish to categorize the responses, the categories should be established *a priori* or prior to unmasking.
#3: Side effects	Circle symptoms from the past two weeks	Not coded	
#4: Frequency of side effects	I did not have the symptom Rarely A few times Fairly often Usually Almost always Always	0 1 2 3 4 5 6	Side effects that the patient did not report on Question #3 are coded as zero. If Question #4 is not completed for an item, then code that item as missing (not as zero).

#5: Bother from side effects	Not at all A little Some Quite a bit Very much so Extremely so	0 1 2 3 4 5	Side effects that the patient did not report on Question #3 are coded as zero. If Question #5 is not completed for an item, then code that item as **missing** (not as zero).
#6: Effect of side effects on quality of life	Not at all A little Some Quite a bit Very much so Extremely so	0 1 2 3 4 5	If the patient reported "None of these symptoms" in Question #4 then Question #6 is coded as zero.
#7: Routine activities	Check activities routinely performed at baseline visit	Not coded	Asked only at baseline.
#8: Activity limitations	Not at all A little Some Quite a bit Very much so Extremely so	0 1 2 3 4 5	Those activities from Question #7 that the patient did not perform at baseline are coded as **not applicable**. If Question #8 is not completed for an item that was reported in Question #7 at baseline, then code that item as **missing** (not as not applicable or zero).
#9: Effect of activity limitations on quality of life	Not at all A little Some Quite a bit Very much so Extremely so	0 1 2 3 4 5	If Question #7 is missing (not done), then code #9 as **missing** (not done). If patient "Performed none of activities" in Question #7, or reported "Not at all" on Question #8 for all the activities reported on Question #7, then code #9 as zero.
#10: Compliance	I did not miss any doses Rarely A few times Fairly often Usually Almost always Always	0 1 2 3 4 5 6	
#11: Patient satisfaction	Totally satisfied Very satisfied Somewhat satisfied Somewhat dissatisfied Very dissatisfied Totally dissatisfied	0 1 2 3 4 5	

Step 2. Calculating Scores for Global Assessments and Domains

Scale	Number of Items	Items in Scale	Scoring Instructions
Medication Preference	1	1	Categorical
Reason for Preference	1	2	
Side Effect Frequency			
Ocular Symptoms (Burning, Redness, Itchy eyes, Discharge, Swelling, Dry eyes, Tearing)	7	4a, 4b, 4f, 4g, 4h, 4l, 4o	Average all items
Taste (Bitter taste, Unusual taste)	2	4d, 4e	Average all items
Vision (Blurred vision, Dimming of vision, Trouble seeing at night)	3	4c, 4j, 4n	Average all items
Accommodation (Difficulty focusing, Trouble reading)	2	4k, 4m	Average all items
Browache	1	4i	Raw score
Side Effect Bother			
Ocular Symptoms (Burning, Redness, Itchy eyes, Discharge, Swelling, Dry eyes, tearing)	7	5a, 5b, 5f, 5g, 5h, 5l, 5o	Average all items
Taste (Bitter taste, Unusual taste)	2	5d, 5e	Average all items
Vision (Blurred vision, Dimming of vision, Trouble seeing at night)	3	5c, 5j, 5n	Average all items
Accommodation (Difficulty focusing, Trouble reading)	2	5k, 5m	Average all items
Browache	1	5i	Raw score
Effect of Side Effects on Quality of Life	1	6	Raw score
Activity Limitations			
Driving (Day driving, Night driving)	Variable (Max=2)	8a, 8b	Average the items reported in Q#7 at baseline*
Reading (Reading newspaper, Reading other)	Variable (Max=2)	8f, 8g	Average the items reported in Q#7 at baseline*
Moderate Activities (Carrying groceries, Climbing stairs, Walking several blocks)	Variable (Max=3)	8c, 8d, 8e	Average the items reported in Q#7 at baseline*
Effect of Activity Limitations on Quality of Life	1	9	Raw score
Compliance	1	10	Raw score
Satisfaction with Medication	1	11	Raw score

*NOTE: The Activity Limitation Domain score at a particular visit will be scored as missing if any of the items reported in Q#7 at baseline are missing at that visit (see example 2.b.iii on next page).

Example of Scoring Question #8

Hypothetical Responses				
Activity	Question 7 at Baseline	Question 8 at Baseline	Question 8 on Day 15	Question 8 on Day 36
Driving during the day	X	Not at all	Not at all	A little
Driving at night		Not at all		
Lifting or carrying groceries	X	Not at all	Some	A little
Climbing 1 flight of stairs	X	Not at all	Quite a bit	Missing
Walking several blocks				Not at all
Reading the newspaper	X	Not at all	Extremely so	Quite a bit
Reading other than the newspaper				
Step 1. Coding				
Driving during the day		0	0	1
Driving at night		Not applicable *	Not applicable	Not applicable
Lifting or carrying groceries		0	2	1
Climbing 1 flight of stairs		0	3	Missing
Walking several blocks		Not applicable	Not applicable	Not applicable *
Reading the newspaper		0	5	3
Reading other than the newspaper		Not applicable	Not applicable	Not applicable
* Coded as "not applicable" since did not report in Q#7 at baseline				
Step 2. Scoring of Activity Limitation Domains				
Driving Domain		0	0	1
Moderate Activities Domain		0	2.5	Missing
Reading Domain		0	5	3

Explanation of Scoring Example

1. Driving Domain: Average of driving items reported at baseline.
   a) "Driving during the day" is only item reported in Question #7 at baseline
   b) Thus, the Driving Domain score will be the average of that single item.
      i) Driving Domain score at baseline = 0/1 = 0
      ii) Driving Domain score at Day 15 = 0/1 = 0
      iii) Driving Domain score at Day 36 = 1/1 = 1
2. Moderate Activities Domain: Average of moderate activity items reported at baseline.
   a) "Lifting groceries" and "Climbing stairs" were reported in Question #7 at baseline
   b) Thus, the Moderate Activities Domain score will be the average of those two items.
      i) Moderate Activities Domain score at baseline = (0+0)/2 = 0
      ii) Moderate Activities Domain score at Day 15 = (2+3)/2 = 2.5
      iii) Moderate Activities Domain score at Day 36 = (1+Missing)/2 = Missing
3. Reading Domain: Average of reading items reported at baseline.
   a) "Reading the newspaper" is the only item reported in Question #7 at baseline
   b) Thus, the Moderate Activities Domain score will be the average of that single item.
      i) Reading Domain score at baseline = 0/1 = 0
      ii) Reading Domain score at Day 15 = 5/1 = 5
      iii) Reading Domain score at Day 36 = 3/1 = 3

Comparison of Ophthalmic Medications For Tolerability (COMTol) Questionnaire

INTERVIEWER: PLEASE READ THE FOLLOWING VERBATIM!

Thank you for participating in our study. Your evaluation of the test eyedrops that you have been taking during the past two weeks *(Interviewer: say "three weeks" at baseline)* is most valuable to us. We would greatly appreciate your assistance by answering the following questions as best as possible. All answers are confidential.

