ORIGINAL RESEARCH

Switching to Preservative-Free Tafluprost/Timolol Fixed-Dose Combination in the Treatment of Open-Angle Glaucoma or Ocular Hypertension: Subanalysis of Data from the VISIONARY Study According to Baseline Monotherapy Treatment

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ABSTRACT

Introduction: The VISIONARY study demonstrated statistically significant intraocular pressure (IOP) reductions with the preservative-free fixed-dose combination of tafluprost 0.0015% and timolol 0.5% (PF tafluprost/timolol FC) in open-angle glaucoma (OAG) or ocular hypertension (OHT) patients, sub-optimally controlled with topical prostaglandin analogue (PGA) or beta-blocker monotherapy. Current subanalyses have examined these data according to the baseline monotherapy.

Methods: A European, prospective, observational study included adults (aged ≥ 18 years)

with OAG or OHT, who were switched to the PF tafluprost/timolol FC from PGA or beta-blocker monotherapy. Treatment outcomes were reported according to prior monotherapy subgroup: beta-blocker, preserved latanoprost, PF-latanoprost, bimatoprost, tafluprost, and travoprost. Endpoints included the mean change from baseline regarding IOP, conjunctival hyperemia, and corneal fluorescein staining (CFS) at Week 4 and Week 12, and at Month 6.

Results: The subanalysis included 577 patients. All prior monotherapy subgroups demonstrated statistically significant IOP reductions from baseline at Week 4, that were maintained through Month 6 ($p < 0.001$). Mean (SD) IOP change at Month 6 was 6.6 (4.16), 6.3 (4.39), 5.6 (3.67), 4.9 (2.97), 4.6 (4.39), and 4.7 (3.64) mmHg for prior beta-blocker, preserved latanoprost, PF-latanoprost, tafluprost, bimatoprost, and travoprost subgroups, respectively. The largest IOP change was observed in the preserved latanoprost subgroup for each of the

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$\geq 20\%$, $\geq 25\%$, $\geq 30\%$, and $\geq 35\%$ IOP reduction categories at Month 6, demonstrating respective reductions of 8.06, 9.20, 10.64, and 11.55 mmHg. CFS was significantly reduced at Month 6 in the prior bimatoprost subgroup ($p = 0.0013$). Conjunctival hyperemia severity was significantly reduced at each study visit for prior preserved latanoprost users ($p < 0.001$).

Conclusion: PF tafluprost/timolol FC therapy provided statistically and clinically significant IOP reductions from Week 4 over the total 6-month period, in patients with OAG/OHT, regardless of the type of prior PGA or beta-blocker monotherapy used. Conjunctival hyperemia severity and CFS decreased significantly in prior bimatoprost and preserved latanoprost users, respectively.

Clinical Study Number: European Union electronic Register of Post-Authorization Studies (EU PAS) register number: EUPAS22204.

Keywords: Beta-blocker monotherapy; Ocular hypertension; Open-angle glaucoma; Preservative-free topical medication; Prostaglandin analogue monotherapy; Real-world evidence; Tafluprost/timolol fixed-dose combination; VISIONARY study

Key Summary Points

Why carry out this study?

Reduction of intraocular pressure (IOP) is the only modifiable risk factor for disease progression and irreversible sight loss in open-angle glaucoma (OAG).

The preservative-free fixed-dose combination of tafluprost 0.0015% and timolol 0.5% (PF tafluprost/timolol FC) has demonstrated IOP-lowering efficacy alongside good tolerability in randomized controlled trials and real-world studies conducted in OAG or ocular hypertension (OHT) patients, including the most recent observational data from the VISIONARY study.

The current subanalysis of data from the VISIONARY study examines the influence of prior beta-blocker monotherapy and each prostaglandin analogue (PGA) monotherapy molecule and formulation on treatment outcomes in OAG/OHT following a switch to PF tafluprost/timolol FC therapy.

What was learned from the study?

Subanalysis of data from the VISIONARY study according to the monotherapy used at baseline showed that a treatment switch to the PF tafluprost/timolol FC was associated with statistically and clinically significant IOP reductions, that were evident from Week 4 and maintained over the 6-month study period for patients in all prior monotherapy subgroups (various PGA molecules and a beta-blocker) ($p < 0.001$).

Mean change in IOP from baseline at Month 6 ranged between 4.6 mmHg (20.5%) in the prior bimatoprost subgroup and 6.3 mmHg (26.3%) in the preserved latanoprost subgroup. Patients in the prior bimatoprost subgroup demonstrated significant reductions in corneal fluorescein staining ($p = 0.0013$) at Month 6 after initiating PF tafluprost/timolol FC therapy, and conjunctival hyperemia severity was significantly reduced in the preserved latanoprost subgroup ($p < 0.001$).

The study provides insights regarding the treatment outcomes that may be expected when switching from a beta-blocker or a PGA monotherapy to the PF tafluprost/timolol FC. All prior monotherapy subgroups achieved IOP reductions of at least 20% from baseline, with the greatest change in IOP seen in the preserved latanoprost group which also had the highest baseline IOP.

INTRODUCTION

Treatment of ocular hypertension (OHT) and open-angle glaucoma (OAG) focuses on powerful reduction of elevated intraocular pressure (IOP), which is the most important modifiable risk factor for glaucoma progression and glaucoma-related irreversible loss of vision [1–6]. Guidelines recommend that topical IOP-lowering monotherapies be used as first-line treatment [3, 5]. Fixed-dose combination (FC) formulations, typically comprising a prostaglandin analogue (PGA) and a beta-receptor blocker (beta-blocker), are recommended for treatment intensification when more active ingredients are necessary to reach the target IOP [3, 7, 8]. FC formulations both simplify the treatment regimen and reduce exposure of the ocular surface to toxic preservatives [3, 5]. In particular, FC formulations help to lower exposure to the most commonly used preservative found in topical glaucoma therapy—benzalkonium chloride (BAK) [3, 5, 9–13]. Preservative-free (PF) FC topical drug formulations provide additional benefits to those of the preserved FCs, since they completely prevent preservative-related ocular surface alterations, and may therefore improve tolerance and support enhanced treatment adherence [5, 12–16].

