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Low-concentration bimatoprost 0.01% and timolol 0.1% eye gel versus bimatoprost 0.03% and timolol 0.5% eye drops in open-angle glaucoma or ocular hypertension: a phase III randomised study

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ABSTRACT

Background/Aims To compare the efficacy and safety of a new preservative-free bimatoprost 0.01%/timolol 0.1% fixed combination (BTFC) eye gel with those of bimatoprost 0.03%/timolol 0.5% fixed combination ophthalmic solution (BTFC eye drops) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Methods In this phase III, international, multi-centre, randomised, parallel group, investigator-masked study, patients receiving a first-line monotherapy, having insufficiently controlled intraocular pressure (IOP) and requiring dual therapy were randomised to receive either BTFC eye gel or BTFC eye drops once daily for 12 weeks. The primary efficacy endpoint was the change in IOP from baseline to week 12 at 08:00 in the assessed eye. Further efficacy and safety endpoints were assessed as secondary outcomes.

Results The mean±SD change in IOP from baseline to week 12 at 08:00 was −10.96±3.43 mmHg for the BTFC eye gel group and −11.14±3.56 mmHg for the BTFC eye drop group. The least-squares mean difference (BTFC eye gel minus BTFC eye drops) was −0.04±0.24 mmHg (95% CI −0.51 to 0.43 mmHg), with the upper bound of the 95% CI lower than the predefined margin of +1.5 mmHg at week 12 at 08:00. Similar IOP-lowering efficacy was demonstrated at all other timepoints. The safety profile was comparable between the treatment groups. No patients in the BTFC eye gel group discontinued the study due to a treatment-related adverse event compared with 8 (2.9%) patients in the BTFC eye drop group.

Conclusion Low-concentration BTFC eye gel can be considered as a safe and effective treatment in the therapeutic management of glaucoma and OHT.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bimatoprost/timolol fixed combination (BTFC) may maximise intraocular pressure (IOP)-lowering in patients with glaucoma; however, both compounds may have ocular and systemic side effects. Therefore, the concentration of these active ingredients should be reduced.

WHAT THIS STUDY ADDS

⇒ Despite reducing the active substance concentration, bimatoprost 0.01%/timolol 0.1% eye gel showed similar efficacy and safety to bimatoprost 0.03%/timolol 0.5% eye drops.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Low-concentration BTFC eye gel lowers the IOP of patients with glaucoma, with a potential improved ocular tolerance over a longer treatment duration.

INTRODUCTION

A high intraocular pressure (IOP) is a crucial determinant of the onset and progression of glaucoma and is currently the only modifiable risk factor.[1] Topical medical therapy is the preferred first-line treatment for glaucoma and ocular hypertension (OHT) and includes topical formulations containing prostaglandins/prostamides such as bimatoprost or non-specific β-blockers such as timolol, as monotherapies.[2 3] However, in up to 75% of patients with glaucoma, monotherapies fail to achieve a satisfactory IOP reduction after >2 years of treatment; therefore, an add-on therapy is required.[4]

Bimatoprost and timolol, which have complementary mechanisms of action, can be prescribed as a dual therapy and have been shown to demonstrate a stronger IOP-lowering effect than either compound administered alone.[5–7] When dual therapies are administered as fixed combinations, they are also associated with better compliance and fewer treatment-related adverse events (AEs) than non-fixed alternatives.[5 8]

Ganfort (Allergan, Ireland), which is a well-established fixed combination of bimatoprost 0.03%/timolol 0.5%, has been shown to be effective in lowering IOP and presents a consistently better ocular safety profile than bimatoprost 0.03% monotherapy.[6 7] Bimatoprost 0.03% is associated with a higher incidence of conjunctival hyperaemia and an increase in the number of patients prematurely stopping treatment.[9 10] Although timolol 0.5% has a good ocular safety profile, its potential to be absorbed systemically can lead to adverse cardiovascular and pulmonary effects.[11]