1. *(Interviewer: Questions 1 and 2 are to be asked only at the conclusion of the crossover trial.)*:

   Now that you have tried both test medications during the study, did you prefer the one you received during Period 1 (the first 2 weeks) or the one you received during Period 2 (the second 2 weeks)? *(Interviewer: Please check the appropriate response below)*:

   ___ Eyedrop received during Period 1

   ___ Eyedrop received during Period 2

   ___ Neither *(Interviewer: Do not read to respondent)*

2. Why did you prefer the test medication you received during Period ___?
   (*Interviewer: Read response from Question 1.*)

_____

_____

In this 201450 study questionnaire Question1:
"At the conclusion of the study".
"Now that you have used both Ganfort® (**period 1**) and Taptiqom® (**period 2**), did you prefer the one you received during the first period or the one you received during the second period ?"

3. (*Interviewer: Read the following*): I am going to read to you a list of various side effects that may occur in some patients when using eyedrops. You may have experienced none, some, or all of these side effects during the past 2 weeks. As I read the list, please tell me if you experienced that particular side effect. (*Interviewer: Circle affirmative responses on the list below Question #4. Place a check under the column marked "I did not have the symptom" below Question #4 for those symptoms not experienced by the patient. If patient experienced none of these side effects, please check "None of these symptoms" below and go to Question #7.*)

4. (*Interviewer: Refer to Question #3 and read the following*): I am now going to read to you the side effects you said you experienced in the last question. For each side effect I mention, please tell me how frequently you experienced each side effect during the past 2 weeks. (*Interviewer - hand respondent Card "A" with frequency scales.*) That is, did you experience the side effect rarely, a few times, fairly often, usually, almost always, or always? (*Interviewer: Place check under appropriate column below for each circled side effect mentioned by respondent.*)

	I did not have the Symptom	Rarely	A Few Times	Fairly Often	Usually	Almost Always	Always
__Burning/stinging in eyes	( )	( )	( )	( )	( )	( )	( )
__Redness in eyes	( )	( )	( )	( )	( )	( )	( )
__Blurred vision	( )	( )	( )	( )	( )	( )	( )
__Bitter taste	( )	( )	( )	( )	( )	( )	( )
__Unusual taste	( )	( )	( )	( )	( )	( )	( )
__Itchy eyes	( )	( )	( )	( )	( )	( )	( )
__Discharge from eyes	( )	( )	( )	( )	( )	( )	( )
__Swelling of eyelids	( )	( )	( )	( )	( )	( )	( )
__Browache	( )	( )	( )	( )	( )	( )	( )
__Dimming of vision	( )	( )	( )	( )	( )	( )	( )
__Difficulty in focusing from near to far	( )	( )	( )	( )	( )	( )	( )
__Dry eyes	( )	( )	( )	( )	( )	( )	( )
__Trouble reading	( )	( )	( )	( )	( )	( )	( )
__Trouble seeing at night	( )	( )	( )	( )	( )	( )	( )
__Tearing	( )	( )	( )	( )	( )	( )	( )

__None of these symptoms

5. ***(Interviewer: Refer to Question #4 and read the following):*** I am again going to repeat the side effects you just mentioned. For each side effect I mention, please tell me if you have been bothered by it: not at all, a little, some, quite a bit, very much so, or extremely so? ***(Interviewer: Please check under appropriate columns below.)***

	Not At All	A Little	Some	Quite A Bit	Very Much So	Extremely So
__Burning/stinging in eyes	( )	( )	( )	( )	( )	( )
__Redness in eyes	( )	( )	( )	( )	( )	( )
__Blurred vision	( )	( )	( )	( )	( )	( )
__Bitter taste	( )	( )	( )	( )	( )	( )
__Unusual taste	( )	( )	( )	( )	( )	( )
__Itchy eyes	( )	( )	( )	( )	( )	( )
__Discharge from eyes	( )	( )	( )	( )	( )	( )
__Swelling of eyelids	( )	( )	( )	( )	( )	( )
__Browache	( )	( )	( )	( )	( )	( )
__Dimming of vision	( )	( )	( )	( )	( )	( )
__Difficulty in focusing from near to far	( )	( )	( )	( )	( )	( )
__Dry eyes	( )	( )	( )	( )	( )	( )
__Trouble reading	( )	( )	( )	( )	( )	( )
__Trouble seeing at night	( )	( )	( )	( )	( )	( )
__Tearing	( )	( )	( )	( )	( )	( )

6. During the past two weeks has your quality of life been interfered with by these side effects: not at all, a little, some, quite a bit, very much so, or extremely so?
   _____Not at all
   _____A little
   _____Some
   _____Quite a bit
   _____Very much so
   _____Extremely so

7. *(Interviewer: Ask at baseline only).* I am now going to show you a list of activities you might do during a typical day. You may perform none, some, or all of these activities. For each one on the list, please tell me whether you perform it on a routine basis. *(Interviewer: Hand respondent Card "B" with activities and check each activity below that is mentioned by respondent. Then circle those activities for each patient on Card "B").*

_____Driving during the day
_____Driving at night
_____Lifting or carrying groceries
_____Climbing 1 flight of stairs
_____Walking several blocks
_____Reading the newspaper
_____Reading other than the newspaper

8. *(Interviewer: Refer to Card "B" items for this patient and read the following.)* I am now going to repeat each of the activities you do routinely. For each one, please tell me if you were limited at all in performing each activity in the past two weeks as a result of your using the eyedrops. That is, were you limited: not at all, a little, some, quite a bit, very much so, or extremely so? *(Interviewer: Please check off under appropriate column below.)*

	Not At All	A Little	Some	Quite A Bit	Very Much So	Extremely So
Driving during day	( )	( )	( )	( )	( )	( )
Driving at night	( )	( )	( )	( )	( )	( )
Lifting or carrying groceries	( )	( )	( )	( )	( )	( )
Climbing 1 flight of stairs	( )	( )	( )	( )	( )	( )
Walking several blocks	( )	( )	( )	( )	( )	( )
Reading the newspaper	( )	( )	( )	( )	( )	( )
Reading other than the newspaper	( )	( )	( )	( )	( )	( )

9. During the past two weeks has your quality of life been interfered with by these activity limitations: not at all, a little, some, quite a bit, very much so, or extremely so?

___Not at all
___A little
___Some
___Quite a bit
___Very much so
___Extremely so

10. During the last two weeks, how often did you miss one or more doses of test medication?

___I did not miss any doses

___Rarely

___A few times

___Fairly often

___Usually

___Almost always

___Always

11. Overall, how satisfied, if at all, have you been with the test medication you have been taking? ***(Interviewer: Hand respondent Card "C" with satisfaction scales.):*** Would you say you were totally satisfied, very satisfied, somewhat satisfied, somewhat dissatisfied, very dissatisfied or totally dissatisfied? ***(Interviewer: Record only one response below.)***

_____Totally satisfied

_____Very satisfied

_____Somewhat satisfied

_____Somewhat dissatisfied

_____Very dissatisfied

_____Totally dissatisfied

Interviewer: Thank respondent and terminate interview.

