Clinical Ophthalmology

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CLINICAL TRIAL REPORT

# Prospective, non-interventional, multicenter study of the intraocular pressure-lowering effects of prostaglandin analog/prostamide-containing therapies in previously treated patients with open-angle glaucoma or ocular hypertension

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This article was published in the following Dove Press journal:
Clinical Ophthalmology
19 April 2017
Number of times this article has been viewed

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**Objective:** The objective of this study was to assess the intraocular pressure (IOP)-lowering efficacy, tolerability, safety, and usage patterns of prostaglandin analog/prostamide (PGA/P)-containing topical ocular hypotensives in ocular hypertension (OHT) and primary open-angle glaucoma in the Turkish clinical setting.

**Methods:** This non-interventional, multicenter study enrolled previously treated patients who failed to achieve target IOP (or experienced unacceptable adverse events [AEs]) and were prescribed a PGA/P-containing IOP-lowering agent. Treatment was initiated at baseline (V1), and patients returned at weeks 4–6 (V2) and 8–12 (V3). The primary efficacy measure was the change in IOP from baseline at V3 in each eye. The secondary measures were physician's assessment of IOP-lowering efficacy, patients (%) reaching target IOP determined at V1, hyperemia score, physician and patient assessment of study treatment tolerability at V3, and AE frequency/severity. A subgroup analysis of patients receiving the most common study treatment was conducted. All analyses were performed using the safety population (patients who received one or more doses and had any data available).

**Results:** Of 358 enrolled patients, 60.6% had primary open-angle glaucoma, 29.9% had secondary open-angle glaucoma (protocol amendment), and 13.1% had OHT; 13 patients had multiple diagnoses. At V3, the mean IOP change from baseline was ≥–4.2 mmHg (≥21.1%). IOP met or was lower than the target in 81.7% of patients, 95% exhibited none to mild conjunctival hyperemia (most common AE), and tolerability was rated good/very good by >91.1% of patients and physicians. The results were similar in patients who received the most common study treatment, bimatoprost 0.03%/timolol 0.5% (bim/tim; n=310).

**Conclusion:** PGA/P-containing medications, including bim/tim, significantly reduced IOP in previously treated patients with open-angle glaucoma or OHT; most reached their target IOP or an IOP even lower than their target and reported good/very good tolerability. PGA/P-containing medications such as bim/tim should be considered as a safe, effective therapeutic option for Turkish patients who exhibit poor response, tolerance, or adherence to their previous therapy.

**Keywords:** glaucoma, ocular hypertension, bimatoprost, timolol, prostaglandin analog, prostamide

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## Introduction

According to recent estimates, glaucoma will affect 76 million people worldwide in 2020 and 111.8 million people in 2040, up from 64.3 million people in 2013.[1]



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Elevated intraocular pressure (IOP) is a major risk factor associated with disease progression and visual impairment in open-angle glaucoma (OAG; the most common form of the disease),[2–5] but most patients can retain visual function over their lifetime if properly treated with topical ophthalmic hypotensive drugs.[3,4,6]

β-Blockers such as timolol (which inhibit the production of aqueous humor and primarily affect diurnal IOP) and prostaglandin analogs/prostamides (PGAs/Ps) such as latanoprost and bimatoprost (which enhance aqueous humor outflow and have a 24-hour IOP-lowering effect)[7–11] are among the agents recommended as first-line therapy by the European Glaucoma Society guidelines.[4] For patients who require combination therapy to reach their target IOP, the PGA/P-based fixed combination bimatoprost 0.03%/timolol 0.5% (bim/tim; Ganfort®; Allergan plc, Dublin, Ireland) has been shown to provide greater IOP reduction than bimatoprost and timolol used as monotherapies[12–14] or adjunctive therapies.[13,15] In patients whose IOP was inadequately controlled on previous therapy, bim/tim has also been shown to provide greater IOP lowering than travoprost/timolol, latanoprost/timolol, and dorzolamide/timolol fixed combinations (in prospective clinical studies).[13,16–23] Moreover, a significantly lower incidence[12,14] of conjunctival hyperemia (the most common adverse event [AE] associated with PGA/P ophthalmic solutions) has been reported with bim/tim in treatment-naïve and previously treated patients compared with PGA/P monotherapy. A reduction in conjunctival hyperemia severity has also been observed in patients previously treated with PGAs/Ps.[24]

Despite the demonstrated efficacy and tolerability of bim/tim, its availability in Europe since 2006,[25] and current wide usage,[26] bim/tim use remains relatively limited in Turkey. The objective of this study was to assess the IOP-lowering effect and tolerability of PGA/P-containing ocular therapy, which includes bim/tim, in previously treated patients with ocular hypertension (OHT) or primary open-angle glaucoma (POAG) in the Turkish clinical setting.