Topical eye drops require a high concentration of active substances because of the short retention times in the eye caused by rapid tear turnover.[12] Consequently, a gel formulation, which has an increased retention time on the ocular surface, could allow a reduction in the drug concentration while maintaining therapeutic efficacy. A timolol 0.1% eye gel (Geltim®, Laboratoires Théa, Clermont-Ferrand, France) has demonstrated similar IOP-lowering effects to timolol 0.5% solution,[13 14] with reduced systemic absorption and side effects.[15] A bimatoprost 0.01% eye gel was found to be non-inferior in lowering IOP to the benzalkonium chloride (BAK)-preserved bimatoprost 0.01% solution (Elymbus, Laboratoires Théa, Clermont-Ferrand, France),[16] which in turn was shown to be as effective as bimatoprost 0.03%, but with an improved safety profile (particularly reduced conjunctival hyperaemia).[10 17] Finally, the phase II study of bimatoprost 0.01%/timolol 0.1% eye gel showed a similar IOP-lowering efficacy to bimatoprost 0.03%/timolol 0.5% eye drops.[18]

This phase III clinical study aimed to evaluate the efficacy and safety of this newly proposed preservative-free (PF) bimatoprost 0.01%/timolol 0.1% fixed combination eye gel (BTFC eye gel) compared with PF bimatoprost 0.03%/timolol 0.5% eye solution (BTFC eye drops) administered once daily for 12 weeks in patients with glaucoma or OHT.

MATERIALS AND METHODS

Study design

This phase III, international, multi-centre, randomised, two-parallel group, investigator-masked, 3-month treatment duration study was conducted in 83 centres in Europe, Great Britain, India, Russia, Tunisia and Ukraine (Eudract No. 2020-003979-18). It was conducted in compliance with Good Clinical Practice (ICH-E6) guidelines, ethical principles of the Declaration of Helsinki (2013) and applicable local legislation. Prior to enrolment, written informed consent was obtained from each patient. The study took place between March 2021 and April 2023.

Study population

Eligible patients were ≥18 years old having both eyes diagnosed with OHT or open-angle glaucoma (OAG) and receiving first-line monotherapy (prostaglandin analogue (PGA) or β-blocker). Patients were required to have insufficiently controlled IOP, defined as IOP levels remaining above the target despite treatment and requiring a dual therapy. Patients with a central corneal thickness between 500 and 600 µm in both eyes were also included.

To determine the IOP-lowering effect of both treatments, patients discontinued their PGA or β-blocker monotherapy for at least 4 weeks before baseline to allow for adequate washout, given the prolonged IOP-lowering effect of these agents. At randomisation, both eyes had to present with an IOP ≥22 mmHg at 08:00, with IOP asymmetry between eyes ≤4 mmHg, and IOP <36 mmHg at all timepoints (08:00, 10:00 and 16:00).

The main exclusion criteria were as follows: advanced stage glaucoma according to the Hodapp, Parrish and Anderson criteria[19]; absence of a reliable VF test within the previous 6 months or failure to perform one at screening; any ocular abnormality preventing accurate assessments; at least one severe ocular sign (conjunctival hyperaemia, corneal fluorescein staining (CFS) and blepharitis); severe dry eye disease; far best-corrected visual acuity (BCVA) ≤20/100 in both eyes; history of ocular trauma, infection or clinically significant inflammation within the previous 3 months; ongoing or known history of uveitis, viral infection or ocular allergy; clinically significant or progressive retinal disease; known history of non-response to bimatoprost and/or timolol; and use of concomitant medications not allowed before and during the study.

Patient randomisation and study treatment

During the washout period, patients discontinued their current treatment for at least 28 days before the baseline visit (day 1) to assess IOP eligibility. An optional visit could be conducted during the washout period if the investigator deemed it necessary to verify the IOP. At baseline (day 1), patients were randomised using a computer-generated randomisation schedule in a 1:1 ratio to treatment with BTFC eye gel or BTFC eye drops for 3 months. A double-masked study design was not feasible because of the different presentation of the unit dose between BTFC eye gel and eye drops. However, the two treatment kits were identical in external appearance to ensure masking. The investigator who was in charge of the ophthalmic examination or questionnaire was unaware of the treatment given to each patient (masked investigator). Another investigator or a hospital pharmacist (unmasked investigator) dispensed the treatments and provided explanations on the dosing regimen for the study treatment. Patients were instructed not to disclose treatment information to other staff members or any investigators other than the unmasked investigator.