_____ _____

Signature of Interviewer Date

CARD A

I did not have the symptom

Rarely

A Few Times

Fairly Often

Usually

Almost Always

Always

CARD B

Driving during the day

Driving at night

Lifting or carrying groceries

Climbing 1 flight of stairs

Walking several blocks

Reading the newspaper

Reading other than the newspaper

CARD C

Totally satisfied

Very satisfied

Somewhat satisfied

Somewhat dissatisfied

Very dissatisfied

Totally dissatisfied

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Changes in ocular signs and symptoms in patients switching from bimatoprost–timolol to tafluprost–timolol eye drops: an open-label phase IV study

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Changes in ocular signs and symptoms in patients switching from bimatoprost–timolol to tafluprost–timolol eye drops: an open-label phase IV study

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ABSTRACT (300/300 words)

Objectives

Bimatoprost–timolol (bimatoprost 0.03%–timolol 0.5% fixed-dose combination [FDC]) and tafluprost–timolol (tafluprost 0.0015%–timolol 0.5% FDC) eye drops are currently the only topical intraocular pressure (IOP)-reducing therapies available as preservative-free (PF) prostaglandin and timolol FDC. The aim of this study was to investigate changes to ocular signs and symptoms when patients with ocular hypertension (OH) or open-angle glaucoma (OAG) switched from PF or benzalkonium chloride (BAK)-preserved bimatoprost–timolol to PF tafluprost–timolol eye drops.

Design

This was a 12-week, open-label, phase IV study

Setting

Sixteen centres in Finland, German, Italy and the United Kingdom.

Participants

Patients with OH or OAG (IOP on medication ≤21 mmHg), treated with PF or BAK-preserved bimatoprost–timolol for ≥4 weeks before screening, and presenting with conjunctival hyperaemia and ≥1 ocular symptom.

Interventions

Patients were switched to PF tafluprost–timolol once daily in the treated eye(s).

Primary and Secondary outcome measures

The primary endpoints were change from screening to Week 12 in conjunctival hyperaemia and worst ocular symptom. The secondary outcome measures were changes from screening in ocular signs (other than conjunctival hyperaemia) and symptoms at Week 12.

Results

Of 123 enrolled patients, 121 were included in the intention-to-treat dataset of which all were Caucasian and 54.5% were female; 76 patients used BAK-preserved bimatoprost–timolol and 45 used PF drops. Conjunctival hyperaemia and severity of worst ocular symptom following switch to PF tafluprost–timolol significantly reduced from screening to Week 12 in all patients ($p<0.001$). The percentage of patients with ocular signs and symptoms was significantly reduced at Week 12 compared with screening ($p<0.001$). IOP was not affected by the change of treatment.

Conclusions

Switching from BAK-preserved or PF bimatoprost–timolol to tafluprost–timolol reduced both signs and symptoms of ocular surface disease with no clinically relevant effect on IOP.

Trial registration: EudraCT 2014-005273-37

Strengths and limitations of this study

- The study allows for comparison between the effects of PF tafluprost–timolol and both BAK-preserved and PF bimatoprost–timolol formulations
- The study was conducted across 16 centres limiting bias
- As this was not a randomised-controlled trial, there was a potential for selection bias; however, a randomised design would have been unethical as patients would have been required to adhere to medication that caused them notable ocular intolerance
- An open-label design could not be avoided for this study because the packages of BAK-preserved and PF bimatoprost–timolol and PF tafluprost–timolol were not identical
- Regression to the mean should be considered when interpreting the results

INTRODUCTION

Glaucoma is a disorder often associated with elevated intraocular pressure (IOP) which, if left untreated, leads to retinal ganglion cell death, thinning of the retinal nerve fibre layer, optic nerve damage and cupping of the optic disc.[1] In 2013, approximately 64.3 million people were affected by glaucoma, and the number is expected to grow to 111.8 million by 2040.[2]

Medical treatment of ocular hypertension (OH) and open-angle glaucoma (OAG) focuses on the long-term control of IOP.[3, 4] Several categories of IOP-lowering topical drugs are available including prostaglandin analogues (PGA) (generally the first-line treatment), β-adrenergic blockers, carbonic anhydrase inhibitors, α-adrenergic agonists and miotics.[1] The greatest reduction of IOP is obtained with PGAs (25%–35%) followed by non-selective β-blockers (20%–25%), such as timolol; however, when patients fail to achieve IOP targets with monotherapy, fixed-dose combinations (FDCs) should be considered.[5]

There are only two available PGA–timolol preservative-free (PF) FDCs; PF bimatoprost 0.03%–timolol 0.5% (bimatoprost–timolol) and PF tafluprost 0.0015%–timolol 0.5% (tafluprost–timolol).[6] Despite numerous comparative efficacy studies to date, few have compared different PF PGA therapies.[7] While non-selective β-blockers, such as timolol, can cause bradycardia, arrhythmias, and reductions in blood pressure, PGAs lack systemic side effects[1] but may be associated with distinctive ocular adverse events (AEs), such as conjunctival hyperaemia.[6] Preservatives such as benzalkonium chloride (BAK) are toxic to the ocular surface and may aggravate the signs and symptoms of ocular surface disease (OSD).[8] In a recent study, conjunctival hyperaemia occurred at similar rates in BAK-preserved and PF bimatoprost–timolol-treated patients, suggesting that bimatoprost may have caused these AEs rather than the preservative.[9] Additionally, switching from BAK-preserved bimatoprost monotherapy to PF tafluprost monotherapy has been shown to

significantly reduce the severity of conjunctival hyperaemia. [10] The objective of the present study was to evaluate the changes in ocular signs and symptoms in patients diagnosed with OH or OAG who were treated with BAK-preserved (0.005%) or PF bimatoprost–timolol eye drops (bimatoprost 0.03%–timolol 0.5%; Allergan, Irvine, CA, USA) prior to the start of the study and switched to PF tafluprost–timolol eye drops (tafluprost 0.0015%–timolol 0.5%; Santen Pharmaceutical Co., Ltd, Osaka, Japan).

MATERIALS AND METHODS

Study design

This was an open-label, phase IV clinical study (EudraCT registration number: 2014-005273-37) conducted at 16 centres in Finland, Germany, Italy and the United Kingdom (UK) from June 2015 through to May 2016. The study was reviewed and approved by the appropriate Independent Ethics Committees in the participating countries and conducted in accordance with the Good Clinical Practice guidelines of the International Council on Harmonisation and the ethical principles of the Declaration of Helsinki.

Patient population

Patients included in this study were aged ≥18 years, diagnosed with OH or OAG, inclusive of both primary OAG and pseudoexfoliation glaucoma, and treated with bimatoprost–timolol in the evening (BAK-preserved or PF single-dose formulation) in one or both eyes for ≥4 weeks before screening. Patients presented at screening with conjunctival redness/hyperaemia of at least moderate severity (grade ≥2) in at least one treated eye and ≥one ocular symptom of at least mild severity (grade ≥2) in either eye. Exclusion criteria included: use of more than two active medicinal agents to treat OH or OAG in the 6 months prior to screening; anterior chamber angle grade <2 (Shaffer classification) in either treated eye; and any corneal abnormality or other condition preventing applanation tonometry, including prior refractive

eye surgery and IOP >21 mmHg in the treated eye(s) at screening. A full list of inclusion and exclusion criteria is presented in supplementary table S1.

Treatments and assessments

Eligible patients had used BAK-preserved or PF bimatoprost–timolol (bimatoprost 0.03%–timolol 0.5%) eye drops in the evening for ≥4 weeks prior to screening. Study treatment kits, containing PF tafluprost–timolol eye drops (tafluprost 0.0015%–timolol 0.5%) in unit-dose containers, were dispensed to patients at the screening visit. Patients were not blinded to treatment because an open-label design could not be avoided owing to differences in packaging between BAK-preserved and PF bimatoprost–timolol and PF tafluprost–timolol. Each patient instilled one drop of tafluprost–timolol once daily at 21:00 (±1 hour) in the affected eye(s) for 12 weeks. Drug accountability documentation and dosing data from case report forms were used to assess treatment compliance. Patients were assessed at screening, and at 2, 6 and 12 weeks post screening. After Week 12, a post-study visit was scheduled, and the investigator was free to prescribe any IOP-lowering medication.