# Methods

## Study design

This prospective, observational, non-interventional, open-label, non-randomized, multicenter study (ClinicalTrials.gov registration number: NCT01735214) was conducted in clinical sites throughout Turkey in accordance with the principles of Good Clinical Practice, the International Conference on Harmonisation, the Declaration of Helsinki, and all applicable local laws. The protocol was approved centrally by the ethics committee of the Istanbul University Cerrahpaşa Medical Faculty, prior to study initiation. Written informed consent was obtained from all patients before data collection at baseline (visit 1).

## Participants

Patients with POAG or OHT who presented consecutively at each site, were ≥18 years of age, previously treated with monotherapy or combination therapy in one or both eyes, and required treatment with a PGA/P-containing topical IOP-lowering therapy (a decision made prior to, and without consideration of, study participation) were eligible. Patients who were pregnant/nursing or had contraindications to PGA/P-containing medications were excluded (per the approved prescribing information for each agent). There were no other specific criteria for inclusion or exclusion.

## Treatment and assessments

The visit at which the PGA/P-containing medication was prescribed was considered the baseline visit (V1). The hypotensive agent and dosing regimen were selected by the physicians per their usual standard of care. Patients were instructed to administer their study treatment once daily in the evening (if latanoprost, travoprost, or bimatoprost, for example, was prescribed) or once daily in the morning (if bim/tim, for example, was prescribed), per the respective product prescribing information. On the visit day, patients in the bim/tim group were asked to administer eyedrops after all assessments were completed.

At V1 (before the new treatment was initiated), the following information was recorded: patient demographics, time since first diagnosis, glaucoma diagnosis in each eye, IOP value, treatment status (treatment-naïve or previously treated), the most recent IOP-lowering medications used prior to the visit, and the reason(s) a PGA/P-containing therapy was being initiated. Target IOP for each eye of individual patients was also determined at V1 by the treating physician per standard clinical practice. Subsequent visits were scheduled at approximately the same time of day (preferably between 8:00 and 10:00 am) at 4–6 weeks (V2) and 8–12 weeks (V3) post treatment initiation per standard clinical practice. Alternatively, a visit was scheduled at early discontinuation.

All diagnostic and care procedures were conducted at physician discretion in keeping with local standards of medical care. IOP was measured using Goldmann applanation tonometry (unmasked) at V1 (prior to the first dose of PGA/P-containing study treatment) and at each of the subsequent visits. At the final visit, IOP-lowering efficacy was rated by

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each physician and categorized as IOP lower than target, reaching target, lower but did not reach target, unchanged, or increased. In addition, tolerability was assessed using the standard Allergan photonumeric bulbar conjunctival hyperemia grading scale[27]: 0/none (normal), +0.5/trace (trace flush, reddish pink), +1/mild (mild flush, reddish color), +2/moderate (bright red color), and +3/severe (deep, bright diffuse redness). Patients and physicians also rated overall tolerability as very good, good, moderate, or poor. The type and occurrence of AEs, as well as discontinuations, were documented throughout the study.

## Outcome measures and analyses

The primary efficacy measure was the change in IOP (mmHg) from baseline at V3 in each eye. Secondary measures included physician's assessment of the IOP-lowering efficacy of the study treatment, the proportion of patients reaching the target IOP determined at V1, bulbar hyperemia score, physician's and patient's overall assessment of the study treatment tolerability at V3, as well as the frequency and severity of AEs (categorized by the Medical Dictionary for Regulatory Activities preferred term). For all discontinuations, every attempt was made to document the reason(s) and outcomes. A supplemental subgroup analysis, which included only patients who received the most common study treatment, was conducted for all measures.