Patients were instructed to administer one drop of the study medication in the conjunctival cul-de-sac of each eye once daily at 20:00 (±1 hour) for the duration of the study. The first dose of the study medication was instilled on day 1 after all baseline

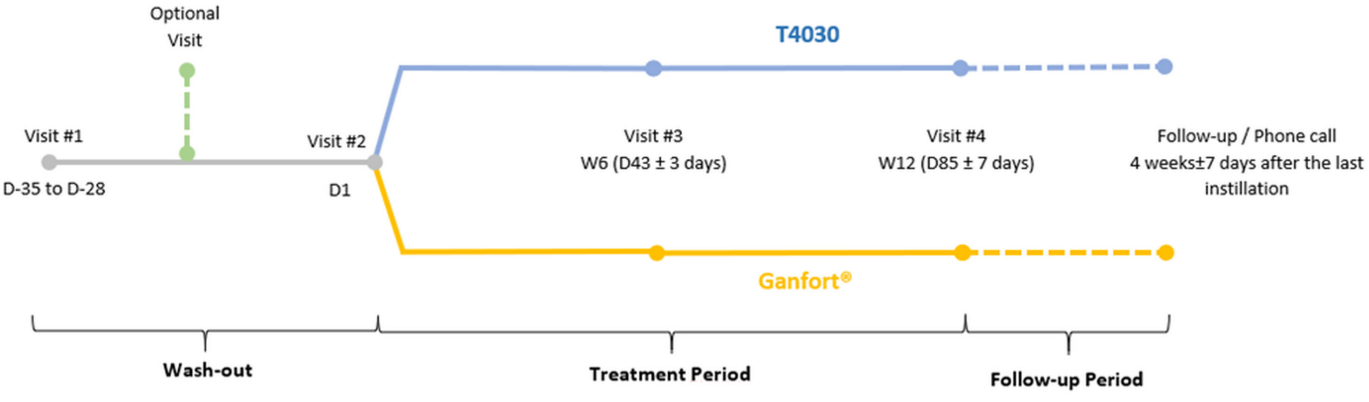


Figure 1 Overall design of the study. D, day; W, week

ocular assessments were completed. Follow-up visits were scheduled at weeks 6 and 12 (figure 1).

Outcome measures

IOP was measured at 08:00 during screening and at 08:00, 10:00 and 16:00 on day 1 (baseline, following a washout period of at least 28 days), week 6 and week 12. The primary efficacy endpoint was the change in IOP from baseline to week 12 at 08:00 in the studied eye (see definition in the statistical analyses). Secondary efficacy endpoints included changes in IOP from baseline to week 12 at 10:00 and 16:00 in the study eye, from baseline to week 6 at the three timepoints in the study eye and from baseline to weeks 6 and 12 at the three timepoints in the contralateral eye, change in the mean diurnal IOP in both eyes to weeks 6 and 12 in the study and contralateral eyes and investigator's overall efficacy assessment, defined as the investigator's subjective overall assessment of treatment efficacy based on all available clinical information at weeks 6 and 12 on a 4-point ordinal scale (very satisfactory, satisfactory, unsatisfactory, or very unsatisfactory).

Safety and tolerability endpoints included AE recording, slit-lamp examination to assess conjunctival hyperaemia (evaluated using the 0–5 McMonnies scale), CFS (Oxford 0–5 grading scale) and other ocular signs (blepharitis, eyelid oedema and follicular/papillary conjunctivitis; graded using a 0–3 point severity scale: 0, none; 1, mild; 2, moderate; 3, severe). Other safety endpoints were far BCVA (expressed in LogMAR), ocular tolerance assessed by the investigator and the patient and cardiovascular parameters (heart rate and blood pressure).

Statistical analyses

Statistical analyses were performed by the biostatistics unit of AIXIAL (Sèvres, France) using SAS version 9.4 (SAS Institute, NC, USA). The primary objective of this study was to assess the non-inferiority of BTFC eye gel to BTFC eye drops. Non-inferiority testing was performed on the basis of the 95% CI for the difference between the two treatment groups in the change in IOP from baseline at week 12 at 08:00 in the study eye using a mixed model for repeated measures (MMRM). Each model included treatment and scheduled visit (weeks 6 and 12)as fixed factors; baseline IOP as a covariate; and treatment by visit interaction, baseline IOP by visit interaction and patient as random factors. Non-inferiority was achieved if the upper bound of the 95% CI for the difference between the treatment groups (BTFC eye gel *minus* BTFC eye drops) was lower than the margin of 1.5 mmHg. Sensitivity analyses were conducted using different multiple imputations methods for missing data (Markov chain Monte Carlo method under the assumption of missing at random (MAR), pattern-mixture model assuming missing not at random (MNAR) by adding a penalty based on reason for missingness, tipping-point approach assuming MAR in BTFC eye drops and MNAR in BTFC eye gel). Analyses of covariance (ANCOVA) models on imputed datasets, including the change in IOP from baseline to week 12 at 08:00 in the study eye as the response variable, baseline IOP as a covariate and treatment as the main effect, were conducted to assess the effect of missing data and robustness of the results.

