ORIGINAL RESEARCH

Treatment of Open-Angle Glaucoma and Ocular Hypertension with the Fixed-Dose Combination of Preservative-Free Tafluprost/Timolol: Clinical Outcomes from Ophthalmology Clinics in Italy

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Introduction: The VISIONARY study examined the intraocular pressure (IOP)-lowering efficacy and tolerability of the preservative-free fixed-dose combination of tafluprost (0.0015%) and timolol (0.5%) (PF tafluprost/timolol FC) in a real-world setting. The country-level data reported herein comprise the largest and first observational study of PF tafluprost/timolol FC therapy in Italy.

Methods: An observational, multicenter, prospective study included adult Italian patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) demonstrating insufficient response or poor tolerability with topical prostaglandin analogue (PGA) or beta-blocker monotherapy. Treatment was switched to PF tafluprost/timolol FC therapy at baseline. Primary endpoint was the absolute mean IOP change from baseline at Month 6. Exploratory and safety endpoints included change in IOP at Weeks 4 and 12, ocular signs, symptom severity and reporting of adverse events (AEs).

Results: Overall, 160 OAG/OHT patients were included. Mean ± standard deviation IOP was reduced from 19.6 ± 3.6 mmHg at baseline to 14.5 ± 2.6 mmHg at Month 6 (reduction of 5.1 ± 3.7 mmHg; 24.1%; p < 0.0001). IOP reduction was also statistically significant at Week 4 (23.1%; p < 0.0001) and Week 12 (24.7%; p < 0.0001). Based on data cutoff values for mean IOP change of ≥20%, ≥25%, ≥30% and ≥35%, respective Month 6 responder rates were 68.1%, 48.7%, 36.2% and 26.9%. Most ocular signs and symptoms were significantly reduced in severity from baseline at Month 6. Two non-serious and mild AEs were reported during the study period, among which, one AE was treatment-related (eyelash growth).

Conclusion: Italian OAG and OHT patients demonstrated a significant IOP reduction from baseline at Week 4 that was maintained over a 6-month period following a switch from topical PGA or beta-blocker monotherapy to PF tafluprost/timolol FC therapy. Severity of most ocular signs and symptoms was significantly reduced during the study period, and PF tafluprost/timolol FC was generally well tolerated.

Keywords: fixed-dose combination therapy, intraocular pressure, ocular hypertension, PF tafluprost/timolol FC, preservative-free topical medication, primary open-angle glaucoma

Introduction

Glaucoma is a leading global cause of blindness.[1,2] An estimated 76 million people worldwide are currently diagnosed with open-angle glaucoma (OAG) or angle closure glaucoma, and this number has been projected to reach 112 million by the year 2040.[1,2] Approximately 3% of the global population aged between 40 and 80 years are believed to have primary open-angle glaucoma (POAG), with prevalence ranging between 2.3% in Asia and 4.2% in Africa.[1,2] Elevated intraocular pressure (IOP) is considered the most important treatable risk factor for disease development and progression.[2–7] Reduction of IOP may slow down visual field loss and deterioration in vision-related quality of life.[3–7]

Topical IOP-lowering therapy is the most common first-line treatment for OAG.[2] When IOP is insufficiently controlled using topical monotherapy, combination therapies containing a prostaglandin analogue (PGA) and beta-blocker are frequently prescribed.[2,8–15] Treatment must balance IOP-lowering efficacy with tolerability since ocular surface disease (OSD) is common among people with glaucoma and can affect patient compliance.[2,16–28] Interventions that improve ocular surface health and reduce exposure to toxic topical agents may enhance IOP control.[18–20] Topical treatments containing preservative agents, such as benzalkonium chloride (BAK), can cause tolerability issues at the ocular surface.[21–29] Preservative-free (PF) fixed-dose combination (FC) therapies reduce the number of daily medication instillations required, compared with administration of multiple monotherapies, without exposing the ocular surface to preservative agents.[2,8,10–12] The PF FC formulation of tafluprost 0.0015% and timolol 0.5% (PF tafluprost/timolol FC) has demonstrated powerful IOP-lowering efficacy and a good tolerability profile in the treatment of OAG and OHT in randomized controlled trials (RCTs) and real-world observational studies.[11,30–37] Although RCTs remain the gold standard for regulatory assessment and approval, restrictive inclusion criteria prevent exploration of certain facets of routine clinical practice and a high proportion of patients who may be considered appropriate for a particular treatment in the clinic would not be included in such tightly controlled studies.[38–40] Real-world studies are more relevant in understanding how patients may tolerate and respond to direct medication changes in clinical situations and provide important pharmacovigilance information.[35,37,39]