Continuous variables were summarized by number (n), mean, and standard deviation (SD). Categorical variables were recorded as frequency distribution. Descriptive statistical analyses were performed using SPSS (v16 or higher) software (IBM Corporation, Armonk, NY, USA) and a two-sided alpha level of 0.05. Nominal and continuous variables were analyzed with the Chi-square and Wilcoxon signed-rank tests, respectively. All analyses used observed values (ie, without imputation for missing values) in the safety population (ie, all patients who received at least one dose of PGA/P-containing therapy and had any data available).

Because of the non-interventional character of the study, protocol violations were not analyzed, and no patient was excluded from analyses of safety and efficacy. Enrollment was planned for 400 patients but was not based on formal statistical hypothesis testing.

# Results

## Primary analysis

### Patient demographics and characteristics at baseline

Between May 2013 and April 2014, a total of 358 patients were enrolled from 11 centers in Turkey. One site failed to enroll patients, preventing achievement of the planned number of participants. Although the protocol specified that patients with POAG or OHT were eligible for enrollment, patients with secondary glaucoma were also included (due to a relatively high prevalence): 90.5% had OAG (POAG, 60.6%; pseudoexfoliation glaucoma, 28.8%; pigmentary glaucoma, 1.1%) and 13.1% had OHT (Table 1). A total of 13 patients had multiple diagnoses (eg, POAG in one eye and OHT in the other eye).

**Table 1** Demographics and patient characteristics at baseline

| Baseline characteristics | Total population (N=358) | Bim/tim subgroup (n=310)[a] |
|---|---|---|
| Gender, n (%) | | |
| Female | 178 (49.7) | 157 (50.6) |
| Male | 180 (50.3) | 153 (49.4) |
| Mean age, years (SD) | 63.2 (12.0) | 63.5 (11.4) |
| <61, n (%) | 136 (38.0) | 116 (37.4) |
| ≥61, n (%) | 222 (62.0) | 194 (62.6) |
| Mean baseline IOP, mmHg (SD) | | |
| Right eye | 19.8 (5.1) | 20.0 (5.4) |
| Left eye | 19.9 (5.5) | 20.1 (5.5) |
| Diagnosis, n (%)[b] | | |
| OAG[c] | 324 (90.5) | 278 (89.7) |
| Right eye | 300 (83.8) | 257 (82.9) |
| Left eye | 302 (84.4) | 256 (82.6) |
| OHT | 47 (13.1) | 45 (14.5) |
| Right eye | 40 (11.2) | 38 (12.3) |
| Left eye | 44 (12.3) | 42 (13.5) |
| Mean time since diagnosis, years (SD) | 5.6 (5.8) | 4.6 (5.4) |
| Years since diagnosis, n (%) | | |
| <5 | 207 (57.8) | 203 (65.5) |
| 5–10 | 87 (24.3) | 75 (24.2) |
| ≥11 | 64 (17.9) | 32 (10.3) |
| Previously treated, n (%) | 358 (100) | 310 (100) |
| Previous hypotensive therapy[d,e] | | |
| Monotherapy | 260 (72.6) | 212 (68.4) |
| Latanoprost | 143 (39.9) | |
| Brimonidine | 70 (19.6) | |
| Travoprost | 54 (15.1) | |
| Bimatoprost | 40 (11.2) | |
| Timolol | 31 (8.7) | |
| Betaxolol | 28 (7.8) | |
| Brinzolamide | 17 (4.7) | |
| Carteolol | 16 (4.5) | |
| Combination therapy | 98 (27.4) | 98 (31.6) |
| Dorzolamide/timolol | 108 (30.1) | |
| Latanoprost/timolol | 27 (7.5) | |
| Brimonidine/timolol | 18 (5.0) | |
| Travoprost/timolol | 11 (3.1) | |

**Notes:** [a]Eight patients received adjunctive therapy in addition to bim/tim. [b]The total is >100% because 13 patients had multiple diagnoses. [c]OAG included primary OAG (n=217), pseudoexfoliation glaucoma (n=103), and pigmentary glaucoma (n=4). [d]Patients with multiple diagnoses could be treated with more than one therapy, or – in this section of the table only – could be counted more than once in one drug category. [e]Therapies used by ≥3% of patients are shown.

**Abbreviations:** Bim/tim, bimatoprost 0.03%/timolol 0.5%; IOP, intraocular pressure; OAG, open-angle glaucoma; OHT, ocular hypertension; SD, standard deviation.

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Mean age ± SD was 63.2±12.0 years, mean time from diagnosis was 5.6±5.8 years, and mean average baseline IOP was 19.9±5.3 mmHg (Table 1). More patients (39.9%) were recorded as having been previously treated with latanoprost than any other ocular hypotensive agent (Table 1).