Main analyses were performed on the modified intent-to-treat (mITT) set, which included all randomised patients who received at least one dose of the study treatment (BTFC eye gel or BTFC eye drops), with at least one baseline and one post-randomisation efficacy assessment and considered as randomised. The per-protocol (PP) (all patients in the mITT set without a major protocol deviation) and intent-to-treat (ITT) (all randomised patients) sets were considered as secondary populations. Safety analyses were conducted on the safety set (all enrolled patients, having received at least one dose of the study drug).

Ocular/systemic AEs and other safety endpoints were analysed using descriptive statistics. Between-group comparisons for conjunctival hyperaemia, ocular signs and corneal staining were performed using a Cochran-Mantel-Haenszel test with modified ridit scores. Ocular tolerance by the investigator and the patient was analysed by the $\chi 2$ or Fisher's exact test.

For data recorded in both eyes, separate analyses were conducted for each eye. The study eye was defined as the eligible eye with the highest IOP at baseline (or the right eye if both eyes had the same IOP).

A sample size of 200 patients in each treatment arm was expected to give >90% power to show that BTFC eye gel was non-inferior to BTFC eye drops.

RESULTS

This section presents data for the study eye. Results for the contralateral eye were consistent with those observed for the study eye.

Patient characteristics and disposition

Overall, 554 patients were randomised in the study, which included 280 in the BTFC eye gel group and 274 in the BTFC eye drops group. No major differences were noted in the demographic data between treatment groups. The mean age was 62.0±13.0 (range, 22–89) years. Most patients were female (57.0%). The main aetiology was primary OAG (POAG) (70.0%), and most patients had previously been treated with a PGA (72.0%) (table 1).

Nineteen patients prematurely discontinued the study: 7 (2.5%) in the BTFC eye gel group and 12 (4.4%) in the BTFC eye drops group. The most common reason for premature discontinuation was withdrawal by patients in the BTFC eye gel group (3 of 7 patients) and an AE in the BTFC eye drop group (8 of 12 patients).

Intraocular pressure-lowering efficacy

The mean IOP values in the study eye in both groups at screening (08:00) and at all timepoints at baseline, week 6 and week 12 are presented in figure 2a. At week 12, the mean changes in IOP from baseline at 08:00 were −10.96±3.43 mmHg in the BTFC eye gel group and −11.14±3.56 mmHg in the BTFC eye drop group. Using an MMRM, the adjusted mean difference between the groups (BTFC eye gel *minus* BTFC eye drops) in the IOP change from baseline to week 12 was −0.04±0.24 (95% CI −0.51 to 0.43) mmHg. Non-inferiority of BTFC eye gel to BTFC eye drops was demonstrated since the upper limit of the 95% CI did not exceed 1.5 mmHg. These results were confirmed in the ITT and PP sets. Sensitivity analyses using ANCOVA models also supported non-inferiority.

Similar IOP-lowering efficacy was demonstrated at all other timepoints post-baseline in both treatment groups (figure 2b) and contralateral eye (not shown). The mean diurnal IOP change from baseline to week 12 was comparable between the BTFC eye gel and BTFC eye drop groups (−10.52±3.27 and −10.70±3.29 mmHg, respectively). In the BTFC eye gel group, the mean changes in OP from baseline to week 12 at 08:00) in the study eye were −10.98±3.36 and −10.90±3.49 mmHg for patients with OHT and POAG, respectively. A similar IOP-lowering efficacy was also observed in the BTFC eye drop group

Table 1 Demographics and other characteristics of randomised patients at baseline (day 1) in the mITT set