The PF FC formulation of tafluprost 0.0015% and timolol 0.5% (PF tafluprost/timolol FC; Santen OY, Finland) has been widely used in the treatment of OAG or OHT since 2014. The clinical value of PF tafluprost/timolol FC has been shown in both randomized controlled trials and observational studies [13, 15–23]. Most recently, the VISIONARY study, a large European prospective observational study, demonstrated statistically and clinically significant IOP reduction with PF tafluprost/timolol FC treatment in OAG or OHT patients, who were insufficiently controlled with or unable to tolerate a topical PGA or beta-blocker monotherapy [23]. The key signs and symptoms of ocular surface health were also improved following the initiation of PF tafluprost/timolol FC treatment [23]. The VISIONARY study examined prospectively recorded clinical data from 577 participants in 11 European countries (66 sites) over a 6-month period [23]. The published results presented data for the overall study population, and demonstrated clinically meaningful and statistically significant improvements in IOP and the signs of ocular health, regardless of the type of the first-line monotherapy (PGA or beta-blocker) used at baseline [23]. These real-world data provide an indication of the IOP reduction that clinicians may see in their own clinical practice when switching medication from a PGA or beta-blocker monotherapy to PF tafluprost/timolol FC therapy [23]. Real-world studies have become increasingly recognized as an important tool in understanding how patients may tolerate direct treatment switches in clinical practice, providing important pharmacovigilance data and expanding the evidence base to inform treatment pathways [24–26].

The majority (72.1%) of patients included in the VISIONARY study population were treated with a PGA monotherapy prior to initiating PF tafluprost/timolol FC therapy. Therefore, in the current analysis, we separately present the IOP reduction results (absolute and percentage IOP reduction, and responder rates) according to the type of PGA monotherapy used before initiating the PF tafluprost/timolol FC. In addition, most PGA users in the VISIONARY study had been prescribed latanoprost prior to baseline, and the high patient numbers in this group enabled further subanalysis to be conducted, in which treatment outcomes were assessed separately for those receiving preserved latanoprost and PF-latanoprost formulations, to explore the potential impact of prior chronic exposure to BAK. Therefore, the change in conjunctival hyperemia severity and corneal fluorescein staining (CFS) during the study period are also presented according to each monotherapy used at baseline. Finally, ophthalmologist-evaluated observations of IOP-lowering effectiveness, clinical signs and treatment compliance, and patient-assessed tolerability are reported for each of the pre-study monotherapy subgroups. This subanalysis aims to provide further insights and clarity regarding the treatment outcomes that may be expected when stepping up to the PF tafluprost/timolol FC from prior PGA or beta-blocker therapy in routine clinical practice.

METHODS

Study Design and Visit Schedule

The design and methods of the VISIONARY study have previously been described in detail [23]. Briefly, this was a 6-month, observational, multicenter, European, prospective clinical study. The institutional review board (IRB) or independent ethics committee (IEC) at each center approved the study protocol, which was registered under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) European Union electronic Register of Post-Authorisation Studies (EU PAS, Register number EUPAS22204). The study complied with the principles of the Declaration of Helsinki and all patients provided written informed consent before enrollment.

Prospective data collection was conducted during routine ophthalmology appointments at 66 participating ophthalmology clinics in Denmark, Hungary, Ireland, Italy, Latvia, Netherlands, Norway, Russia, Spain, Sweden, and the United Kingdom (between April 2017 and January 2019). Attendance at baseline and Month 6 visits was compulsory for study participation, although data were also recorded at interim visits (Week 4 and Week 12) where patients chose to attend. Baseline measures were recorded under a topical PGA or a beta-blocker monotherapy within 7 days of implementing the switch to PF tafluprost/timolol FC treatment.

Patient Population and Study Treatment

Male/female adults (aged $\geq$ 18 years) with a diagnosis of OAG or OHT were included in the study. In accordance with the licensed indication for PF tafluprost/timolol FC, participants had demonstrated either insufficient IOP control or poor tolerance with their current PGA or beta-blocker monotherapy, and were considered likely to benefit from the use of a PF topical formulation according to the judgement of the investigator ophthalmologist [23, 27].

Participants had not undergone ophthalmic surgery within 6 months prior to the study period, and had never received previous PF tafluprost/timolol FC treatment. Patients who were pregnant or breast-feeding at the screening visit, and those with any contraindication against tafluprost or timolol treatment according to the approved licensed indication, were not included in the study.

During the 6-month study period, the participants treated their affected eye(s) with the PF tafluprost/timolol FC (one drop daily). Study treatment was instilled either in the morning or in the evening, based on patient preference.

Assessment of Exploratory Endpoints

Endpoints examined in the current analysis were based upon data reported for the VISIONARY study full analysis set (FAS) population, and examined treatment outcomes according to the monotherapy (PGA or beta-blocker) used before initiating PF tafluprost/timolol FC treatment [23]. Where available, data were examined for each of the following prior monotherapy subgroups: all PGA therapies, beta-blocker therapies, preserved latanoprost, PF-latanoprost, bimatoprost, tafluprost, and travoprost. Based on the available formulation in each of the countries that participated in the study, preserved and PF PGA formulations were used at baseline. Subject numbers were sufficient to allow a subdivision of the latanoprost subgroup to PF and preserved formulations of this PGA monotherapy, but numbers were not high enough to enable further analysis in the subgroups for other PGA therapies.

The reasons for initiating PF tafluprost/timolol FC treatment were analyzed according to the type of prior monotherapy used. The protocol allowed the investigator to indicate more than one reason for patient selection. The categories comprised insufficient IOP control, progression of glaucoma on the current monotherapy, conversion of OHT to OAG, poor local tolerance of the current topical medication, insufficient adherence to the medication used, or "other reasons".

The mean (standard deviation [SD]) IOP change from baseline was measured at Week 4, Week 12, and Month 6 using Goldmann

applanation tonometry. The mean absolute (mmHg) and relative (%) IOP change from baseline was reported at Week 4, Week 12, and Month 6 according to prior monotherapy. Responders were defined as patients achieving an IOP reduction of at least 20% from baseline at Week 12, and further analysis was conducted to explore Month 6 IOP reductions of ≥ 20%, ≥ 25%, ≥ 30%, and ≥ 35% from baseline. The Month 6 mean absolute (mmHg) and relative (%) IOP change from baseline was reported for all patients included in the FAS, as well as for patients in each of the following prior monotherapy subgroups: beta-blockers, preserved latanoprost, PF-latanoprost, bimatoprost, tafluprost, and travoprost.

Evaluation of CFS (Oxford Grade Scale; grades 0–V) was conducted at all study visits [28]. The change in CFS score from baseline was reported for all prior PGA and beta-blocker users, as well as for patients previously treated with preserved latanoprost, PF-latanoprost, bimatoprost, tafluprost, and travoprost. The change from baseline in conjunctival hyperemia severity (graded as none, mild, moderate, or severe) was evaluated for each study visit, and was compared between patients treated with preserved latanoprost and PF-latanoprost.