This article reports country-level real-world data from Italy concerning a multicenter, European, observational, 6-month study (the VISIONARY study) that evaluated the IOP-lowering effectiveness, tolerability and safety of PF tafluprost/timolol FC therapy in patients with OAG and OHT, who were previously treated with either a topical PGA or beta-blocker monotherapy.[35] Europe-wide data from the VISIONARY study demonstrated significant IOP reductions of up to 5.4 mmHg (approximately 24%) with PF tafluprost/timolol FC therapy from Week 4 that were maintained through Month 6 (p<0.0001).[35] However, country-level data already published from the UK, Hungary, Russia and Spain revealed variations in baseline IOP and the relative change in IOP, probably because baseline pressure typically predicts treatment outcome with topical glaucoma therapy.[41–45] This suggests that ophthalmologists in some countries selected patients with differing baseline IOPs for treatment intensification, which may relate to local clinical practice or treatment pathways.[41–44] The current analysis represents the largest study of PF tafluprost/timolol FC treatment conducted in Italy to date, including both real-world and randomized studies. Italian ophthalmology centers enrolled more patients in the VISIONARY study than any of the other participating countries, making this dataset highly relevant when interpreting the outcomes reported from the full European study population. Analysis of data from Italy provides an important opportunity to gain insights regarding the management of OAG and OHT in Italian ophthalmologic centers.

Materials and Methods
Study Design and Visit Schedule

The VISIONARY study methodology has already been described in detail.[35,41–44] Briefly, the study comprised a 6-month, observational, multicenter, prospective clinical investigation (EU PAS register number EUPAS22204). Data were prospectively collected during routine visits, between 10 April 2017 and 9 January 2019, at 14 ophthalmology centers in Italy. Patients were required to attend study visits at baseline and Month 6, whereas interim study visits (Week 4 and Week 12) were optional.[35,41–44] The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at participating centers approved the protocol, and all patients provided written informed consent. The study complied with the principles of the Declaration of Helsinki.

Patient Population

Male/female adults (aged ≥18 years) with OAG or OHT currently treated with any locally available PF or preservative-containing formulation of topical PGA or beta-blocker monotherapy were allowed to enter the study. Patients were considered by the treating clinician to have shown insufficient IOP control or poor tolerance to ongoing monotherapy and were likely to benefit from a PF FC formulation. Participants were treatment-naïve for PF tafluprost/timolol FC therapy, had not undergone ophthalmic surgery (within 6 months) and were not pregnant or breast feeding. Patients with any contraindication for tafluprost or timolol treatment were not allowed to enter the study.

Investigators could indicate multiple reasons for selecting patients from the following options: insufficient IOP control or progression of glaucoma on the current monotherapy; conversion of OHT to OAG; poor local tolerance and/or insufficient adherence to the medication used; other reasons.

Study Treatment

Participants instilled one drop daily of PF tafluprost/timolol FC into their affected eye(s), as prescribed/instructed by their ophthalmologist. Study medication was either administered in the morning or evening and the preferred time of instillation was recorded at study visits.

Study Assessments and Outcome Measures

Baseline data were recorded prior to PF tafluprost/timolol FC treatment initiation (±7 days). The eye with the highest baseline IOP value was selected as the "study eye". If IOP was equal in both eyes at baseline, the right eye was selected for analysis.

IOP was measured at each study visit using Goldmann applanation tonometry and the primary endpoint was absolute mean IOP change (mmHg) at Month 6, compared to baseline, following the initiation of PF tafluprost/timolol FC treatment. Secondary endpoints included the mean IOP change from baseline at interim visits (Weeks 4 and 12), the responder rate (defined as those patients demonstrating ≥20% IOP change from baseline at Week 12) and the percentage of responders achieving IOP reductions of at least 25%, 30% and 35% from baseline at each study visit. Sub-analysis examined the mean IOP change from baseline according to diagnostic group (containing >10 patients), baseline monotherapy (PGA or beta-blocker), the reasons for initiating PF tafluprost/timolol FC therapy, baseline presence of dry eye/ocular discomfort symptoms and the chosen time of treatment instillation (morning or evening).

Changes from baseline regarding ocular signs and subjective symptoms were assessed at Week 4, Week 12 and Month 6. Severity of conjunctival hyperemia was reported using a 4-grade scale (none, mild, moderate, severe) and best corrected visual acuity (BCVA) data were collected in decimal, logMAR or fraction (foot or meters) scales and then converted to the decimal scale.[46] Other assessments included corneal fluorescein staining (CFS; Oxford Grade Scale; 0 to V grade), Schirmer's test (mm/5 minutes, with/without anesthesia) and tear break up time (TBUT), measured in seconds (s).[47] Subjective symptom severity was assessed using a 4-grade scale (none, mild, moderate and severe), and the parameters examined comprised dry eye, irritation, itching, foreign body sensation and eye pain.

Investigators used a 3-grade scale (better than prior medication, same as prior medication, worse than prior medication) to indicate their evaluation of treatment effectiveness as well as patient compliance with PF tafluprost/timolol FC therapy, compared with prior monotherapy. Patient assessment of tolerability with PF tafluprost/timolol FC treatment was reported using a 4-grade scale (very good, good, satisfactory, poor). Reported adverse events (AEs) and treatment-related AEs were documented throughout the study period.