Screening characteristics	BTFC eye gel (n=280)	BTFC eye drops (n=274)	Total (n=554)
Age (years), mean±SD	62.1 (12.9)	61.9 (13.1)	62.0 (13.0)
Min; Max	22; 88	24; 89	22; 89
Sex			
Male, n (%)	132 (47.1)	106 (38.7)	238 (43.0)
Female, n (%)	148 (52.9)	168 (61.3)	316 (57.0)
Diagnosis (study eye)			
Primary OAG, n (%)	197 (70.4)	191 (69.7)	388 (70.0)
Ocular hypertension, n (%)	75 (26.8)	74 (27.0)	149 (26.9)
Secondary OAG: exfoliation glaucoma, n (%)	6 (2.1)	7 (2.6)	13 (2.3)
Secondary OAG: pigmentary glaucoma, n (%)	2 (0.7)	2 (0.7)	4 (0.7)
Time to diagnosis (months), median	36.7	48.0	42.4
Previous treatment			
Prostaglandin, n (%)	200 (71.4)	199 (72.6)	399 (72.0)
Latanoprost, n (%)	124 (62.0)	123 (61.8)	247 (61.9)
Tafluprost, n (%)	34 (17.0)	29 (14.6)	63 (15.8)
Bimatoprost, n (%)	23 (11.5)	26 (13.1)	49 (12.3)
Travoprost, n (%)	19 (9.5)	21 (10.6)	40 (10.0)
β-blocker, n (%)	80 (28.6)	75 (27.4)	155 (28.0)
IOP (mmHg) (study eye)			
At screening (08:00), mean±SD	21.81±3.23	21.92±3.18	21.87±3.21
At randomisation (08:00), mean±SD	26.55±2.51	26.69±2.71	26.62±2.61
Central corneal thickness (µm) (study eye)			
Mean±SD	547.0±25.8	544.6±26.1	545.8±26.0

BTC eye gel, bimatoprost 0.01%/timolol 0.1% fixed combination eye gel; BTFC, bimatoprost/timolol fixed combination; BTFC, bimatoprost 0.03%/timolol 0.5% fixed combination ophthalmic solution; IOP, intraocular pressure; mITT, modified intent-to-treat; n (%), number (%) of patients; OAG, open-angle glaucoma.

(−11.11±3.44 and −11.13±3.62 mmHg for patients diagnosed with OHT and POAG, respectively). The masked investigator assessed the overall efficacy of the study treatments as 'very satisfactory' or 'satisfactory' for at least 95% of patients in both treatment groups at post-baseline visits.

Safety and tolerability

Adverse events

The most frequent treatment-related ocular AE was conjunctival hyperaemia, reported for 26 (9.4%) patients in the BTFC eye gel group and 36 (13.1%) in the BTFC eye drop group (table 2). No serious ocular AEs were reported in the study. Ocular AEs were of mild or moderate intensity, except for one patient in the BTFC eye gel group (severe conjunctival hyperaemia) and two in the BTFC eye drop group (one had severe eye allergy, and the other had severe blepharal pigmentation/iris hyperpigmentation/growth of eyelashes), all of which were considered as related to the treatment. No patients in the BTFC eye gel group discontinued the study because of a treatment-related AE, compared with 8 (2.9%) patients (21 AEs) in the BTFC eye drop group. Of