### Study treatment

At baseline, 310 (86.6%), 32 (8.9%), 12 (3.4%), and 4 (1.1%) patients had been prescribed bim/tim (Ganfort®), latanoprost (Xalatan®; Pfizer Inc., Collegeville, PA, USA, or Glokoprost; Generica, Istanbul, Turkey), travoprost (Travatan®; Alcon, Fort Worth, TX, USA), and bimatoprost (Lumigan®; Allergan plc), respectively, to replace their previous therapy. There was no gap between termination of previous therapy and initiation of PGA/P-containing therapy in 323 (90.2%) patients; 13 (3.6%), 6 (1.7%), and 8 (2.3%) patients had stopped their previous treatment <2, 2–4, and >4 weeks before initiating study treatment, respectively. The main reason for switching to a PGA/P-containing therapy was insufficient IOP reduction with previous therapy (76.8%; Table 2), and the mean duration of study treatment was 10.9±6.1 weeks (median, 10.3 weeks; range, 0.3–57 weeks); 49.2% and 27.9% of patients were treated for 9–12 and ≥13 weeks, respectively.

### Efficacy

When the data reported by the clinicians were analyzed, it was determined that the mean/median target IOP at study initiation was 16 mmHg for each eye, ranging from 7 to 24 mmHg. At the final visit, mean IOP was statistically significantly reduced from baseline in the right and left eyes (Figure 1), and the mean IOP change from baseline (primary end point) ranged from −4.2 to −4.5 mmHg. Among the 323 patients with available data at study end, physician-rated IOP-lowering efficacy indicated that IOP met or was lower than target IOP in 81.7% (n=264) of patients; 12.1% (n=39) benefited from their study treatment but did not reach their target IOP, and IOP remained unchanged in 0.9% (n=3) of patients, while it increased in 5.3% (n=17).

**Table 2** Reasons for prescribing PGA/P-containing therapy

| Reasons[a] | Total population (N=358), n (%) | Bim/tim subgroup (n=310)[b], n (%) |
|---|---|---|
| Insufficient IOP reduction | 275 (76.8) | 236 (76.1) |
| Evidence of disease progression | 42 (11.7) | 41 (13.2) |
| Poor tolerability of previous treatment | 37 (10.3) | 30 (9.7) |
| Lack of compliance with prior treatment | 37 (10.3) | 37 (11.9) |
| Other reason | 13 (3.6) | 9 (2.9) |

**Notes:** [a]Some patients had more than one reason to switch to a PGA/P-containing therapy. [b]Eight patients also received adjunctive hypotensive therapy.
**Abbreviations:** Bim/tim, bimatoprost 0.03%/timolol 0.5%; IOP, intraocular pressure; PGA/P, prostaglandin analog/prostamide.

### Tolerability, safety, and discontinuations

Photonumeric bulbar conjunctival hyperemia grading indicated that 95% of patients with available data exhibited none to mild hyperemia at the final visit (Table 3). Notably, the proportion of patients that experienced conjunctival hyperemia with study treatment was similar whether they had been diagnosed with OAG or OHT within the prior 5, 5–10, or ≥11 years ($P$=0.224, Chi-square test; Table 4).

Overall, treatment tolerability was rated as good or very good by 92.2% of physicians (297/322 with ratings) and by 91.1% of patients (287/315 with ratings); 2.5% (n=8) of physicians and 1.9% (n=6) of patients rated tolerability as poor, while 5.3% (n=17) and 7.0% (n=22) rated it as moderate, respectively. A total of 48 (13.4%) patients reported at least one treatment-related AE, conjunctival hyperemia being the most frequent (Table 5). Consistent with this assessment, the number of patients who discontinued the study due to treatment-related AEs was 27 (8.3% of 326 patients with available data).

## Post hoc subgroup analysis

In the subgroup of patients (n=310) who received the most common study treatment, bim/tim, the demographics, baseline characteristics, and reasons for switching from their previous therapy to a PGA/P-containing therapy were similar to those of the total population (Tables 1 and 2). The mean duration of study treatment was 10.9±6.6 weeks (median: 10.3 weeks; range: 0.3–57 weeks), and 42.9% and 31.1% of patients were treated for 9–12 and ≥13 weeks, respectively, similar to what was reported earlier for the total population.