Investigator and Patient Assessments

Investigator evaluation and patient-assessed data were analyzed according to the prior monotherapy subgroup. Investigators reported their evaluation of IOP-lowering effectiveness, clinical signs, and treatment compliance with PF tafluprost/timolol FC at Month 6, compared with baseline monotherapy, using a 3-point scale (better than prior therapy, same as prior therapy, worse than prior therapy). Patient-assessed tolerability with PF tafluprost/timolol FC therapy at Month 6 was reported using a 4-point scale (very good, good, satisfactory, poor).

Statistical Analysis

ICON (Dublin, Ireland) conducted all statistical analyses on behalf of the VISIONARY study group [23]. Data distribution was assessed using Q–Q plots, histograms, and the Shapiro–Wilk or the Kolmogorov–Smirnov tests, as needed. For normally distributed data, the mean and SD values were reported, and the paired t test was used for the comparisons. A linear mixed model was used with IOP as the dependent variable and all timepoints as independent variables to compare the IOP change between each study visit and the baseline value, separately, using the paired t test. Change from baseline concerning CFS and conjunctival hyperemia was assessed using the Bhapkar test [29]. The p value used as the cut-off for statistical significance was < 0.05.

RESULTS

Study Population Demographics and Reasons for a Change in Treatment

As reported previously by Oddone et al. [23], 721 participants were screened for inclusion in the study and 713 were treated with the PF tafluprost/timolol FC. Of these, 577 went on to complete the 6-month visit and were included in the analysis [23].

Baseline demographics are shown in Table 1. The analysis included 577 patients (FAS). Mean (SD) age was 67.8 (11.67; range 23.7–96.1) years, and 59.6% of the final population were female. At baseline most participants (72.1%) were treated with a PGA and 27.9% with beta-blocker monotherapy. Of those treated with a PGA monotherapy at baseline, preserved latanoprost was the most frequently used (27.6%), while 15.1%, 11.1%, 10.9% and 7.3% of the participants used tafluprost, bimatoprost, travoprost and PF-latanoprost, respectively.

Table 2 shows the reasons reported for changing the prior monotherapy to PF tafluprost/timolol FC therapy. Insufficient IOP control was the most common reason for switching therapy in all prior monotherapy subgroups: PF-latanoprost (95.2%), preserved latanoprost (81.8%), tafluprost (85.1%), bimatoprost (70.3%), travoprost (66.7%), and beta-blockers (85.1%). Poor local tolerance was the second most common reason for the

Table 1 Baseline demographics (full analysis set)

Demographic characteristics	
Sex, n (%)	
Male	233 (40.4)
Female	344 (59.6)
Age (years)	
Mean (SD)	67.8 (11.67)
Range	23.7–96.1
Prior monotherapy, n (%)	
PGA therapy	416 (72.1)
Preserved latanoprost	159 (27.6)
PF-latanoprost	42 (7.3)
Tafluprost	87 (15.1)
Bimatoprost	64 (11.1)
Travoprost	63 (10.9)
Unknown	1 (0.2)
Beta-blocker therapy	161 (27.9)

n number of patients, *PF* preservative-free, *PGA* prostaglandin analogue, *SD* standard deviation

treatment switch in prior users of bimatoprost (35.9%), travoprost (30.2%), and preserved latanoprost (23.9%). Progression of glaucoma was reported as the second most popular reason for switch in the beta-blocker (16.1%) and PF-latanoprost (4.8%) subgroups, while this was the third most common reason given for patients in the travoprost (20.6%), preserved latanoprost (17.0%), tafluprost (16.1%), and bimatoprost (12.5%) subgroups.

Subanalysis of Intraocular Pressure Data

Data concerning the change in mean (SD) IOP from baseline according to the type of the prior monotherapy (PGA or beta-blocker) are shown in Table 3. Statistically significant IOP reductions were observed at Week 4 that were sustained through the 6-month study period, regardless of the prior monotherapy subgroup ($p < 0.001$). When examining the mean (SD) IOP change from baseline at Month 6 for all PGA and beta-blocker users, respective reductions of 5.4 (4.04) mmHg and 6.6 (4.16) mmHg were observed ($p < 0.0001$ for both subgroups). Mean (SD) IOP reductions from baseline in each prior PGA monotherapy subgroup at Month 6

Table 2 Reasons for a change to the preservative-free tafluprost/timolol fixed-dose combination from a prior prostaglandin analogue or beta-receptor blocker monotherapy (full analysis set)

	Preserved latanoprost n = 159 n (%)	PF-latanoprost n = 42 n (%)	Tafluprost n = 87 n (%)	Bimatoprost n = 64 n (%)	Travoprost n = 63 n (%)	Beta-blocker n = 161 n (%)
Reason(s) for change of therapy						
Insufficient IOP control	130 (81.8)	40 (95.2)	74 (85.1)	45 (70.3)	42 (66.7)	137 (85.1)
Progression of glaucoma	27 (17.0)	2 (4.8)	14 (16.1)	8 (12.5)	13 (20.6)	26 (16.1)
Conversion of OHT to glaucoma	4 (2.5)	0	0	1 (1.6)	0	3 (1.9)
Poor local tolerance	38 (23.9)	0	7 (8.0)	23 (35.9)	19 (30.2)	16 (9.9)
Poor compliance	3 (1.9)	0	0	2 (3.1)	2 (3.2)	3 (1.9)
Other reasons	2 (1.3)	0	1 (1.1)	0	1 (1.6)	0

Detailed information on the previous treatment was not recorded beyond PGA for one patient. Investigators were allowed to indicate multiple reasons for selecting patients to initiate PF tafluprost/timolol FC therapy

IOP intraocular pressure, *OHT* ocular hypertension, *n* number of patients, *PF* preservative-free

Table 3 Mean intraocular pressure change from baseline following initiation of preservative-free tafluprost/timolol fixed-dose combination treatment according to prior monotherapy at Week 4, Week 12, and Month 6 (full analysis set)