Statistical Analysis

ICON Plc (Dublin, Ireland) conducted all statistical analyses on behalf of the VISIONARY study group. Normally distributed data were reported as mean values ± standard deviation (SD) and paired t-test was used for comparisons. Median and interquartile range (IQR) values were given for data that were not normally distributed and Wilcoxon signed rank test was used to assess the change from baseline. Comparisons between Italian and non-Italian patient demographics for age, sex and diagnosis used t-test, Chi-Square and Fisher's Exact test, respectively. Changes from baseline concerning CFS, conjunctival hyperemia and subjective symptoms were assessed using the Bhapkar test.[48] P values <0.05 indicated statistical significance.

Results

Study Population Demographics

Of the 577 patients included in the VISIONARY study full analysis set, 160 participants attended ophthalmology centers in Italy. Table 1 shows baseline study population demographics for study participants in Italy. The mean ± SD age was 68.7 ± 11.5 years (range 27–89 years) and 54.4% of the study participants were female. The most common diagnostic groups were POAG (68.1%), OHT (25.0%), pseudoexfoliation glaucoma (PEX; 2.5%) and normal tension glaucoma (NTG; 1.2%). Most participants (66.3%) were treated with PGA monotherapy prior to baseline, whereas 33.7% were using beta-blocker therapy. Among PGA monotherapy users, 21 (19.8%) were using latanoprost, 33 (31.1%) were on bimatoprost, 31 (29.2%) had been prescribed tafluprost and 21 (19.8%) were using travoprost.

Change in Intraocular Pressure from Baseline

Table 2 reports the mean IOP change at each study visit for patients in Italy. Mean ± SD baseline IOP was slightly lower in the Italian population compared with the European VISIONARY population; 19.6 ± 3.6 mmHg (Italy) versus 21.5 ± 4.5 mmHg (Europe-wide population).[35]

The primary endpoint of absolute mean IOP change at Month 6 was statistically significant for study participants in Italy (p<0.0001; two-sided paired *t*-test). Mean ± SD IOP was reduced from 19.6 ± 3.6 mmHg at baseline to 14.5 ± 2.6 mmHg at Month 6, with a mean ± SD reduction of 5.1 ± 3.7 mmHg (24.1%). The mean reduction in IOP from baseline was statistically significant at each of the interim study visits (p<0.0001; two-sided paired *t*-test). Mean ± SD IOP reduction was 4.8 ± 3.4 mmHg (23.1%) and 5.1 ± 3.4 mmHg (24.7%) at Weeks 4 and 12, respectively. Responder rate in

Table 1 Demographics of the Participants

Demographic/Characteristic	Italy (n=160)
Sex, n (%)	
Male	73 (45.6)
Female	87 (54.4)
Age (years)	
Mean ± SD	68.7 ± 11.5
Range	27–89
Diagnosis, n (%)	
POAG	109 (68.1)
OHT	40 (25.0)
PEX	4 (2.5)
NTG	2 (1.2)
Pigmentary glaucoma	2 (1.2)
Other glaucoma	3 (1.9)
Study eye, n (%)	
Right	108 (67.5)
Left	52 (32.5)
Previous treatment, n (%)	
Beta-blocker therapy	54 (33.7)
PGA therapy	106 (66.3)
IOP at baseline (mmHg), mean ± SD	19.6 ± 3.6
CFS score (Oxford Grade Scale), mean ± SD (n=73)	1.0 ± 1.1
BCVA decimal score, median (IQR) (n=128)	1.0 (0.2)
Schirmer's test (mm/5 minutes), median (IQR) (n=65)	10.0 (11.0)
TBUT (seconds), median (IQR) (n=87)	6.0 (5.0)

Abbreviations: BCVA, best corrected visual acuity; CFS, corneal fluorescein staining; IOP, intraocular pressure; IQR, interquartile range; NTG, normal tension glaucoma; OHT, ocular hypertension; PGA, prostaglandin analogue; POAG, primary open-angle glaucoma; PEX, pseudoexfoliative glaucoma; SD, standard deviation; TBUT, tear film break up time.

Table 2 Change in Intraocular Pressure from Baseline at Week 4, Week 12 and Month 6

Visit	N	Mean ± SD IOP (mmHg)	Mean ± SD Reduction in IOP from Baseline (mmHg)	Mean Percentage Reduction in IOP from Baseline (%)	P value[a]
VISIONARY study population in Italy					
Baseline	160	19.6 ± 3.6			
Week 4 (± 7 days)	158	14.8 ± 2.5	4.8 ± 3.4	23.1	<0.0001
Week 12 (± 7 days)	153	14.4 ± 2.4	5.1 ± 3.4	24.7	<0.0001
Month 6 (± 7 days)	160	14.5 ± 2.6	5.1 ± 3.7	24.1	<0.0001

Note: [a]Significance testing using two-sided paired *t*-test for change in mean IOP from baseline to Week 4, Week 12 and Month 6.
Abbreviations: IOP, intraocular pressure, N, number of patients; SD, standard deviation.

the Italian cohort at Month 6 was 68.1%, 48.7%, 36.2% and 26.9% based on data cutoff values for change in mean IOP from baseline of ≥20%, ≥25%, ≥30% and ≥35%, respectively (Figure 1).