At the final visit, both eyes in this subgroup exhibited a reduction in mean IOP from baseline that was statistically significant and nearly identical to that of the total population (Figure 1); the mean IOP change from baseline ranged from −4.2 to −4.6 mmHg. Physicians reported that IOP met or was lower than target IOP in 78.5% of patients (ie, 216/275 with physician reports). An additional 14.2% (n=39) benefited from treatment without reaching the target IOP, and the proportions of patients with unchanged (1.1%; n=3) and increased (6.2%; n=17) IOP were also similar to those in the total population.

Photonumeric bulbar conjunctival hyperemia grading indicated that 94.1% of patients with the available data exhibited none to mild hyperemia at the final visit (Table 3). Tolerability was rated as good or very good by the majority

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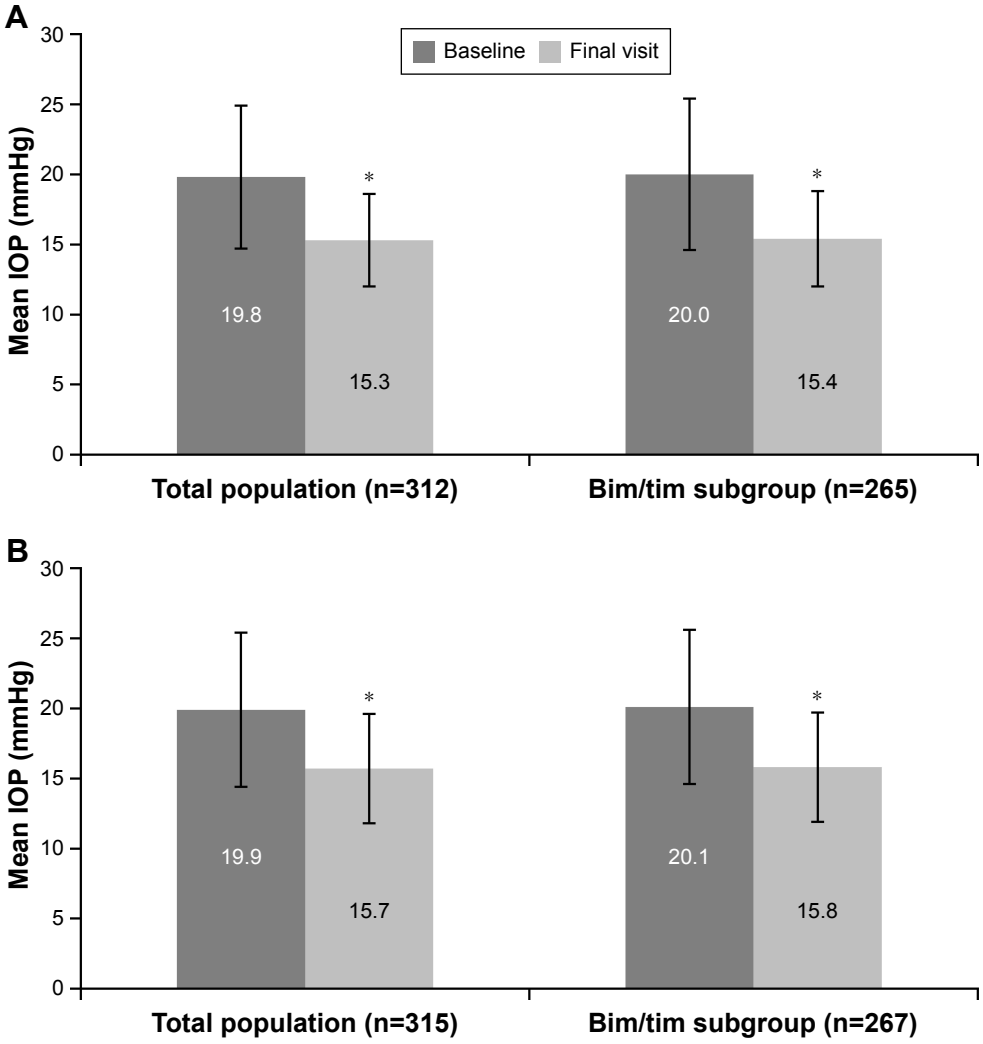