Visit	n	Mean (SD), mmHg	Change from baseline, mean (SD), mmHg	Percentage of IOP reduction from baseline	p value*
All prior PGA therapies					
Baseline	416	21.4 (4.48)			
Week 4	384	16.2 (3.21)	5.3 (3.83)	23.1	< 0.0001
Week 12	362	15.8 (2.97)	5.6 (3.97)	24.6	< 0.0001
Month 6	416	16.0 (3.23)	5.4 (4.04)	23.6	< 0.0001
Preserved latanoprost users					
Baseline	159	22.4 (5.27)			
Week 4	146	16.7 (3.43)	6.0 (4.44)	24.9	< 0.001
Week 12	143	16.4 (3.10)	6.2 (4.64)	25.6	< 0.001
Month 6	159	16.1 (3.32)	6.3 (4.39)	26.3	< 0.001
PF-latanoprost users					
Baseline	42	22.1 (3.44)			
Week 4	34	16.4 (3.50)	6.0 (2.74)	26.6	< 0.001
Week 12	28	16.1 (3.48)	6.3 (3.23)	27.8	< 0.001
Month 6	42	16.5 (3.23)	5.6 (3.67)	24.6	< 0.001
Tafluprost users					
Baseline	87	20.8 (3.29)			
Week 4	83	15.8 (3.03)	5.1 (3.14)	23.6	< 0.0001
Week 12	73	15.4 (2.73)	5.5 (3.12)	25.2	< 0.0001
Month 6	87	15.9 (2.75)	4.9 (2.97)	22.7	< 0.0001
Bimatoprost users					
Baseline	64	20.6 (4.39)			
Week 4	61	16.1 (2.95)	4.4 (4.14)	18.9	< 0.0001
Week 12	58	15.6 (2.98)	4.7 (3.46)	21.5	< 0.0001
Month 6	64	15.9 (3.86)	4.6 (4.39)	20.5	< 0.0001
Travoprost users					
Baseline	63	20.0 (3.90)			
Week 4	59	15.7 (2.96)	4.3 (2.90)	20.2	< 0.0001
Week 12	60	14.9 (2.35)	5.0 (3.79)	23.1	< 0.0001
Month 6	63	15.3 (2.62)	4.7 (3.64)	21.3	< 0.0001

Table 3 continued

Visit	*n*	Mean (SD), mmHg	Change from baseline, mean (SD), mmHg	Percentage of IOP reduction from baseline	*p* value*
Beta-blocker users					
Baseline	161	21.9 (4.36)			
Week 4	157	16.2 (3.44)	5.8 (3.56)	25.2	< 0.0001
Week 12	141	15.5 (3.00)	6.5 (3.63)	28.1	< 0.0001
Month 6	161	15.3 (3.10)	6.6 (4.16)	28.5	< 0.0001

IOP intraocular pressure, *n* number of patients, *PF* preservative-free, *SD* standard deviation

*Two-sided paired *t* test for change in mean IOP from baseline to Weeks 4 and 12, and Month 6, respectively

were 6.3 (4.39) mmHg ($p < 0.001$; preserved latanoprost), 5.6 mmHg (3.67) mmHg ($p < 0.001$; PF-latanoprost), 4.9 mmHg (2.97) mmHg ($p < 0.0001$; tafluprost), 4.6 mmHg (4.39) mmHg ($p < 0.0001$; bimatoprost), and 4.7 mmHg (3.64) mmHg ($p < 0.0001$; travoprost). Mean (SD) reduction from baseline at Month 6 for users of all latanoprost formulations (preserved and PF) was 6.1 (4.25) mmHg (25.9%; $p < 0.0001$). The change in mean IOP at Month 6 was 26.3%, 24.6%, 22.7%, 20.5%, and 21.3% for prior preserved latanoprost, PF-latanoprost, tafluprost, bimatoprost, and travoprost users, respectively.

Table 4 presents the mean IOP change from baseline and the responder rates at Month 6 for patients achieving an IOP reduction of $\geq 20\%$, $\geq 25\%$, $\geq 30\%$, or $\geq 35\%$ from baseline. Data are shown for all study participants, all beta-blocker users, and for each of the prior PGA therapy subgroups. Overall, 77.6%, 62.7%, 49.1%, and 36.0% of patients using beta-blocker monotherapy at baseline achieved an IOP reduction of $\geq 20\% \geq 25\%$, $\geq 30\%$, and $\geq 35\%$, respectively, at Month 6. The mean IOP on prior monotherapy was highest for patients treated with preserved latanoprost at baseline (22.4 mmHg), and the absolute IOP reduction in this group was the greatest of the prior PGA subgroups. Mean IOP was reduced by 8.06, 9.20, 10.64, and 11.55 mmHg at Month 6 for responders achieving IOP reductions of $\geq 20\%$, $\geq 25\%$, $\geq 30\%$, and $\geq 35\%$, respectively. The percentage of responders in each of the prior PGA subgroups achieving an IOP

reduction $\geq 20\%$ was 69.8% (preserved latanoprost), 66.7% (PF-latanoprost), 64.4% (tafluprost), 63.5% (travoprost), and 60.9% (bimatoprost). An IOP reduction $\geq 25\%$ was achieved at Month 6 by 54.8%, 52.2%, 50.0%, 47.6%, and 46.0% in the prior PF-latanoprost, preserved latanoprost, bimatoprost, travoprost, and tafluprost subgroups, respectively. The percentage of responders in each PGA subgroup with an IOP reduction $\geq 30\%$ at Month 6 was 42.9% (PF-latanoprost), 36.5% (preserved latanoprost), 34.9% (travoprost), 34.4% (bimatoprost), and 29.9% (tafluprost). The percentage of responders with an IOP reduction $\geq 35\%$ in each of the PGA subgroups was 27.7% (preserved latanoprost), 23.4% (bimatoprost), 21.4% (PF-latanoprost), 16.1% (tafluprost), and 14.3% (travoprost).

Change in Corneal Fluorescein Staining (CFS) According to Baseline Monotherapy

Table 5 shows the mean (SD) change in CFS score at each study visit according to the prior monotherapy subgroup. The mean baseline CFS score was typically < 1.0 in each of the subgroups examined with the exception of the prior bimatoprost group, in which the mean (SD) CFS score was 1.34 (1.16) before initiating PF tafluprost/timolol FC therapy.

Overall, mean (SD) CFS score was reduced from 0.82 (0.97) at baseline to 0.49 (0.73; $p = 0.0001$) at Month 6 for all prior PGA users and from 0.48 (0.75) at baseline to 0.35 (0.59; $p = 0.1907$) at Month 6 for prior beta-blocker

Table 4 Mean intraocular pressure change from baseline at Month 6 following medication change to preservative-free tafluprost/timolol fixed-dose combination treatment according to different cut-off values for all study participants and prior monotherapy subgroups (full analysis set)

	n	Responders (%)	Mean IOP (mmHg)	Mean IOP reduction (mmHg)
All study participants				
≥ 20% change in IOP	399	69.2	15.13	7.65
≥ 25% change in IOP	309	53.6	14.72	8.53
≥ 30% change in IOP	225	40.0	14.34	9.56
≥ 35% change in IOP	149	25.8	13.61	10.62
Preserved latanoprost users				
≥ 20% change in IOP	111	69.8	15.58	8.06
≥ 25% change in IOP	83	52.2	15.14	9.20
≥ 30% change in IOP	58	36.5	14.81	10.64
≥ 35% change in IOP	44	27.7	14.36	11.55
PF-latanoprost users				
≥ 20% change in IOP	28	66.7	15.36	7.61
≥ 25% change in IOP	23	54.8	14.91	8.17
≥ 30% change in IOP	18	42.9	14.50	8.83
≥ 35% change in IOP	9	21.4	12.78	10.11
Tafluprost users				
≥ 20% change in IOP	56	64.4	15.21	6.59
≥ 25% change in IOP	40	46.0	14.95	7.45
≥ 30% change in IOP	26	29.9	14.46	8.38
≥ 35% change in IOP	14	16.1	13.36	9.21
Bimatoprost users				
≥ 20% change in IOP	39	60.9	14.67	7.26
≥ 25% change in IOP	32	50.0	14.41	7.91
≥ 30% change in IOP	22	34.4	14.05	8.95
≥ 35% change in IOP	15	23.4	13.13	9.60
Travoprost users				
≥ 20% change in IOP	40	63.5	14.73	6.75
≥ 25% change in IOP	30	47.6	14.23	7.50
≥ 30% change in IOP	22	34.9	14.14	8.32
≥ 35% change in IOP	9	14.3	12.33	9.89