Sub-analysis of Italian data according to baseline diagnosis showed that the respective mean ± SD IOP at baseline was 19.2 ± 3.7 mmHg, 20.9 ± 3.2 mmHg, 21.2 ± 4.1 mmHg and 15.0 ± 1.4 mmHg for patients with POAG, OHT, PEX and NTG. At Month 6, IOP reductions of 22.5%, 30.3%, 28.5% and 16.5% were achieved for those with POAG, OHT, PEX and NTG, respectively. The IOP reduction from baseline was statistically significant at Month 6 among those with POAG and OHT (p<0.0001; two-sided paired *t*-test). Statistical analysis was not conducted for the NTG and PEX subgroups because the numbers were too low.

Subgroup analysis according to prior monotherapy showed that the mean ± SD IOP was reduced from 19.5 ± 3.7 mmHg at baseline to 14.7 ± 2.3 mmHg at Month 6 among those previously treated with PGA monotherapy, representing a reduction from baseline of 4.8 ± 3.6 mmHg (22.7%; p<0.0001). Prior PGA users were treated with latanoprost (n=21), tafluprost (n=31), bimatoprost (n=33) and travoprost (n=21) with respective mean ± SD IOP at baseline being 19.9 ± 3.7 mmHg, 19.8 ± 2.7 mmHg, 19.4 ± 4.6 mmHg and 18.9 ± 3.6 mmHg. At Month 6, mean relative reductions in IOP from baseline were statistically significant in each PGA subgroup (p<0.0001; two-sided paired *t*-test); 27.4% (latanoprost),
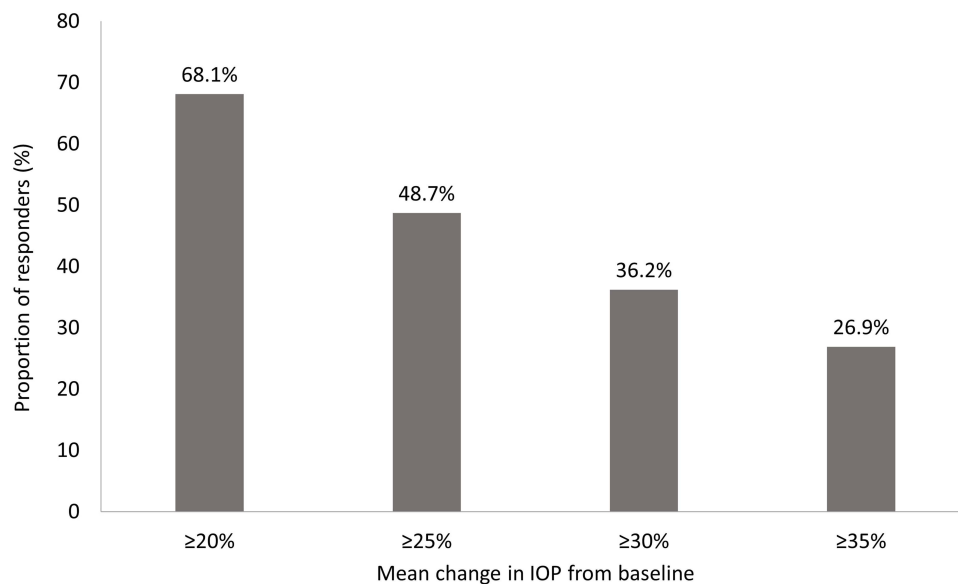

Figure 1 Percentage of responders according to different intraocular pressure reduction cutoff values at Month 6 (full analysis set). The graph shows the percentage of patients achieving IOP reductions from baseline of ≥20%, ≥25%, ≥30% and ≥35% at Month 6.
Abbreviation: IOP, intraocular pressure.

24.6% (tafluprost), 21.0% (bimatoprost) and 18.0% (travoprost). Among prior beta-blocker users, the mean ± SD IOP was reduced from 19.8 ± 3.5 mmHg at baseline to 14.2 ± 3.9 mmHg at Month 6, reaching a reduction of 5.6 ± 3.9 mmHg (26.8%; p<0.0001; two-sided paired *t*-test).