Ocular signs and symptoms

Ocular signs and symptoms were assessed at every visit and were defined by the criteria described in supplementary table S2. Ocular symptoms were evaluated per patient and treated eyes were considered together. Ocular signs were analysed in the worst eye designated for each sign at screening. The co-primary endpoints were changes from screening in conjunctival hyperaemia and worst ocular symptom at Week 12. The severity of conjunctival hyperaemia was assessed from screening through to Week 12. Use of the Ora Calibra™ Redness Scale #6.0 (0–4 scale) was made under licence from Ora, Inc. Patients indicated their perceived worst ocular symptom at screening.

Secondary endpoints were changes from screening in ocular signs and symptoms, other than conjunctival hyperaemia, at Week 12. The patient was asked about each symptom by a

leading question, with symptoms graded 0 (none), 1 (trace), 2 (mild), 3 (moderate) or 4 (severe). A total symptom score (0–20) was calculated. Fluorescein tear break-up time was assessed by examination of tear film under a slit lamp following instillation of 2 µL of non-preserved 2% sodium fluorescein dye to the eyes. The time taken (in seconds) to form micelles or for dry spots to develop was recorded as the break-up time. Corneal and conjunctival fluorescein staining were also evaluated. Using reference pictures (Oxford Grading scale) the corneal fluorescein staining and nasal and temporal conjunctival fluorescein stainings were scored from 0 to V each. The presence of blepharitis was also evaluated, and the severity was graded 0 (none), 1 (mild), 2 (moderate) or 3 (severe). Tear production was assessed using the Schirmer-I test for 5 minutes without anaesthesia.

AEs

Treatment-emergent ocular and non-ocular AEs were reported at each post-screening visit. The information obtained included event term, report source, the seriousness of the event, onset and resolution date, frequency, severity, relation to study drop instillation, location (left/right eye, both or not applicable), study drug treatment action, and the investigator's causality assessment of the study treatment and outcome. All AEs were coded using the latest Medical Dictionary for Regulatory Activities.

Ocular safety and quality of life

At each visit, IOP was measured in both eyes using Goldmann applanation tonometry; the right eye was measured first. Two consecutive measurements were taken to determine the mean IOP. If the initial two measurements differed by ≥3 mmHg, then a third measurement was taken and the median IOP was determined. Other measures of ocular safety and quality of life (QOL) are described in the supplementary information.

Sample size

A mean change of 0.37 units (SD 1.12) from screening in conjunctival redness/

hyperaemia was assumed from the previous tafluprost switch studies [11]. Using these estimates, it was determined using a paired t-test that 100 patients would be required for a power of 90% for conjunctival hyperaemia and >99% for worst ocular symptom. [11,12]. The calculations were done using the nQuery Advisor (version 6.0). The paired t-test was initially used to calculate sample size. However, the Wilcoxon signed rank test was found to perform better for heavy-tailed distributions and was thus used for the primary analysis..

Statistical methods

The intention-to-treat (ITT) dataset included all enrolled patients who received at least one dose of tafluprost–timolol and had at least one post-screening primary outcome measurement available. The safety set included all enrolled patients who had at least one dose of study treatment and had a subsequent safety measurement. The primary outcome measures for ocular signs and symptoms were assessed using the Wilcoxon signed rank test. No imputations for missing data were carried out. However, sensitivity analyses using the last observation carried forward imputation were carried out for the primary outcome measures. The analyses of secondary outcome and IOP measures were completed using standard statistical methods for paired data (e.g. McNemar's test for binary data, Wilcoxon signed rank test for ordinal data and the paired t-test for continuous data). For AEs, both patient and event counts were calculated, and events leading to discontinuations were summarised. Best corrected visual acuity, biomicroscopy, ophthalmoscopy, visual field test, drop discomfort and Comparison of Ophthalmic Medications for Tolerability (COMTol) are ocular safety and QOL outcomes, which were analysed descriptively.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of this study. There are no plans to involve patients in the dissemination of results as the open-label nature of the study meant that patients were aware of which medication they received.

RESULTS

Patient demographics and baseline characteristics

A total of 126 patients were screened. Of the 123 patients enrolled, two had no post-screening data and were excluded; therefore, 121 (98.4%) patients were included in the ITT analysis, of which 114 (94.2%) patients completed the study (BAK-preserved, n=71; PF, n=43) (figure 1). The safety set comprised of 123 patients. The mean (range) age was 66 (36–86) years, and more than half of the patients were female (54.5%) (table 1). Of the patients, ~70% in both BAK-preserved and PF subgroups had used bimatoprost–timolol for at least 6 months; 76 patients had used BAK-preserved (62.8%) and 45 had used PF (37.2%) bimatoprost–timolol. Approximately 20% of patients were diagnosed with OH and 75% with OAG. Most patients (91.7%) required treatment in both eyes.

Table 1 Demographics and baseline characteristics of enrolled patients

Variable	Bimatoprost–timolol		Total (n=121)
	BAK-preserved (n=76)	PF (n=45)	
Mean age, years	66.14	67.02	66.47
SD	10.17	10.71	10.34
Sex, n (%)			
Male	34 (44.7)	21 (46.7)	55 (45.5)
Female	42 (55.3)	24 (53.3)	66 (54.5)
Race, n (%)			
Caucasian	76 (100)	45 (100)	121 (100)
Hyperaemia, n (%)	76 (100)	45 (100)	121 (100)
Hyperaemia grade, mean Ora calibra™ redness scale (SD)	2.24 (0.43)	2.30 (0.48)	2.26 (0.45)
Severity of worst ocular symptom, n (%)			
Mild	30 (39.5)	17 (37.8)	47 (38.8)
Moderate	39 (51.3)	23 (51.1)	62 (51.2)
Severe	7 (9.2)	5 (11.1)	12 (9.9)
Abnormal ocular signs, n (%)			
Fluorescein tear break-up time	52 (68.4)	32 (71.1)	84 (69.4)
Corneal fluorescein staining	63 (82.9)	42 (93.3)	105 (86.8)
Conjunctival fluorescein staining	55 (72.4)	36 (80.0)	91 (75.2)
Blepharitis	32 (42.1)	22 (48.9)	54 (44.6)
Tear secretion/Schirmer test	47 (61.8)	29 (64.4)	76 (62.8)

Abnormal ocular symptoms, n (%)			
Irritation/burning/stinging	55 (72.4)	32 (71.1)	87 (71.9)
Foreign body sensation	41 (53.9)	19 (42.2)	60 (49.6)
Tearing	31 (40.8)	25 (55.6)	56 (46.3)
Itching	36 (47.4)	26 (57.8)	62 (51.2)
Dry eye sensation	49 (64.5)	28 (62.2)	77 (63.6)

Please refer to supplementary table S2 for criteria of abnormal signs and symptoms.

BAK, benzalkonium chloride; PF, preservative-free; SD, standard deviation.