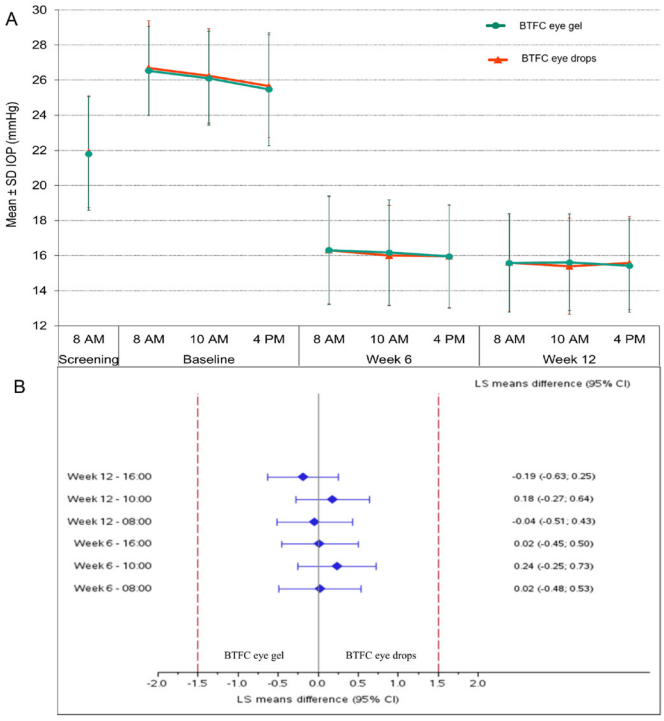


Figure 2 (A) Mean±SD of IOP at screening, baseline, week 6 and week 12 in the study eye (mITT set). (B) Forest plot for the adjusted mean differences (BTFC eye gel minus BTFC eye drops) of the change in IOP from baseline (mmHg) in the study eye (mITT set). BTFC eye drop, bimatoprost 0.03%/timolol 0.5% fixed combination ophthalmic solution; BTFC eye gel, bimatoprost 0.01%/timolol 0.1% fixed combination; LS, lease squares; mITT, modified intent-to-treat; IOP, intraocular pressure.

the 21 AEs experienced by the eight patients, the most common were instillation site irritation (3 cases), followed by instillation site discomfort, instillation site erythema and instillation site reaction (2 cases each).

Slit lamp examination

At baseline, 39.6% of the patients in the BTFC eye gel group and 44.4% in the BTFC eye drop group had conjunctival hyperaemia (McMonnies score>0). The percentage of patients who experienced a worsening of conjunctival hyperaemia from baseline to week 6 was higher in the BTFC eye drop group (23.7%) than in the BTFC eye gel group (19.3%), which remained similar at week 12 (22.7% and 18.3%, respectively). At baseline, 5 (1.8%) patients had a conjunctival hyperaemia score ≥3 in the BTFC eye gel group compared with no patients in the BTFC eye drop group. At weeks 6 and 12, the percentage of patients who had a conjunctival hyperaemia score ≥3 was greater in the BTFC eye drops group than in the BTFC eye gel group (figure 3).

The percentage of patients who experienced a worsening in the CFS score from baseline to week 6 was lower in the BTFC eye gel group with 8.4% than in the BTFC eye drop group with 12.0% and was comparable at week 12 (12.8% and 11.7%, respectively). No significant between-group difference was found in other ocular signs throughout the study.

Global tolerance

Assessment of study drug tolerance as very satisfactory/satisfactory was higher in the BTFC eye gel group than in the BTFC eye drop group at week 6 for the investigators (96.4%

Table 2 Summary of ocular AEs* related to treatment (safety set)

System organ class Preferred term	BTFC eye gel (n=278)	BTFC eye drops (n=275)
Patients with at least one treatment-related AE	**56 (20.1)**	**75 (27.3)**
Eye disorders	**47 (16.9)**	**62 (22.5)**
Abnormal eye sensation	1 (0.4)	5 (1.8)
Blepharal pigmentation	1 (0.4)	4 (1.5)
Blepharitis	2 (0.7)	4 (1.5)
Conjunctival hyperaemia	26 (9.4)	36 (13.1)
Dry eye	6 (2.2)	6 (2.2)
Eye irritation	4 (1.4	)5 (1.8)
Eye pain	2 (0.7)	5 (1.8)
Eye pruritus	1 (0.4)	1 (0.4)8 (2.9)
Eyelid oedema	–	4 (1.5)
Foreign body sensation in eyes	1 (0.4)	10 (3.6)
Growth of eyelashes	2 (0.7)	5 (1.8)
Non-infectivee conjunctivitis	2 (0.7)	6 (2.2)
Ocular hyperaemia	7 (2.5)	9 (3.3)
Vision blurred	1 (0.4)	4 (1.5)
General disorders and administration site conditions	**23 (8.3)**	**29 (10.5)**
Instillation site foreign body sensation	6 (2.2)	4 (1.5)
Instillation site irritation	8 (2.9)	17 (6.2)
Instillation site pruritus	2 (0.7)	7 (2.5)
Investigations	**5 (1.8)**	**11 (4.0)**
Vital dye staining of the cornea present	5 (1.8)	10 (3.6)

BTFC eye gel indicates bimatoprost 0.01%/timolol 0.1% fixed combination; BTFC eye drops indicate bimatoprost 0.03%/timolol 0.5% fixed combination.
*All treatment-related adverse events reported for ≥1.5% of patients in any treatment group are listed.

vs 91.6%, respectively) and patients (96.7% vs 92.3%, respectively) (figure 4). At week 12, a numerical trend was noted in favour of BTFC eye gel over BTFC eye drops for the investigators (96.0% and 93.2%, respectively) and patients (95.3% and 91.3%, respectively).