Investigators could indicate multiple reasons for ceasing prior monotherapy and initiating PF tafluprost/timolol FC therapy. The main reasons provided were insufficient IOP control (64.4%), poor local tolerance (25.0%), progression of glaucoma (23.1%), poor compliance (3.1%) and conversion of OHT to an initial glaucomatous damage (0.6%). At Month 6, participants switching to PF tafluprost/timolol FC therapy due to insufficient IOP control and/or progression of glaucoma showed a mean relative IOP reduction of 26.8% from baseline (p<0.0001; two-sided paired *t*-test). Those switching due to poor tolerance with their previous monotherapy demonstrated a mean IOP change from baseline of 17.9% at Month 6 (p=0.0003; two-sided paired *t*-test). Patients who did not have dry eye/ocular discomfort symptoms before initiating study treatment demonstrated a mean ± SD IOP lowering from baseline of 5.6 ± 3.2 mmHg (26.9%) at Month 6 (p<0.0001; two-sided paired *t*-test), whereas participants with these symptoms (of any severity) at baseline showed a mean ± SD IOP reduction of 4.7 ± 4.1 mmHg (22.2%; p<0.0001; two-sided paired *t*-test). Most participants (85.0%) instilled PF tafluprost/timolol FC treatment in the evening. The mean ± SD relative IOP reduction from baseline in this group at Month 6 was 4.9 ± 3.6 mmHg (23.7%; p<0.0001; two-sided paired *t*-test). Patients who instilled study treatment in the morning achieved a reduction of 4.9 ± 4.6 mmHg (22.2%) at Month 6 (from baseline p=0.0006; two-sided paired *t*-test).

Ocular Signs and Symptoms

Mean ± SD and median (IQR) CFS score at baseline and at each study visit are shown in Table 3. Mean ± SD CFS score at baseline in Italy was 1.0 ± 1.1. CFS score was significantly reduced from baseline at all visits during the study period. At Month 6, mean ± SD CFS score was 0.6 ± 0.6, providing a reduction of 0.5 ± 1.1 (p=0.0004; two-sided paired *t*-test). The median (IQR) CFS score at baseline was 1.0 (2.00). At Week 4, Week 12 and Month 6 the median (IQR) CFS score was 0.0 (1.00). Median CFS score was reduced by 0.5 at Week 4 (p=0.0030) and by 1.0 at Week 12 (p=0.0013) and Month 6 (p=0.0003; Wilcoxon signed rank test).

Among those switching to the PF tafluprost/timolol FC due to insufficient IOP control, mean ± SD CFS grade was reduced from 2.0 ± 1.1 at baseline to 1.6 ± 0.6 at Month 6. Among those switching treatment due to poor local tolerance with PGA/beta-blocker monotherapy, mean ± SD CFS grade was reduced from 2.8 ± 1.1 at baseline to 1.8 ± 0.7 at Month 6. Patients who switched therapy due to insufficient IOP control demonstrated significantly greater reductions in mean CFS score at Month 6, compared to those switching due to poor local tolerance (p=0.0376; two-sided paired *t*-test).

Table 3 Italian VISIONARY Study Population: Change in Corneal Fluorescein Staining Score (Oxford Grade Scale) During the Study Period

	N[a]	CFS Score	Change in CFS Score	*P* value
Mean ± SD				
Baseline	73	1.0 ± 1.1		
Week 4 (± 7 days)	64	0.7 ± 0.9	0.3 ± 0.9	0.0037[b]
Week 12 (± 7 days)	59	0.6 ± 0.8	0.4 ± 1.0	0.0020[b]
Month 6 (± 45 days)	64	0.6 ± 0.6	0.5 ± 1.1	0.0004[b]
Median (IQR)				
Baseline	73	1.0 (2.0)		
Week 4 (± 7 days)	64	0.0 (1.0)	0.5	0.0030[c]
Week 12 (± 7 days)	59	0.0 (1.0)	1.0	0.0013[c]
Month 6 (± 45 days)	64	0.0 (1.0)	1.0	0.0003[c]

Notes: [a]Number of patients with data available at baseline and at the relevant study visit. [b]significant testing using two-sided paired *t*-test. [c]Wilcoxon signed rank test.
Abbreviations: CFS, corneal fluorescein staining; IQR, interquartile range; N, number of patients; SD, standard deviation.

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Schirmer's test and TBUT showed slight improvement without reaching a statistically significant change. Median (IQR) Schirmer's test result was increased from 10.0 (11.0) mm/5 minutes at baseline to 11.0 (12.0) mm/5 minutes at Month 6 (p=0.628; two-sided Wilcoxon signed rank test). Median (IQR) TBUT increased from 6.0 (5.0) s at baseline to 8.0 (4.0) s at Month 6 (p=0.156; two-sided Wilcoxon signed rank test). The median (IQR) BCVA decimal score was unchanged at Month 6 from baseline (1.0 [0.2]).

Severity of conjunctival hyperemia was significantly reduced from baseline, at all study visits through Month 6 in the Italian dataset (p<0.0001; Bhapkar test). Conjunctival hyperemia was mild or absent at baseline for 60.0%, 82.6%, 42.3% and 47.7% of prior PGA users on latanoprost, tafluprost, bimatoprost and travoprost, respectively (Figure 2). Moderate or severe hyperemia was reported for the remaining patients in these subgroups at baseline. Reductions in hyperemia were observed across each PGA subgroup, although statistical significance could not be assessed due to low patient numbers. Conjunctival hyperemia was either mild or absent in 91.8% of patients on beta-blocker therapy at baseline. At Month 6, the severity of conjunctival hyperemia was either stabilized (43.2%) or improved (35.1%) among prior beta-blocker users.