Changes to signs and symptoms

A significant improvement was observed in the severity of both conjunctival hyperaemia and worst ocular symptom compared with screening after switching from bimatoprost–timolol to tafluprost–timolol ($p<0.001$ at Weeks 2, 6 and 12). The mean ± standard deviation grade of conjunctival hyperaemia for all patients decreased from 2.26±0.45 at screening to 0.94±0.64 at Week 12 (a mean reduction of 58.5%) (figure 2A). The percentage of patients with conjunctival hyperaemia significantly reduced from 76 (100%) and 45 (100%) patients at screening in BAK-preserved and PF bimatoprost–timolol groups, respectively, to 47 (66.2%) and 31 (72.1%) at Week 12 (figure 2B). All patients identified a worst ocular symptom at screening, which was at least mild in severity; the number of patients with the identified symptom was reduced to 47 (41.2%) at Week 12. The number of patients with moderate and severe worst ocular symptom decreased from 62 (51.2%) and 12 (9.9%) at screening, to 11 (9.6%) and one (0.9%) at Week 12, respectively (figure 2C). In the BAK-preserved and PF bimatoprost–timolol subgroups, the number of patients with moderate and severe worst ocular symptom decreased from 46 (60.5%) to five (7.0%) patients and from 28 (62.2%) to seven (16.3%) patients, respectively (figure 2D).

The frequencies of abnormal ocular signs and symptoms were significantly reduced at Week 12 after switching from bimatoprost–timolol to tafluprost–timolol ($p<0.012$ for signs and

p<0.001 for symptoms) (figures 3A, B, C and D). For ocular signs, the greatest relative reductions from screening were observed in tear secretion (screening, 62.8%; Week 12, 37.7%) and blepharitis (screening, 44.6%; Week 12, 27.2%). For ocular symptoms, all relative reductions were over 50%, and the greatest were observed in foreign body sensation (screening, 49.6%; Week 12, 20.2%) and itching (screening 51.2%; Week 12, 21.9%).

AEs

Overall, 70 treatment-emergent AEs based on the safety dataset (n=123) were reported by 41 (33.3%) patients during the study, of which 15 events in 12 (9.8%) patients were ocular and 55 events in 34 (27.6%) patients were non-ocular (table 2). Only 12 AEs in ten (8.1%) patients were classified as being related to tafluprost–timolol. Two patients had serious AEs: worsening of arterial branch occlusion (resolved after 4 weeks) and paroxysmal atrial flutter with high-grade atrioventricular block (resolved in 2 days); both of which were adjudicated by the investigator and sponsor to be unrelated to tafluprost–timolol treatment. A total of five patients discontinued the study because of AEs, which were: two cases of moderate increase in IOP; moderate pruritus and eye pruritus, a moderate urticaria; and a severe increase in lacrimation. There were no deaths during the study.

Table 2 The occurrence of related and unrelated ocular and non-ocular AEs in patients (n=123) after switching from bimatoprost–timolol to tafluprost–timolol

MedDRA preferred term	Mild/moderate	Severe
Related ocular AEs		
Lacrimation increased	0	1
IOP increased	3	0
Eye pruritus	1	0
Pruritus	1	0
Eyelid irritation	1	0
Related non-ocular AEs		
Urticaria	1	0
Abdominal pain upper	1	0
Dysgeusia	1	0
Headache	1	0
Somnolence	1	0
Unrelated ocular AEs in ≥2 patients		
Ocular hyperaemia	1	1
Unrelated non-ocular AEs in ≥2 patients		
Headache	10	0
Nasopharyngitis	4	0
Pyrexia	3	0
Rhinitis	3	0
Cough	3	0
Arthralgia	2	0
Back pain	2	0

AE, adverse event; IOP, intraocular pressure; MedDRA, Medical Dictionary for Regulatory Activities.

Ocular safety and QOL

At screening, IOP was well controlled with bimatoprost–timolol treatment (n=123; mean IOP 15.9±2.1 mmHg); this was sustained at Week 12 (n=114; mean IOP 16.3±2.3 mmHg) and was clinically insignificant and statistically non-inferior compared with screening (0.34 mmHg; 95% upper limit 0.86 mmHg; P=0.134). IOP was maintained at ≤21 mmHg for >97% of patients and ≤18 mmHg for >80% of patients. Other results for ocular safety and QOL are described in the supplementary information (table S3).

DISCUSSION

Medical treatment of glaucoma aims to maintain patients' visual function and QOL; however, nearly all patients with glaucoma will require a combined therapy to attain a greater than 30% 24-hour IOP reduction.[13, 14] Currently there are only two PF prostaglandin–timolol formulations available: PF bimatoprost–timolol and tafluprost–timolol. In this study, the effects of switching from bimatoprost–timolol to tafluprost–timolol on signs and symptoms of OSD and the effect of these changes in QOL were evaluated.

The study met both co-primary endpoints showing significant improvements in conjunctival hyperaemia and worst ocular symptom from screening to Week 12. No statistical evidence of heterogeneity in the occurrence of ocular signs and symptoms was found between prior BAK-preserved and PF bimatoprost–timolol. This study has shown that patients receiving bimatoprost–timolol who present with signs and symptoms of OSD benefit from switching to tafluprost–timolol. Control of IOP was maintained, and there were no reports of unexpected AEs related to tafluprost–timolol or significant findings in ocular safety during the study. In this study, both the preserved and PF groups experienced a reduction in overall signs and symptoms. These results agree with a previous study, which found that the severity of both conjunctival hyperaemia and punctuate keratitis was significantly higher with bimatoprost than tafluprost ($p<0.02$ and $p<0.04$ respectively) [10]. Additionally, these results agree with a previous double-blind phase III study where no significant differences in safety and

tolerability between BAK-preserved and PF bimatoprost–timolol were observed except for more frequent skin pigmentation with PF bimatoprost–timolol.[9] The observed ocular surface abnormalities and improved tolerability may thus be related to the prostamide-mimetic properties of bimatoprost as opposed to the preservative component of the bimatoprost–timolol formulation. However, there are studies that suggest that BAK may have a significant role in causing tolerability issues with PGA monotherapy despite once-daily dosing. A recent meta-analysis of two Phase 3 studies including 339 patients who had switched from BAK-preserved latanoprost to PF tafluprost resulted in significant reductions in ocular signs and symptoms.[11] Timolol treatment has been shown to induce only minimal hyperaemia or irritation in the eye.[6] In this study, the percentage of symptom-free patients increased by Week 12 concomitantly with improved ocular tolerability as reported in the COMTol questionnaire after switching from bimatoprost–timolol to tafluprost–timolol. This agrees with a previous study that found an association between advanced OSD and poorer glaucoma-related QOL than in patients without OSD.[15] The aforementioned study also reported that OSD was associated with higher daily doses of BAK.

This study had several limitations. This was not a randomised controlled trial, and there was a potential for selection bias; however, a parallel-group (randomised) design with bimatoprost–timolol was considered unethical, because the patients would have continued using medication that caused them notable ocular intolerance. An open-label design could not be avoided for this study because the packages of BAK-preserved and PF bimatoprost–timolol and PF tafluprost–timolol were not identical. IOP readings were unmasked and may also have been subject to bias. ‘Regression toward the mean’ is the observation that if a variable is extreme on the first measurement, it will tend to be closer to the average on its second measurement. This may have introduced reduction in some ocular signs and should also be considered in the interpretation of these results. Compliance is likely to be higher in a study setting, and so these results may not be reflective of a real-world setting. Treatment persistence could not be investigated thoroughly because PF tafluprost–timolol was only

commercially available for 26 patients in two of the participating countries (UK and Finland) at the time of the study.