Table 4 continued

	n	Responders (%)	Mean IOP (mmHg)	Mean IOP reduction (mmHg)
Beta-blocker users				
≥ 20% change in IOP	125	77.6	14.90	8.17
≥ 25% change in IOP	101	62.7	14.47	8.99
≥ 30% change in IOP	79	49.1	14.05	9.84
≥ 35% change in IOP	58	36.0	13.55	10.71

IOP intraocular pressure, *OHT* ocular hypertension, *PF* preservative-free, *n* number of patients

users. Numerical reductions in CFS score were observed at Month 6 in each of the prior PGA monotherapy subgroups. However, the reduction in CFS score was only statistically significant in the prior bimatoprost subgroup, in which a mean (SD) reduction from baseline at Month 6 of 0.71 (1.17) was observed ($p = 0.0013$).

Change in Conjunctival Hyperemia According to Baseline Monotherapy

Figure 1 shows the change in the severity of conjunctival hyperemia at each study visit for patients treated with all prior PGA monotherapies and beta-blockers at baseline, separately. Change in conjunctival hyperemia was statistically significant at each study visit among prior PGA users ($p < 0.0001$). Hyperemia was absent in 30.3% of PGA users at baseline and 53.8% at Month 6. Moderate hyperemia was reported in 21.3% of PGA users at baseline and 4.3% at Month 6. Conjunctival hyperemia was absent in 52.3% of prior beta-blockers at baseline and 61.7% at Month 6. The change in the severity of hyperemia was not statistically significant among baseline beta-blocker users ($p = 0.5232$).

Figure 2 shows the change in the severity of conjunctival hyperemia for prior preserved latanoprost and PF-latanoprost users. The change was statistically significant at each study visit for those in the preserved latanoprost subgroup ($p < 0.001$), whereas the change in conjunctival hyperemia severity was not significant during the study period for prior PF-

latanoprost users. At baseline, 22.0% of prior preserved latanoprost users had moderate conjunctival hyperemia and this was reduced to 6.2% at Month 6, while the percentage with no hyperemia was increased from 28.0% at baseline to 46.9% at Month 6. Conjunctival hyperemia was typically mild or absent in prior PF-latanoprost users at both baseline (97.1%) and Month 6 (95%).

Investigator Evaluation of Clinical Effectiveness, Clinical Signs and Treatment Compliance

Figure 3a shows investigator evaluations at Month 6 regarding IOP-lowering effectiveness, clinical signs, and treatment compliance with PF tafluprost/timolol FC compared with baseline monotherapy for each of the PGA subgroups and for prior beta-blocker users. Investigators rated treatment effectiveness to be better with PF tafluprost/timolol FC for most patients (≥ 77%) in each of the prior treatment subgroups. Clinical signs with PF tafluprost/timolol FC treatment were considered to be either improved or the same as previous therapy in the majority of patients (> 95%) in each of the prior treatment subgroups. Treatment compliance was also reported to be improved or comparable with prior monotherapy in > 96% of patients in each of the prior treatment subgroups.

Figure 3b shows patient-assessed tolerability data for PF tafluprost/timolol FC treatment at Month 6, compared with prior monotherapy for each of the PGA subgroups and for prior beta-

**Table 5** Mean corneal fluorescein staining score (Oxford Grade Scale) and mean change in score following initiation of the preservative-free tafluprost/timolol fixed-dose combination according to prior monotherapy (full analysis set)

	n	Mean (SD)	*n*[a]	Mean (SD) decrease from baseline	*p* value*
All prior PGA therapies					
Baseline	188	0.82 (0.97)			
Week 4	195	0.60 (0.79)	160	0.19 (0.81)	0.0030
Week 12	184	0.61 (0.82)	153	0.19 (0.98)	0.0186
Month 6	220	0.49 (0.73)	177	0.29 (1.01)	0.0001
Preserved latanoprost					
Baseline	68	0.75 (0.97)			
Week 4	63	0.57 (0.76)	54	0.17 (0.8)	0.1463
Week 12	63	0.59 (0.91)	54	0.07 (1.11)	0.7308
Month 6	70	0.53 (0.79)	60	0.15 (1.1)	0.3745
PF-latanoprost					
Baseline	21	0.52 (0.75)			
Week 4	24	0.25 (0.74)	15	0.13 (0.52)	0.6250
Week 12	23	0.57 (0.84)	14	-0.07 (0.47)	1.0000
Month 6	33	0.33 (0.82)	21	0.1 (0.54)	0.6875
Tafluprost					
Baseline	40	0.58 (0.71)			
Week 4	46	0.52 (0.75)	36	-0.03 (0.56)	1.0000
Week 12	37	0.41 (0.69)	31	0.1 (0.47)	0.4531
Month 6	49	0.49 (0.62)	39	0.15 (0.63)	0.2101
Bimatoprost					
Baseline	35	1.34 (1.16)			
Week 4	36	0.92 (0.87)	33	0.42 (1.17)	0.0635
Week 12	36	0.83 (0.85)	32	0.5 (1.24)	0.0312
Month 6	42	0.57 (0.77)	34	0.71 (1.17)	0.0013
Travoprost					
Baseline	24	0.96 (1.00)			
Week 4	26	0.69 (0.74)	22	0.32 (0.65)	0.0625
Week 12	25	0.68 (0.63)	22	0.32 (0.95)	0.2012
Month 6	26	0.50 (0.58)	23	0.48 (1.2)	0.0986

Table 5 continued

	n	Mean (SD)	n^{a}	Mean (SD) decrease from baseline	p value*
Beta-blocker therapy					
Baseline	46	0.48 (0.75)			
Week 4	48	0.33 (0.56)	42	0.19 (0.45)	0.0215
Week 12	42	0.21 (0.47)	36	0.30 (0.62)	0.0098
Month 6	52	0.35 (0.59)	43	0.16 (0.69)	0.1907