Other safety parameters

No relevant change was noted in far BCVA, mean resting systolic blood pressure, diastolic blood pressure or heart rate.

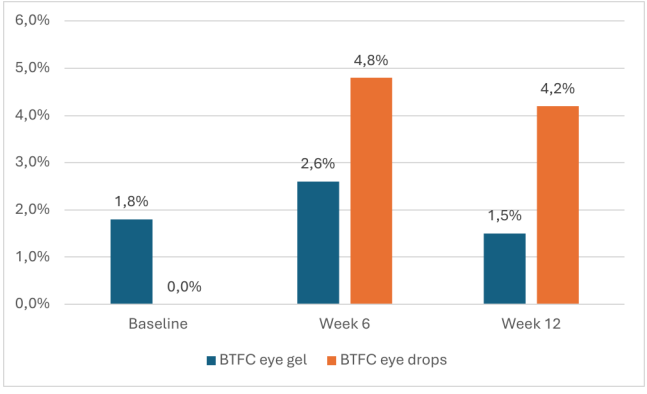


Figure 3 Percentage of patients with moderate or severe conjunctival hyperaemia (grade ≥3 on the McMonnies scale) at baseline, week 6 and week 12. BTFC eye drop, bimatoprost 0.03%/timolol 0.5% fixed combination ophthalmic solution; BTFC eye gel, bimatoprost 0.01%/timolol 0.1% fixed combination eye gel

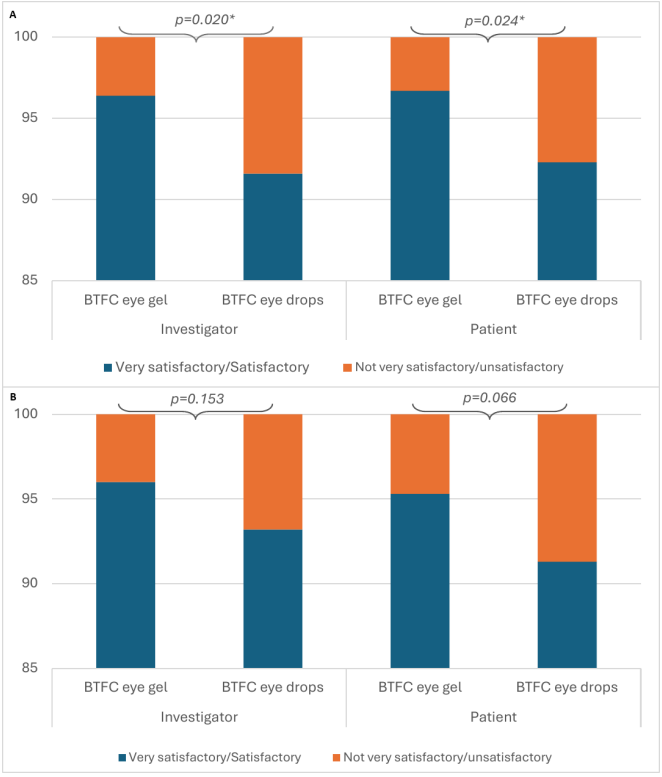


Figure 4 (A) Ocular tolerance assessment of the study treatment at week 6 was considered very satisfactory or satisfactory by the investigators or patients. (B) Ocular tolerance assessment of the study treatment at week 12 was considered very satisfactory or satisfactory by the investigators or patients. *Significant difference between the groups.

DISCUSSION

In this phase III study, the non-inferiority of a lower-concentration BTFC (PF bimatoprost 0.01%/timolol 0.1% eye gel) to a higher-concentration BTFC (PF bimatoprost 0.03%/timolol 0.5% eye drops) was demonstrated at week 12 in patients with OAG or OHT. The non-inferiority analysis required that the upper limit of the 95% CI of between-group differences in the mean change in IOP from baseline to week 12 (08:00) in the study eye be <1.5 mmHg, which was achieved. Non-inferiority would have also been achieved based on these criteria at all other timepoints at weeks 6 and 12 in the study and contralateral eyes. These results indicate that the newly developed BTFC gel formulation with a lower concentration of the two active drugs (bimatoprost 0.01%/timolol 0.1%) has a similar IOP-lowering efficacy to the higher-concentration BTFC (bimatoprost 0.03%/timolol 0.5%), which has been well established.[5–7] Although modest differences in IOP can be clinically relevant over the long term, the observed between-group difference in this study was <0.25 mmHg, which lies within the expected day-to-day variability of IOP measurements[20] and is not considered clinically meaningful in glaucoma trials.[21]