In conclusion, switching from bimatoprost–timolol to tafluprost–timolol yielded clinical benefits in the presence of signs and symptoms of OSD in patients with OH and OAG over 12 weeks. Tafluprost–timolol provides a potential alternative treatment option for patients with OH or OAG.

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Author Contributions

RRAB, KK, KL and CET contributed to the conduction of the study. JV contributed to the study design, statistical analyses and regulatory writing of the study. AR contributed to the study design, direction and monitoring. All authors contributed towards the writing of this publication.

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Competing interests

RRAB has received travel expenses from Santen. KK has received a Consultant fee from Santen for an advisory board. KL has no conflicts of interest to report. CET has received department funding for the conduction of this study, personal fees, and non-financial support from Santen not related to this study or manuscript, and department funding from Novartis

and Allergan. JV has received fees for statistical services from Santen. AR is an employee at Santen Oy.

Patient consent

Each patient received verbal and written communication regarding the objectives and procedures and the possible risks involved prior to inclusion in the study. The investigator obtained written informed consent prior to any study procedures being undertaken.

Data sharing statement

Data are available. Please contact corresponding author at rb@rupertbourne.co.uk.

Ethics approval

The study protocol was reviewed and approved by Independent Ethics Committees and national competent authorities in each participating country. The study adhered to the International Council on Harmonisation Good Clinical Practice guidelines and provisions of the Declaration of Helsinki.

Provenance and peer review

Not commissioned; externally peer reviewed.

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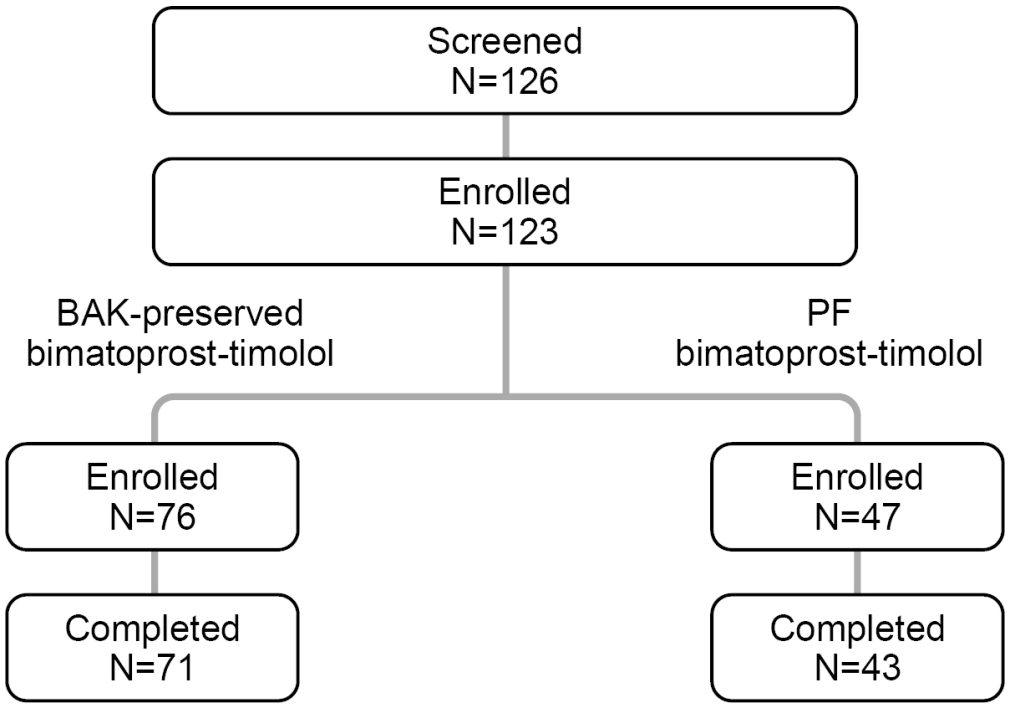
Figure 1 Patient disposition by previous bimatoprost–timolol treatment. After initial screening, three patients did not meet the inclusion criteria. A total of nine (7.4%) patients discontinued the study; five discontinued because of AEs and four withdrew from the study. BAK, benzalkonium chloride; PF, preservative-free.

Figure 2 Comparison of Week 12 outcomes with screening in conjunctival hyperaemia and worst ocular symptom after switching from bimatoprost–timolol to tafluprost–timolol (A) change in conjunctival hyperaemia from screening (n=121) to Week 12 (n=114); (B) breakdown of changes in conjunctival hyperaemia severity by subgroup at Week 12 compared with screening. One patient in the ITT dataset violated inclusion criterion 2 and only had mild conjunctival hyperaemia at screening; (C) severity of worst ocular symptom at screening and Week 12 in all patients; and (D) changes in severity of worst ocular symptom by subgroup at Week 12 compared with screening. BAK, benzalkonium chloride; ITT, intention-to-treat; PF, preservative-free.

Figure 3 Secondary endpoints (A) abnormal ocular signs at screening (n=121); (B) abnormal ocular signs at Week 12 (n=114); (C) abnormal ocular symptoms at screening; (D) abnormal ocular symptoms at Week 12. BAK, benzalkonium chloride; PF, preservative-free.



Patient disposition by previous bimatoprost–timolol treatment. After initial screening, three patients did not meet the inclusion criteria. A total of nine (7.4%) patients discontinued the study; five discontinued because of AEs and four withdrew from the study. BAK, benzalkonium chloride; PF, preservative-free.

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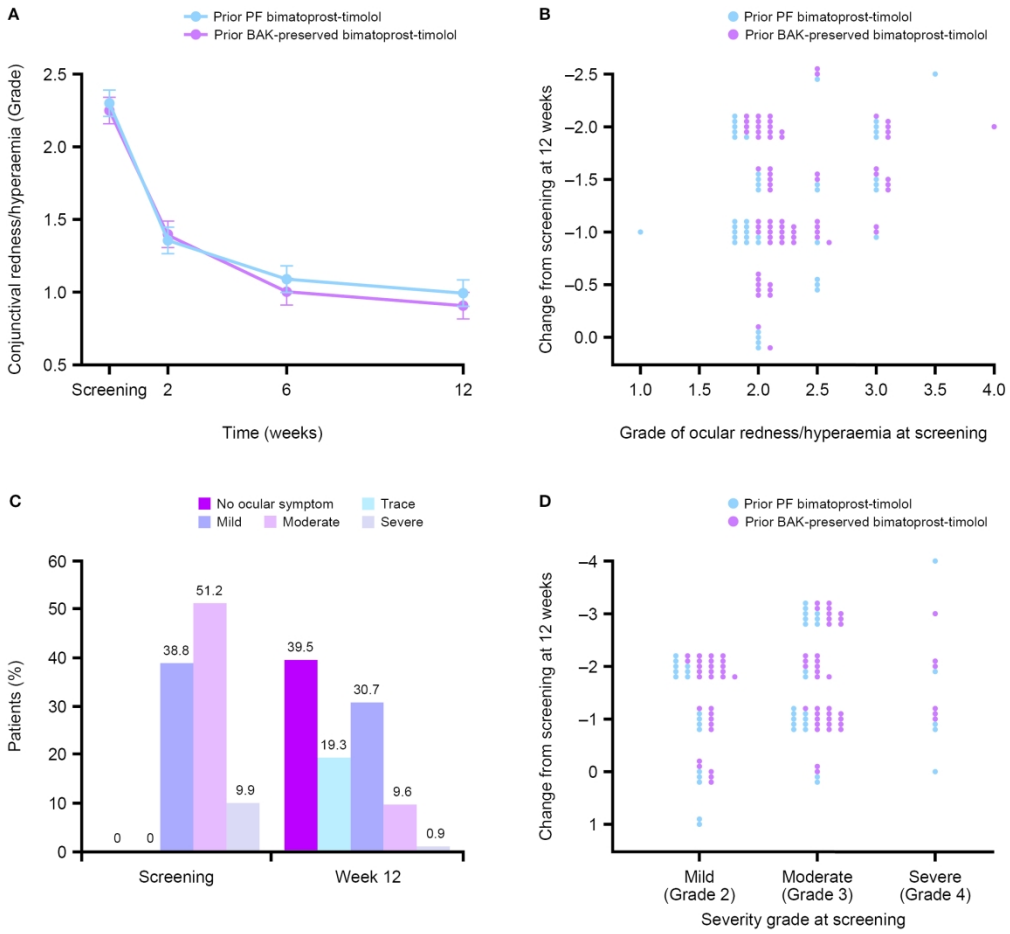