**Figure 1** Mean IOP in the right eye (**A**) and left eye (**B**) of the total population and subgroup of patients who received bim/tim during the study.
**Notes:** Results are expressed as mean ± SD at baseline and 8–12 weeks after switching to a PGA/P-containing therapy (final visit). *$P<0.001$, compared with baseline (Wilcoxon signed-rank test).
**Abbreviations:** Bim/tim, bimatoprost 0.03%/timolol 0.5%; IOP, intraocular pressure; PGA/P, prostaglandin analog/prostamide; SD, standard deviation.

of physicians (90.9%; 249/274 with ratings) and patients (89.5%; 239/267 with ratings); 2.9% (n=8) of physicians and 2.2% (n=6) of patients rated tolerability as poor, and 6.2% (n=17) of physicians and 8.2% (n=22) of patients rated it as moderate. Also consistent with findings in the total population, conjunctival hyperemia was the most frequently reported AE in the subgroup of patients who received bim/tim as study treatment (Table 5), and 8.7% of patients (27/278 with reported AEs) discontinued the study due to a treatment-related AE.

**Table 3** Hyperemia grading at the final visit, evaluated using a photonumeric bulbar conjunctival hyperemia grading scale

| Hyperemia grade | Total population[a] (n=318), n (%) | | Bim/tim subgroup[a] (n=271), n (%) | |
|---|---|---|---|---|
| 0 (none) | 202 (63.5) | 302 (95.0)[b] | 155 (57.2) | 255 (94.1)[b] |
| +0.5 (trace) | 68 (21.4) | | 68 (25.1) | |
| +1 (mild) | 32 (10.1) | | 32 (11.8) | |
| +2 (moderate) | 11 (3.5) | 16 (5.0)[c] | 11 (4.1) | 16 (5.9)[c] |
| +3 (severe) | 5 (1.6) | | 5 (1.8) | |

**Notes:** [a]Data were missing for 40 patients in the total population and 39 patients in the bim/tim subgroup. [b]Patients with hyperemia graded ≤+1. [c]Patients with hyperemia graded +2–+3.
**Abbreviation:** Bim/tim, bimatoprost 0.03%/timolol 0.5%.

## Discussion

Because elevated IOP is a key modifiable risk factor in the development and progression of visual impairment associated with OAG, current treatments aim to most effectively reduce IOP while minimizing AEs. In this prospective, multicenter, observational study conducted in the clinical setting in Turkey, the primary analysis demonstrated that PGA/P-containing medications (bim/tim, latanoprost, travoprost, and bimatoprost) were effective at lowering IOP in patients who

**Table 4** Distribution of patients with conjunctival hyperemia reported as an AE by previous treatment and time since diagnosis

| Previous treatment | Time since diagnosis, n (%[a]/%[b]) | | | Total[a] |
|---|---|---|---|---|
| | <5 years (n=207) | 5–10 years (n=87) | ≥11 years (n=64) | |
| Betaxolol (n=28) | 0 | 0 | 1 (3.6/1.6) | 1 (3.6) |
| Brimonidine (n=70) | 2 (2.9/1.0) | 0 | 1 (1.4/1.6) | 3 (4.3) |
| Brimonidine/timolol (n=18) | 1 (5.6/0.5) | 2 (11.1/2.3) | 0 | 3 (16.7) |
| Brinzolamide (n=17) | 1 (5.9/0.5) | 0 | 0 | 1 (5.9) |
| Dorzolamide/timolol (n=105) | 7 (6.7/3.4) | 1 (1.0/1.1) | 1 (1.0/1.6) | 9 (8.6) |
| Latanoprost (n=143) | 1 (0.7/0.5) | 0 | 0 | 1 (0.7) |
| Latanoprost/timolol (n=27) | 2 (7.4/1.0) | 0 | 0 | 2 (7.4) |
| Travoprost (n=54) | 0 | 3 (5.6/3.4) | 0 | 3 (5.6) |
| Total[b] | 14 (6.8)[c,d] | 6 (6.9)[c] | 3 (4.7)[c] | – |

**Notes:** [a]Relative to the total number of patients who previously received the indicated treatment. [b]Relative to the total number of patients diagnosed <5, 5–10, and ≥11 years prior to study initiation. [c]Patients with hyperemia reported as an AE. [d]$P$=0.224, Chi-square test.
**Abbreviation:** AE, adverse event.