Despite subjective symptoms being typically mild or absent at baseline, statistically significant reductions from baseline were reported at Month 6 regarding severity of dry eye symptoms (p<0.001; Bhapkar test), irritation (p=0.0002; Bhapkar test) and foreign body sensation (p=0.0008; Bhapkar test). The change in severity of itching (p=0.1975; Bhapkar test) and eye pain (p=0.2184; Bhapkar test) symptoms was not significant at Month 6, compared with baseline.

Physician and Patient Assessments

When comparing the clinical effectiveness against baseline monotherapy, most investigators (78.8%) reported improved IOP control with PF tafluprost/timolol FC treatment at Month 6, whereas 19.2% of them considered the study treatment to be equally effective. Investigators perceived patient compliance with PF tafluprost/timolol FC treatment to be the same as (46.4%) or improved (52.3%), compared with baseline medication, at Month 6. Patients typically reported tolerability
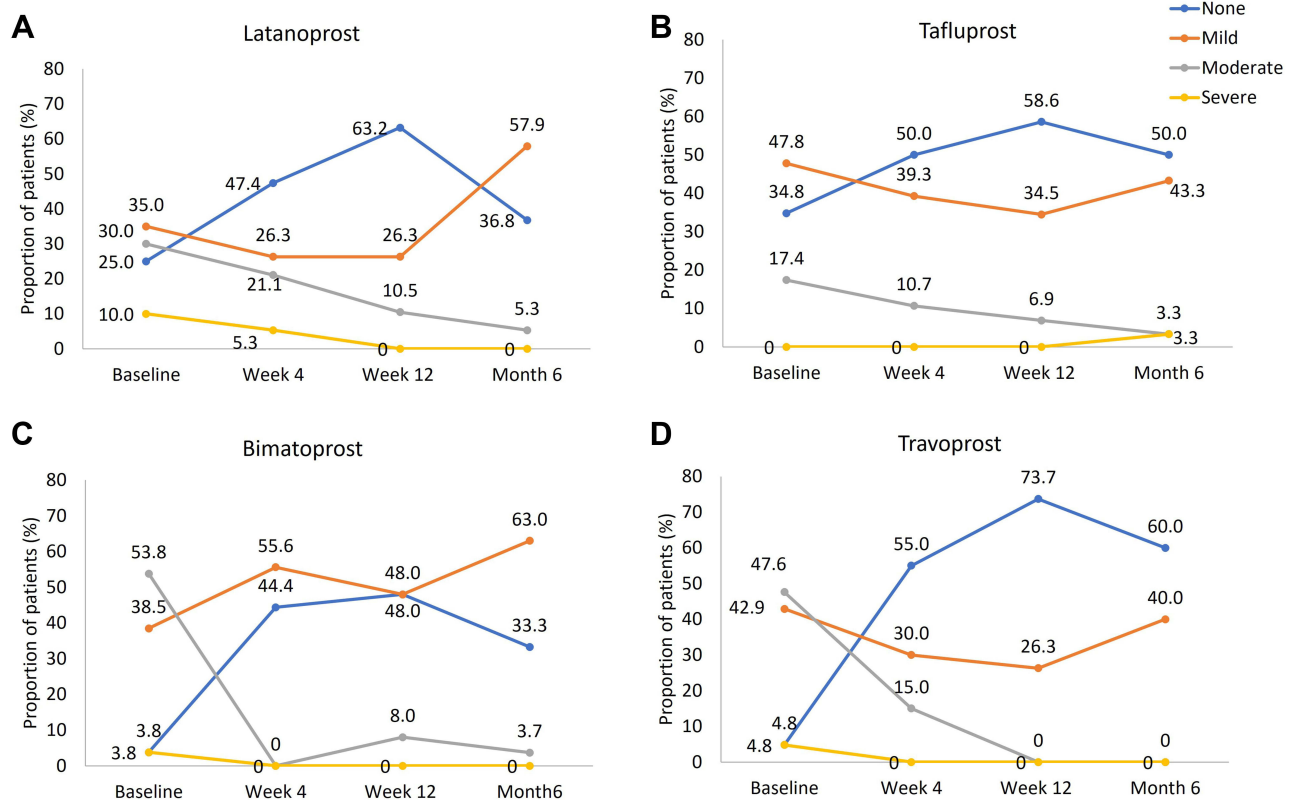

Figure 2 Change in conjunctival hyperemia severity according to the previous prostaglandin analogue treatment (full analysis set). Severity of conjunctival hyperemia at each study visit for those previously treated with (A) latanoprost, (B) tafluprost, (C) bimatoprost or (D) travoprost.