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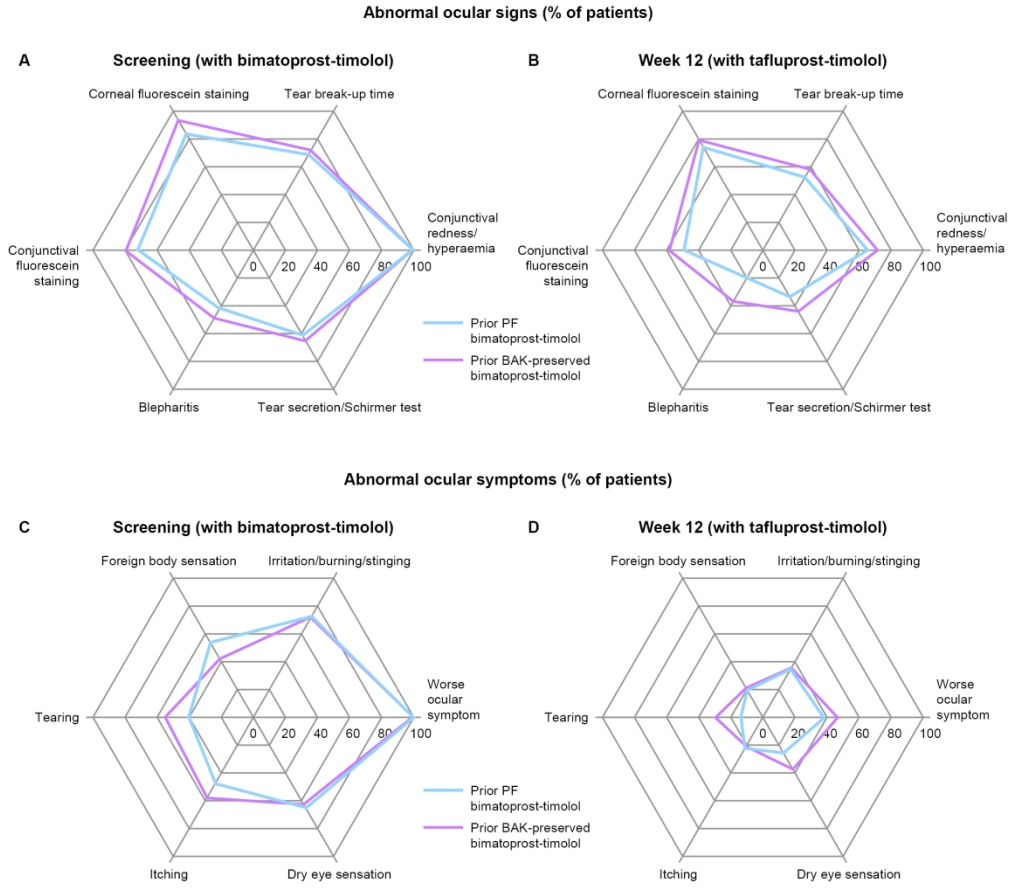

Secondary endpoints (A) abnormal ocular signs at screening (n=121); (B) abnormal ocular signs at Week 12 (n=114); (C) abnormal ocular symptoms at screening; (D) abnormal ocular symptoms at Week 12. BAK, benzalkonium chloride; PF, preservative-free.

230x202mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

Contents

METHODS

Inclusion and exclusion criteria

The full inclusion and exclusion criteria are summarised in table S1.

Supplementary table S1 Inclusion and exclusion criteria

Inclusion	Exclusion
OH or OAG diagnosis (IOP ≤21 mmHg on medication)	≥2 OH or OAG treatments or ocular surgery within 6 months prior to screening
Prior treatment with preserved or PF bimatoprost–timolol FDC eye drops for ≥4 weeks before screening and grade ≥2 (moderate) conjunctival hyperaemia in one treated eye	Grade <2 anterior chamber angle, angle closure glaucoma or secondary glaucoma other than PEX
≥1 grade 2 (mild) ocular symptom	Use of other preserved drops within 2 weeks prior to screening
Best corrected ETDRS visual acuity score of +0.6 logMAR or better in both eyes	Corneal abnormality or prior refractive surgery
Aged 18 years or over	Females who are pregnant, nursing or planning a pregnancy, or females of childbearing potential who are not using a reliable method of contraception
Provided written informed consent	Anterior chamber angle in either eye to be treated less than grade 2 according to Schaffer classification as measured by gonioscopy
	IOP greater than 21 mmHg in treated eye(s) at screening
	Use of preserved eye drops (other than bimatoprost–timolol) including artificial tears at screening or within 2 weeks prior to screening visit

ETDRS, early treatment diabetic retinopathy study; FDC, fixed-dose combination; IOP, intraocular pressure; logMAR, Logarithm of the Minimum Angle of Resolution; OAG, open-angle glaucoma; OH, ocular hypertension; PEX, pseudoexfoliation**;** PF, preservative-free.

Assessment of abnormal ocular signs and symptoms

Abnormal signs and symptoms were defined by the criteria shown in table S2.

Supplementary table S2 Grading criteria of abnormal ocular signs and symptoms investigated in this study

Ocular sign	Units/grades	Abnormal
Fluorescein tear break-up time	Seconds*	<10 seconds
Corneal fluorescein staining	0–V†	≥I
Conjunctival fluorescein staining	0–X‡	≥II
Blepharitis	0–3§	≥1
Conjunctival hyperaemia	0–4¶	≥1
Tear production	mm‖	≤10 mm
Ocular symptom	**Grades**	**Abnormal**
Irritation/burning/stinging	0–4**	≥2
Foreign body sensation	0–4**	≥2
Tearing	0–4**	≥2
Itching	0–4**	≥2
Dry eye sensation	0–4**	≥2

Treated eyes were considered together for ocular symptoms whereas ocular signs were evaluated by eye; the eye with the worse grade at screening was analysed.