CFS corneal fluorescein staining, *n* number of patients, *PF* preservative-free, *PGA* prostaglandin analogue, *SD* standard deviation

*Significance testing using a two-sided *t* test for change of mean CFS from baseline to Weeks 4 and 12, and Month 6, respectively

[a]Number of patients with data available at both baseline and at each relevant study visit
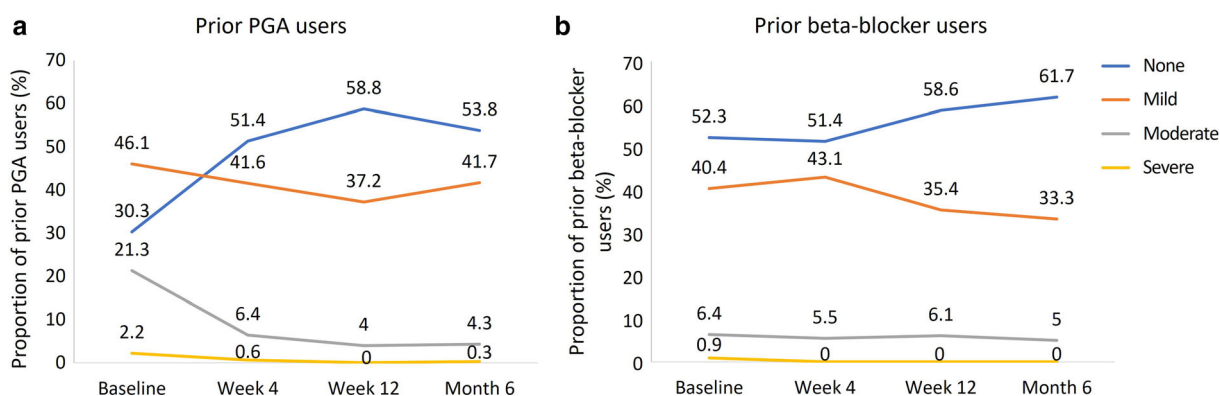
Fig. 1 Change in severity of conjunctival hyperemia following initiation of the preservative-free tafluprost/timolol fixed-dose combination according to the prior PGA or beta-blocker monotherapy use (full analysis set). **a** Change in severity of hyperemia from baseline following the initiation of PF tafluprost/timolol FC in prior PGA users: $p < 0.0001$ at each study visit. **b** Change in severity of hyperemia from baseline following the initiation of PF tafluprost/timolol FC in prior beta-blocker users: $p = 0.6916$ at Week 4, $p = 0.5498$ at Week 12, $p = 0.5232$ at Month 6. *FC* fixed combination, *n* number of patients, *PF* preservative-free, *PGA* prostaglandin analogue

blocker users. More than 85% of patients in each subgroup evaluated tolerability with PF tafluprost/timolol FC to be good or very good (Fig. 3b).

DISCUSSION

The current subanalysis of data from the VISIONARY study provides further evidence to support the IOP-lowering efficacy and tolerability of the PF tafluprost/timolol FC when used in a real-world setting. VISIONARY comprised a large, European, observational, multicenter study that examined treatment outcomes following a direct switch (without a washout period) to the PF tafluprost/timolol FC in patients with OAG or OHT, who were either insufficiently controlled with or unable to tolerate PGA or beta-blocker monotherapy [23]. The current subanalysis demonstrated that statistically significant IOP reductions were
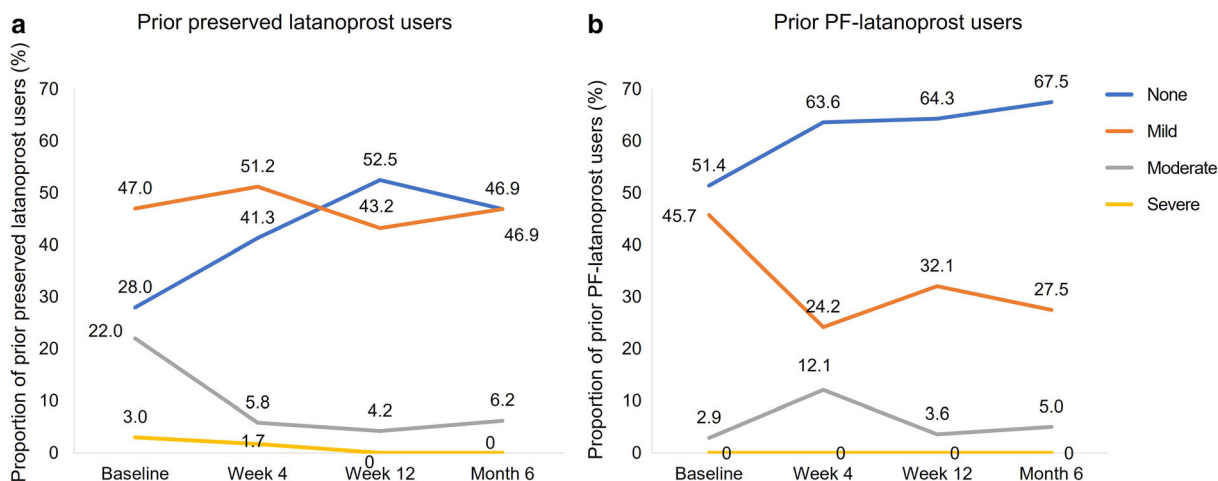
Fig. 2 Change in severity of conjunctival hyperemia following a switch to the preservative-free tafluprost/timolol fixed-dose combination from preserved and preservative-free latanoprost monotherapy, respectively (full analysis set). **a** Change in severity of hyperemia from baseline following the initiation of PF tafluprost/timolol FC in prior preserved latanoprost users ($n = 159$): $p < 0.001$ at each visit. **b** Change in severity of hyperemia from baseline following the initiation of PF tafluprost/timolol FC in prior PF-latanoprost users ($n = 42$): $p = 0.377$ at Week 4, $p = 0.472$ at Week 12, $p = 0.148$ at Month 6. *FC* fixed combination, *n* number of patients, *PF* preservative-free

achieved from Week 4 through Month 6 in prior beta-blocker users, as well as in each of the prior PGA monotherapy subgroups examined. The study represents the largest European on-label real-world study to specifically examine the IOP lowering-efficacy of the PF tafluprost/timolol FC in patients switching directly from PGA or beta-blocker monotherapy, and the first to include subanalyses of these data according to the individual PGA treatment used at baseline. The high number of patients included in the study, who had been treated at baseline with preserved latanoprost, provides an indication of treatment practices in ophthalmology clinics across Europe, and the subanalyses reported here reveal the efficacy and tolerability outcomes that may be expected when switching to the PF tafluprost/timolol FC from each PGA monotherapy or from a topical beta-blocker.