Table 4 Adverse Events Reported in Italy During the Study Period

System/Organ Class	Number of AEs
Eye disorders	
Conjunctival hyperemia	1
Growth of eyelashes	1
Total	**2**

Abbreviation: AEs, adverse events.

with PF tafluprost/timolol FC treatment to be good or very good at Week 4 (87.4%), Week 12 (94.0%) and Month 6 (91.7%).

Discontinuations from Study Treatment and Safety Outcomes

Overall, 19 patients (11.9%) discontinued their PF tafluprost/timolol FC treatment during the study period. Investigators were allowed to report multiple reasons for discontinuation from the study treatment. Reasons for ceasing treatment were poor local tolerance (4 patients), poor compliance (1 patient) and other reasons (3 patients). Data were missing for 11 patients. No discontinuation was attributed to insufficient IOP control.

In total, 2 AEs were reported by 2 different patients during the 6-month study period (Table 4). All AEs were non-serious and mild in severity, and 1 case of eyelash growth was considered to be related to study treatment.

Discussion

The current analysis of data from Italian patients, predominantly with POAG and OHT, participating in the Europe-wide VISIONARY study demonstrated that a rapid, sustained and significant IOP reduction from baseline was achieved when switching from PGA or beta-blocker monotherapy to the PF tafluprost/timolol FC. Statistically and clinically significant IOP reduction was shown from Week 4 with PF tafluprost/timolol FC therapy and continued over the 6-month study period. Treatment effectiveness, tolerability and compliance were rated as high with PF tafluprost/timolol FC therapy, with only 2 non-serious and mild AEs reported, while the severity of most ocular signs and symptoms was significantly reduced at Month 6. The study was conducted in a real-world setting that reflected usual clinical practice regarding glaucoma and OHT treatment changes in Italy. No wash-out period was implemented during the therapeutic switch, providing an indication of the outcomes that ophthalmologists may observe in their own centers when stepping up to PF tafluprost/timolol FC therapy from prior monotherapy.[35,37] The Italian data analysis was broadly aligned with that of the full Europe-wide VISIONARY study population, highlighting the reproducibility of treatment results with PF tafluprost/timolol FC therapy.[35,41–44] The current analysis represents the largest real-world/randomized study of PF tafluprost/timolol FC therapy conducted to date in Italy and the Italian cohort represents the largest country-level subgroup included in the VISIONARY study.[35,41–44] These data strengthen the existing evidence base regarding the role of PF tafluprost/timolol FC therapy in clinical practice.[11,31–37]

Italian participants achieved a mean IOP reduction from baseline of 5.1 ± 3.7 mmHg at Month 6 (24.1%; p<0.0001), which was similar to the primary outcome shown in the full VISIONARY study population (5.7 ± 4.1 mmHg [24.9%; p<0.0001]), despite the Italian cohort having a slightly lower baseline IOP (19.6 ± 3.6 mmHg) compared with the Europe-wide dataset (21.5 ± 4.5 mmHg) and pre-treatment pressure being predictive of IOP reduction.[35,45] Published baseline IOP levels from the Hungarian (20.8 mmHg), UK (22.0 mmHg), Russian (23.8 mmHg) and Spanish (21.9 mmHg) VISIONARY datasets suggest that ophthalmologists in Italy tended to select PGA/beta-blocker monotherapy users with lower pressures for treatment intensification to FC therapy compared to other countries.[41–44] In addition, the data from Italy indicate that even patients with IOP values below 20 mmHg may experience significant clinical benefit following a switch to PF tafluprost/timolol FC.[45] Indeed, the relative change in IOP at Month 6 observed in the Italian dataset was slightly greater than the reductions published for Hungary and was similar to those for the UK and Spain where the starting IOP was marginally higher.[41,42,44] At Month 6, the majority of the Italian ophthalmologists considered

PF tafluprost/timolol FC to be associated with better IOP control (78.8%), compared with previous monotherapy, and this is likely to have been supported by the reassuringly high levels of treatment compliance observed by investigators during this real-world study. Change in IOP was significant, regardless of whether patients instilled their medication in the morning or evening. The fact that the majority administered their medication at night-time might be related to country-wide clinical practice and recommendations on timing in Italy.