Although this first phase III study assessed the IOP-lowering efficacy of bimatoprost 0.01% and timolol 0.1% as a fixed combination, the lower concentration of each component showed a similar IOP-lowering efficacy profile to the higher concentration. In a study by Katz *et al*, bimatoprost 0.01% exhibited comparable efficacy to bimatoprost 0.03% based on pre-determined criteria for non-inferiority, with the difference between bimatoprost 0.01% and 0.03% being <0.9 mmHg

throughout follow-up.[10] However, this study used a higher BAK concentration to improve ocular penetration of bimatoprost 0.01%, and a more recent study demonstrated that PF bimatoprost 0.01% in a gel formulation has the same IOP-lowering efficacy as preserved bimatoprost 0.01% eye drops.[16] Similarly, a study compared timolol 0.1% gel with timolol 0.5% solution and demonstrated equivalence as the 95% CI of the between-group difference was within the pre-specified limits of −1.5 to +1.5 mmHg (−0.09; 1.33 mmHg).[22]

In a recent preclinical study, the ocular pharmacokinetics of a PF bimatoprost 0.01% eye gel showed improved ocular penetration compared with preserved bimatoprost 0.01% solution and similar to those of preserved bimatoprost 0.03% solution (area under the curve$_{0.5\text{-}8h}$ 134.0, 67.0 and 148.0 ng.h/mL, respectively) in aqueous humour following a single administration,[23] supporting the hypothesis that a gel formulation enhances drug delivery to the target ocular tissues.[24] This is due to longer residence time on the corneal surface observed with mucoadhesive gels, which can last for >40 min after instillation, compared with saline solutions that disappear in <20 min.[25] Consequently, the viscosity properties of ophthalmic gels may improve ocular penetration; therefore, a smaller concentration of the active substance is required, which is supported by the results in this study.

Local tolerability was similar between the treatment groups; however, a greater number of patients in the BTFC eye drops (8 [2.9%] patients experiencing 21 AEs) compared with the BTFC eye gel group (no patients) withdrew from the study due to a treatment-related AE. Almost half of these (10/21 AEs) were considered ocular administration site reactions and most occurred within the first 6 weeks of treatment. These findings are supported by the results of global tolerance assessment by investigators and patients at week 6. Compared with bimatoprost 0.01%, bimatoprost 0.03% is generally well tolerated; however, it is associated with a higher incidence of conjunctival hyperaemia, which can lead to a higher treatment discontinuation rate, as observed in previous clinical studies.[10 17] These AEs are usually reported at treatment initiation, particularly conjunctival hyperaemia, which frequently peaks at the start of treatment and diminishes over time.[26] As demonstrated by the early safety findings in the first 6 weeks of treatment with BTFC eye gel and BTFC eye drops, in addition to the higher prevalence of moderate to severe conjunctival hyperaemia in the BTFC eye drop group, the encouraging trend for BTFC eye gel could translate into an improved patient compliance and persistence with their treatment.

Although the 12-week treatment period can be considered sufficient to evaluate changes in IOP levels and assess the presence or absence of many potentially AEs, a longer follow-up period would be required to assess long-term persistence and differences in visual function. However, as BTFC eye drops have been used in routine clinical practice for >15 years, a lower dose of both active molecules is likely to have a similar, if not better, overall safety profile, particularly for systemic AEs associated with β-blockers in patients with some cardiovascular risks. To minimise potential bias related to sponsor involvement, the study incorporated independent randomisation and statistical analyses by a Contract Research Organisation, whereas investigator assessments and blinding procedures (detailed in the Methods) further ensured objectivity.

In conclusion, the results of this study indicate that bimatoprost 0.01%/timolol 0.1% fixed combination has a similar IOP-lowering efficacy compared with a higher-concentration formulation and a comparable safety profile. The clinical relevance of these findings is underscored by the potential for improved patient adherence, reduced side effects and sustained IOP control, all of which are essential in slowing disease progression in glaucoma. This gel formulation can be considered as a safe and effective treatment in the long-term therapeutic management of glaucoma and OHT.

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