Irrespective of the baseline monotherapy used (PGA or beta-blocker), most patients initiating PF tafluprost/timolol FC had been unable to achieve sufficient IOP control with monotherapy alone. Between 66% and 95% of participants in each baseline treatment

subgroup were switched to PF tafluprost/timolol FC therapy because of poor IOP control. More than 23% of those previously treated with preserved latanoprost, bimatoprost, or travoprost were switched due to poor local tolerance, whereas tolerability issues were not cited as a reason for changing therapy among any prior PF-latanoprost users. These results are aligned with previous studies suggesting that issues regarding ocular surface tolerance may be due to either the presence of preservative agent or the active prostaglandin agent itself [21, 30]. It is interesting to note that patient-reported tolerability with PF tafluprost/timolol FC therapy was rated as good or very good by the majority of participants (> 85%) in each of the prior treatment subgroups, and this aspect of treatment is likely to have driven the high rates of compliance (as evaluated by investigators) reported in both the primary publication and the current subanalysis [23].

IOP subanalysis according to prior monotherapy showed that clinically meaningful and statistically significant IOP reductions from baseline were demonstrated at all study visits, regardless of the monotherapy used prior
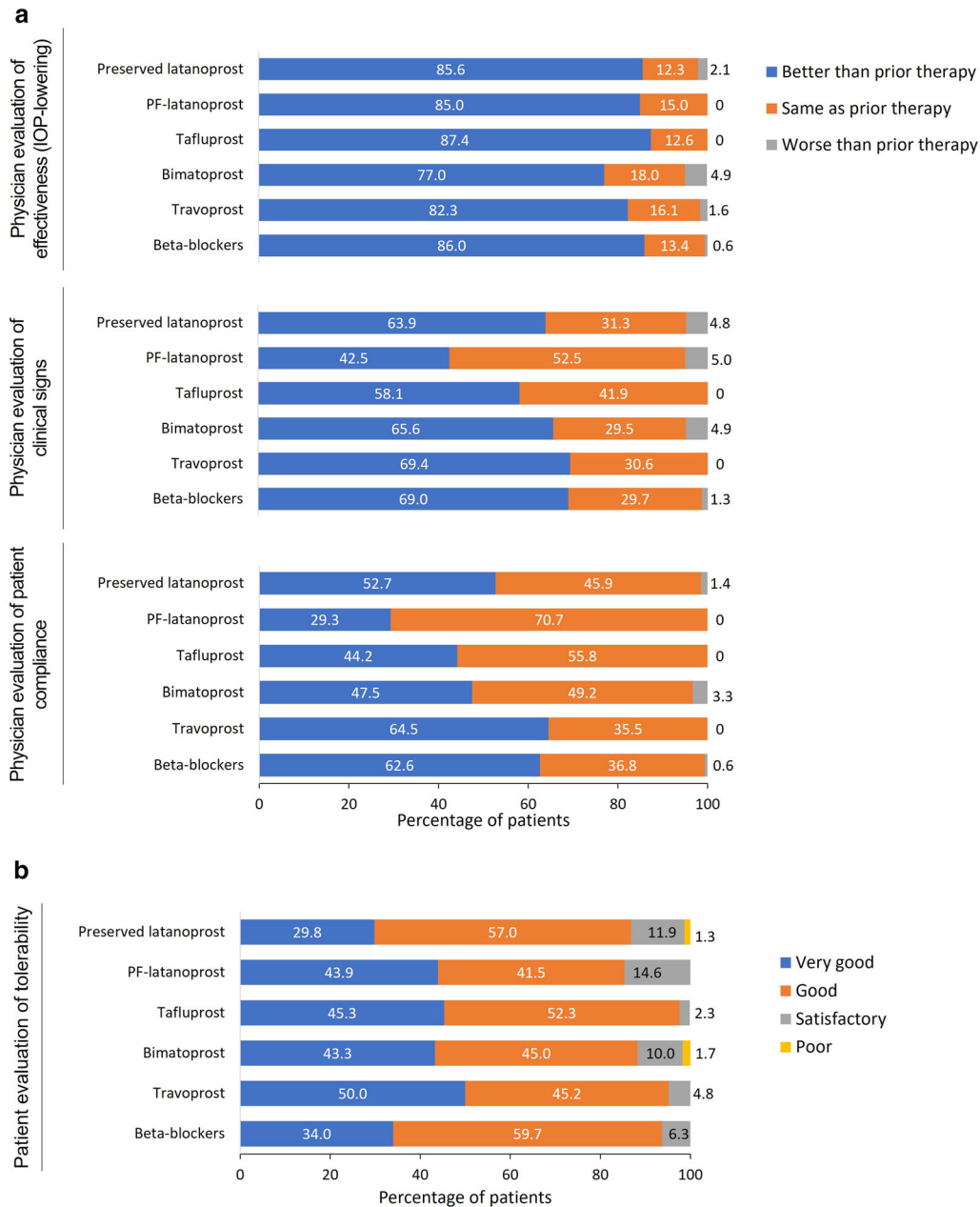
Fig. 3 **a** Physician evaluation of effectiveness, clinical signs and treatment compliance after 6 months of treatment with preservative-free tafluprost/timolol fixed-dose combination therapy compared with prior prostaglandin analogue or beta-blocker monotherapy (full analysis set).

b Patient evaluation of tolerability after 6 months of treatment with preservative-free tafluprost/timolol fixed-dose combination therapy (full analysis set). *PF* preservative-free

to initiating PF tafluprost/timolol FC treatment ($p < 0.001$). At Month 6, the mean IOP in each prior treatment subgroup was ≤ 16.5 mmHg, with the highest relative reductions from baseline seen in the prior preserved latanoprost subgroup (6.3 mmHg; 26.3%). Patients in all subgroups achieved a mean IOP reduction of at least 4.6 mmHg (20.5%). Regardless of the prior monotherapy subgroup, statistically and clinically significant IOP reductions were present