Response rates showed that approximately 68% of the participants achieved an IOP reduction ≥20% at Month 6. In addition, around 49%, 36% and 27% achieved an IOP reduction exceeding 25%, 30% and 35%, respectively. These outcomes were similar to the published Europe-wide responder rates, reflecting the clinically meaningful IOP reductions that may be achieved when changing to PF tafluprost/timolol FC treatment from prior PGA or beta-blocker monotherapy.[35,41–44] Participants with POAG and OHT achieved significant IOP reductions from baseline (p<0.0001) and those with NTG and PEX demonstrated numerical improvements. Italian patients with OHT and PEX achieved the highest mean IOP reductions from baseline (30.3% and 28.5%, respectively), whereas the same subgroups in the Europe-wide analysis demonstrated mean reductions of 26.1% and 17.6%.[35] The IOP reduction achieved in Italy for the OHT subgroup was impressive, particularly as the starting IOP was lower in this group (20.9 ± 3.18 mmHg) than the corresponding European subgroup (22.3 ± 4.1 mmHg).[35,45]

Patients treated with beta-blocker monotherapy at baseline achieved greater IOP reductions (26.8%) at Month 6, compared with prior PGA users (22.7%). These data are similar to the findings for the Europe-wide VISIONARY population regarding IOP reductions in prior beta-blocker (28.5%) and PGA (23.6%) users.[35] Italian patients previously using latanoprost, tafluprost and bimatoprost demonstrated mean IOP reduction of 21.0–27.4% at Month 6, which was comparable with the European VISIONARY dataset (20.5–25.9%).[35] Italian patients previously using travoprost showed a smaller IOP reduction at Month 6 (18.0%) compared with other PGA user groups and the travoprost subgroup in the European VISIONARY population (21.3%).[35] However, baseline IOP was slightly higher in the other PGA user groups and the Europe-wide travoprost subgroup, and this may have influenced the difference in outcomes observed here.[35,45] Subjects enrolled in Italy due to insufficient IOP control and/or progression of OAG demonstrated greater IOP reductions (26.8%) compared to those who were switched due to poor tolerance with prior medication (17.9%), which was expected – based upon the published results for the Europe-wide study population.[35]

A significant IOP reduction was achieved irrespective of whether patients had dry eye/ocular discomfort symptoms at baseline (p<0.0001), although the presence of symptoms was associated with a slightly smaller mean reduction in IOP at Month 6 (22.2%), versus those without dry eye (26.9%). PF tafluprost/timolol FC therapy was associated with improved tolerability outcomes and indicators of ocular health, regardless of prior monotherapy. Significant improvements were observed concerning conjunctival hyperemia across the whole Italian cohort (p<0.0001) and regardless of the prior PGA therapy used. These data reflect outcomes in the Europe-wide study population.[35] Although median TBUT and Schirmer's test improved, the changes from baseline were not significant. BCVA remained unchanged at Month 6. Similar future studies would benefit from the collection and reporting of additional data relating to visual field parameters at baseline and follow-up study visits to establish the impact of PF tafluprost/ timolol FC treatment on the rate of disease progression and associated sight loss.

Despite ocular symptoms being reported as generally mild or absent at baseline, significant improvements in severity were demonstrated concerning dry eye (p<0.001), irritation (p=0.0002) and foreign body sensation (p=0.0008) at Month 6, while eye pain and itching were unchanged. Given that people with glaucoma are susceptible to OSD, and even PF PGA formulations may be associated with tolerability issues (potentially caused by eye drops excipients), any improvements in signs or symptoms of ocular surface health and/or tolerability that accompany a switch to topical PF FC therapy from prior monotherapy may be welcomed by patients and their treating clinician.[16–29,49,50]

Patient-reported tolerability was typically good/very good (91.7%) at Month 6 and only 2 non-serious AEs were reported; both were mild in severity and 1 (eyelash growth) was considered to be treatment-related. Early termination was recorded in 19 patients (11.9%). Multiple reasons could be given for discontinuation from study treatment and the known reasons for study discontinuation were poor ocular tolerance (4 patients), poor compliance (1 patients) and other reasons (3 patients). It should be noted that no discontinuations were attributed to insufficient IOP control. Due to the observational nature of the investigation the reason of study discontinuation was not clarified for 11 participants. This loss of information, resulting from participants choosing not to attend all visits, represents a limitation of the study that is also reflective of the practical challenges with patient follow-up faced by ophthalmologists in routine clinical practice. As data were collected during routine ophthalmology appointments in the

VISIONARY study, it was not possible to measure diurnal IOP variation to understand the level of IOP control (and fluctuation) achieved over a 24-hour period with PF tafluprost/timolol FC therapy. Future studies would also benefit from a design that allowed deeper analysis of IOP change alongside indicators of ocular surface improvement and the inclusion of a control group so that outcomes with PF tafluprost/timolol FC therapy may be compared against those for patients treated with other PGA/timolol FC treatments.

Conclusions

In a real-world setting, Italian patients with OAG/OHT demonstrated statistically and clinically significant reductions in IOP following a switch to PF tafluprost/timolol FC treatment from PGA or beta-blocker monotherapy. Despite some minor differences in baseline characteristics, the clinical outcomes reported in Italy were similar to those of the European VISIONARY dataset. A significant IOP reduction was observed from Week 4 and maintained over a 6-month period. PF tafluprost/timolol FC was generally well tolerated, with most ocular signs and symptoms being significantly reduced in severity during the study period.

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Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki of 1964, as revised in 2013, and 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 protocol was approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each center/institution and written informed consent was obtained from subjects prior to enrolment.

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Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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