*Slit-lamp microscope. †Oxford grading scale (0–V). ‡Combined nasal (0–V) and temporal (0–V) score by Oxford grading scale. §0=none, 1=mild, 2=moderate and 3=severe. ¶Ocular redness scale; used under license from Ora, Inc., Andover, MA, USA; 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe; half grades were allowed. ‖Schirmer's test; **0=none, 1=trace, 2=mild, 3=moderate and 4=severe.

Ocular safety and quality of life

Best corrected visual acuity was measured at each visit using an Early Treatment Diabetic Retinopathy Study chart, and the Logarithm of the Minimum Angle of Resolution (logMAR) scores were calculated. The base logMAR value is the value of the last line in which a letter was read correctly (>0.2 logMAR score was considered abnormal). A biomicroscopic assessment of the lids, conjunctiva, cornea, anterior chamber and iris was performed at all visits. Evaluations were graded as mild, moderate, severe or not applicable. The biomicroscopic assessment of the lens was performed at screening, Week 12 and post study. Ophthalmoscopy examinations of the vitreous, retina and the optic nerve with the pupil dilated were performed at screening and Week 12. The findings were graded for severity as 1 (mild), 2 (moderate) and 3 (severe). This was repeated at the post-study visit for treatment-related abnormalities at Week 12. Visual field testing was performed using the Humphrey 24-2/30-2 (full threshold or Swedish interactive threshold algorithm standard) or Octopus G2 program (normal or dynamic strategy) with one test used consistently in each patient. Visual field testing was assessed for changes between screening and the post-study visit and was graded for severity as 1 (mild), 2 (moderate) and 3 (severe). Drop discomfort was assessed using a four-point scale as 1 (mild), 2 (moderate) and 3 (severe). Quality of life (QOL) was evaluated using the Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire[1] at all visits up to Week 12. The questionnaire consisted of 11 questions, which scored discomfort from 0 to 5–6, and was divided into five side-effect domains (ocular symptoms, taste, vision, accommodation and brow ache), three activity-limitation domains (driving, reading and moderate activities) and five global assessments (preference, effect of side effects on QOL, effect of activity limitations on QOL, compliance and satisfaction).

RESULTS

Ocular safety and QOL

At Week 12, there were no clinically relevant changes in visual acuity (deterioration by 0.2 LogMAR) attributable to tafluprost–timolol treatment and no severe biomicroscopy or ophthalmoscopy—including visual field—findings. The number of patients that did not report drop discomfort increased from 28 (22.8%) patients at screening (n=123) to 61 (53.5%) at Week 12 (n=114). Worsening of drop discomfort at Week 12 was observed in 6 (5.3%) patients and improvement was observed in 65 (57.0%) patients (p<0.001).

By Week 12, the COMTol questionnaire indicated that more patients were symptom-free for common ocular side effects and activity limitations compared with screening (supplementary table S3). Overall, 62.0% of the patients whose QOL was affected by the side effects that were prevalent at screening (n=123) reported improved QOL at Week 12 (n=114) because of alleviated side effects. Accordingly, 66.7% of patients reported improved QOL owing to decreased activity limitations. Approximately 66% of patients in the prior benzalkonium chloride (BAK) bimatoprost–timolol and 51% of patients in the prior preservative-free (PF) bimatoprost–timolol group preferred tafluprost–timolol. Only 12% and 13% preferred BAK and PF bimatoprost–timolol, respectively. The remaining patients had no preference. Satisfaction with medication increased after switching from bimatoprost–timolol to tafluprost–timolol. The number of patients who were totally or very satisfied increased from 41 (33.3%) at screening to 84 (73.7%) at Week 12. Fewer patients in the BAK bimatoprost–timolol group were totally or very satisfied with medication than in the PF bimatoprost–timolol group at screening (25.0% and 46.8%, respectively). By Week 12, satisfaction in both groups had improved substantially compared with screening (77.5% and 67.4%, respectively). Compliance during the final 2 weeks of the study improved after switching from bimatoprost–timolol to tafluprost–timolol. The number of patients who claimed not to miss a dose increased from 89.4% at screening to 94.7% at Week 12.

Supplementary table S3 The percentage of patients without symptoms or limitations after switching from bimatoprost–timolol to tafluprost–timolol

Symptom-free patients, n (%)	Screening			Week 12		
	BAK-preserved	PF	Total	BAK-preserved	PF	Total
Burning/stinging	14 (18.4)	10 (21.3)	24 (19.5)	33 (46.5)	23 (53.5)	56 (49.1)
Redness	8 (10.5)	8 (17.0)	16 (13.0)	32 (45.1)	19 (44.2)	51 (44.7)
Itchy eyes	31 (40.8)	14 (29.8)	45 (36.6)	37 (52.1)	20 (46.5)	57 (50.0)
Discharge from eyes	45 (59.2)	31 (66.0)	76 (61.8)	62 (87.3)	34 (79.1)	96 (84.2)
Swelling of eyelids	57 (75.0)	38 (80.9)	95 (77.2)	62 (87.3)	42 (97.7)	104 (91.2)
Dry eyes	21 (27.6)	15 (31.9%)	36 (29.3)	37 (52.1)	18 (41.9)	55 (48.2)
Tearing	34 (44.7)	21 (44.7)	55 (44.7)	47 (66.2)	27 (62.8)	74 (64.9)
Bitter taste	62 (81.6)	43 (91.5)	105 (85.4)	68 (95.8)	40 (93.0)	108 (94.7)
Unusual taste	70 (92.1)	43 (91.5)	113 (91.9)	69 (97.2)	42 (97.7)	111 (97.4)
Blurred vision	34 (44.7)	27 (57.4)	61 (49.6)	52 (73.2)	32 (74.4)	84 (73.7)
Dimming of vision	62 (81.6)	39 (83.0)	101 (82.1)	65 (91.5)	40 (93.0)	105 (92.1)
Trouble seeing at night	48 (63.2)	33 (70.2)	81 (65.9)	62 (87.3)	39 (90.7)	101 (88.6)
Difficulty in focusing	49 (64.5)	32 (68.1)	81 (65.9)	59 (83.1)	36 (83.7)	95 (83.3)

Trouble in reading	51 (67.1)	31 (66.0)	82 (66.7)	59 (83.1)	36 (83.7)	95 (83.3)
Brow ache	68 (89.5)	44 (93.6)	112 (91.1)	68 (95.8)	41 (95.3)	109 (95.6)
Limitation-free patients						
Day driving	42 (79.2)	23 (63.9)	65 (73.0)	43 (87.8)	30 (93.8)	73 (90.1)
Night driving	30 (71.4)	16 (64.0)	46 (68.7)	36 (90.0)	22 (95.7)	58 (92.1)
Reading newspaper	55 (74.3)	34 (73.9)	89 (74.2)	64 (92.8)	41 (95.3)	105 (93.8)
Reading other	55 (75.3)	32 (74.4)	87 (75.0)	64 (92.8)	38 (7.4)	102 (94.4)
Carrying groceries	72 (97.3)	37 (84.1)	109 (92.4)	69 (100.0)	41 (97.6)	110 (99.1)
Climbing stairs	72 (96.0)	36 (80.0)	108 (90.0)	71 (100.0)	41 (100.0)	112 (100.0)
Walking blocks	66 (91.7)	37 (84.1)	103 (88.8)	67 (98.5)	41 (100.0)	108 (99.1)

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