from Week 4 and sustained over the 6-month study period. These data are reflective of the primary VISIONARY publication and of other real-world data concerning IOP-lowering efficacy with PF tafluprost/timolol FC following a switch away from different topical glaucoma medications [22, 23]. Emerging country-level data from the VISIONARY study has revealed differences in baseline IOP, with clinicians in some countries selecting patients with higher IOPs for inclusion in the study [31–34]. As pre-treatment pressure is predictive of IOP change, it is likely that these differences may have influenced the IOP reductions observed in the full Europe-wide dataset, and further subanalysis of these data according to country would be of value [16]. Improved adherence with PF tafluprost/timolol FC treatment, compared with prior monotherapy, may also have contributed to the IOP reductions and maintained IOP control observed during the current study. Clinicians rated compliance with PF tafluprost/timolol FC to be better than prior monotherapy in 44.2–64.5% patients previously treated with preserved latanoprost, bimatoprost, travoprost, or tafluprost. Approximately 30% of prior PF-latanoprost users were considered to have better compliance with treatment following the switch to PF tafluprost/timolol FC. The improvements seen concerning conjunctival hyperemia among those previously treated with preserved latanoprost, and the reduction in CFS score associated with a change to PF tafluprost/timolol FC from bimatoprost monotherapy, suggest that patients may have experienced tolerability issues with these PGA monotherapies, which might also have affected their adherence [21, 30, 35–41]. Patients who subsequently had better adherence with PF tafluprost/timolol FC therapy would therefore show improved IOP-lowering efficacy. There is a need for further data in this area to understand the impact of improved ocular tolerability on treatment efficacy with glaucoma medications. Phase 3 randomized studies examining PF tafluprost/timolol FC therapy also demonstrated statistically significant IOP-lowering efficacy, although those trials included a washout period prior to the treatment, which provided untreated baseline values and may have

helped to minimize any tolerability issues associated with the prior therapies [15, 16, 19]. The current subanalysis offers an indication of the IOP reduction that clinicians may expect in their own clinics when directly switching therapy from either PGA or beta-blocker monotherapy. Subanalysis of IOP data according to the cut-off values of $\geq 20\%$, $\geq 25\%$, $\geq 30\%$, and $\geq 35\%$ showed respective responder rates to be at least 60%, 46%, 29%, and 14%, across all prior monotherapy subgroups. For each of the preset IOP reduction categories, the greatest relative reductions were seen in the prior preserved latanoprost subgroup, where mean IOP reductions of 8.06, 9.20, 10.64, and 11.55 mmHg were reported for patients achieving IOP reductions of $\geq 20\%$, $\geq 25\%$, $\geq 30\%$, and $\geq 35\%$, respectively. Unfortunately, statistical analysis was not available to directly compare IOP-lowering outcomes between treatment groups, but this may represent an interesting area for further studies to inform future treatment pathways for OAG or OHT. The IOP-lowering efficacy demonstrated with PF tafluprost/timolol FC treatment during the study period was supported by the clinical evaluations of investigators. Irrespective of the prior monotherapy subgroup examined, most ophthalmologists ($\geq 77\%$) rated the clinical effectiveness of PF tafluprost/timolol FC to be better than the prior monotherapy. Across the prior treatment subgroups, clinical signs were also considered to have improved (42.5–69.4%), or to be the similar (29.7–52.5%), when compared with prior monotherapy. These outcomes were broadly similar to those published in the primary VISIONARY study analysis [23].

The primary VISIONARY study publication reported that, although baseline CFS was typically low, the CFS score was significantly reduced for the FAS during the 6-month study period ($p < 0.0001$) [23]. Data in the current subanalysis for all prior PGA users showed significant reductions in CFS score following a change to PF tafluprost/timolol FC at each study visit ($p \leq 0.0186$), although this appeared to have been largely driven by reductions in CFS grade within the prior bimatoprost subgroup. While numerical reductions in CFS score were

observed in each prior treatment subgroup, statistically significant reductions were only observed at Week 12 and Month 6 in the prior bimatoprost subgroup. The mean (SD) baseline CFS grade was slightly higher [1.34 (1.16)] in the prior bimatoprost subgroup compared with the other groups (typically ≤ 0.97), suggesting that there was more scope for improvement during the study period in patients moving to PF tafluprost/timolol FC treatment from bimatoprost.

Although typically mild or absent at baseline, conjunctival hyperemia was significantly reduced at each study visit for prior all PGA users ($p < 0.0001$). These results reflect the primary VISIONARY study publication, which showed that conjunctival hyperemia was significantly reduced at Month 6, regardless of the subtype of PGA treatment used prior to switch [23]. However, our further subanalysis showed that, while prior preserved latanoprost users demonstrated a statistically significant reduction from baseline concerning conjunctival hyperemia severity, the change was not significant for those in the prior PF-latanoprost subgroup, suggesting that hyperemia may be associated with the presence of preservative agent in latanoprost users. Glaucoma patients are considered to be susceptible to ocular surface disease, and previous studies have indicated that preserved PGA formulations and some active agents may be associated with local tolerance issues [21, 30, 35–41]. It is well established that PGA-timolol FC therapies are associated with lower incidence of hyperemia than PGAs alone, although the exact mechanism remains undetermined [9–11]. Our results suggest that a switch to the PF tafluprost/timolol FC may have helped to resolve such ocular surface tolerability problems for patients included in the VISIONARY study [30, 35–41]. Despite overwhelming in vitro evidence, high-quality data from controlled studies are lacking regarding the potential tolerability advantages of PF medications in glaucoma therapy [35–41]. Further studies are required to explore whether local tolerability issues might influence the IOP-lowering efficacy of glaucoma therapies.

While real-world studies, such as the VISIONARY study, provide an important opportunity to examine the treatment outcomes achieved in routine clinical practice, this type of study is associated with a number of limitations. Patients were able to leave the study without providing a reason, and attendance at follow-up appointments also represents a major challenge for ophthalmologists in clinical practice [42]. Patients were only mandated to attend study visits at baseline and Month 6, meaning that fewer patients attended interim visits at Weeks 4 and 12, and this is reflected in the data reported at these timepoints. However, enough patients in each monotherapy subgroup attended interim visits to provide an indication of the rapidity of treatment efficacy and consistency of IOP control during the study period. Although patients treated with all formulations of PGA and beta-blocker monotherapy were allowed to enter the study, there were only sufficient patients included in the prior latanoprost group to enable further subanalysis according to whether they had used a preserved and PF formulation. Future studies would be of value to examine the impact of prior treatment with preserved or PF formulations of other PGA monotherapies on IOP-lowering efficacy, treatment adherence, and tolerability following a switch to the PF tafluprost/timolol FC. In addition, further subanalysis of VISIONARY data to explore the potential relationship between observed improvements in the signs of ocular health (e.g., hyperemia, CFS score) and IOP-lowering efficacy would be of value.

CONCLUSIONS

When switched to PF tafluprost/timolol FC treatment in a real-world setting, without a washout period, patients with OAG or OHT demonstrated clinically and statistically significant IOP reductions from baseline at Week 4, that were maintained over the 6-month study period regardless of the type of prior PGA treatment used. Improvements were observed regarding CFS score and conjunctival hyperemia, providing further evidence to support the good tolerability profile for PF tafluprost/timolol FC treatment.

ACKNOWLEDGEMENTS

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