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were previously treated with monotherapy or combination therapy, and well tolerated. At study end, mean IOP reduction from baseline ranged from 4.2 to 4.5 mmHg, and >81% of patients had reached their target IOP or had a lower IOP than target; 5.3% of patients had increased IOP, suggesting the possibility of nonresponse to study treatment in these patients as has been reported previously for latanoprost.[28]

Conjunctival hyperemia was the most frequent AE; it was reported by 6.4% of patients, a considerably lower rate than that reported in other studies evaluating PGA/P-containing ophthalmic solutions (including those enrolling previously treated patients).[29–34] This finding may reflect the fact that – in this study – more patients were previously treated with latanoprost than any other therapy, and there was no washout period between termination of previous therapy and initiation of PGA/P-containing therapy in >90% of patients. Patients may indeed be less likely to experience hyperemia after switching from latanoprost (or other PGAs/Ps) to bimatoprost.[35] Hyperemia is also a common AE associated with fixed-combination dorzolamide/timolol[36–38] (the most frequent combination therapy previously used by patients in this study), which could have impacted the results similarly. Alternatively, it is possible that while receiving latanoprost or fixed-combination dorzolamide/timolol, hyperemia severity led patients to discontinue treatment or switch to another type of ocular hypotensive, making them ineligible for participation in the study.

**Table 5** Treatment-related AEs reported in >1% of patients

| Treatment-related AEs | Total population (N=358), n (%) | Bim/tim subgroup (n=310), n (%) |
|---|---|---|
| Conjunctival hyperemia | 23 (6.4) | 23 (7.4) |
| Irritation | 15 (4.2) | 15 (4.8) |
| Itchy eyes | 6 (1.7) | 6 (1.9) |
| Hyperemia | 5 (1.4) | 5 (1.6) |
| Allergic reaction | 4 (1.1) | 4 (1.3) |
| Stinging sensation | 4 (1.1) | 4 (1.3) |
| Serious AEs | 0 | 0 |

**Abbreviations:** AE, adverse event; bim/tim, bimatoprost 0.03%/timolol 0.5%.

Bim/tim was the most commonly used agent during the study, having been prescribed for 86.6% of patients at the baseline visit. Post hoc analysis showed that bim/tim was effective at lowering IOP and well tolerated, consistent with overall findings. Specifically, mean IOP reduction from baseline ranged from 4.2 to 4.6 mmHg, >78% of patients had reached their target IOP or had a lower IOP than the target value, and conjunctival hyperemia was the most commonly reported AE (consistent with the results from other studies of bim/tim[12,15,20,39]).

The abovementioned results are clinically relevant because literature searches for prospective studies reporting the IOP-lowering effects of PGA/P-containing therapies in glaucoma in Turkey did not identify any that were conducted in the clinical setting. The efficacy findings of the post hoc analysis, however, reflect those of investigations of bim/tim in previously treated patients with OHT or glaucoma evaluated in clinical trials[12,14,16,17,20,39] or clinical settings[13,40] in other countries, supporting the use of bim/tim in Turkish patients with OHT or OAG who were previously treated. Considering that the risk of OAG progression has been shown to decrease by 10%–19% with each 1 mmHg of IOP reduction from baseline,[4,41,42] and that the importance of lowering IOP even at the preperimetric stage has recently been confirmed in a long-term (>5-year) study,[43] continuing treatment with the current regimen may not always be therapeutically optimal. With a mean IOP reduction of >4 mmHg, this study demonstrates that PGA/P-containing therapy, including bim/tim, can provide additional IOP lowering in patients who exhibited poor response, tolerance, or

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adherence to their previous therapy (including latanoprost monotherapy and fixed-combination dorzolamide/timolol, two of the most frequently prescribed topical IOP-lowering medications in Turkey).

It is noteworthy that despite the prespecified inclusion criteria, 28.8% of patients enrolled in this study had pseudoexfoliation glaucoma, due to the relatively high prevalence of this secondary form of glaucoma in Turkey.[44–46] Like IOP, exfoliation syndrome is another major risk factor for disease progression[4,5] that should be considered when determining a management strategy.[4] In addition, Turkish patients have been shown to have a higher prevalence (57%) of depression due to glaucoma-associated decrease in quality of life[47] than that of patients in other countries (11%–18%).[48–52] IOP and target IOP should thus be reassessed regularly during follow-up, as recommended by the European Glaucoma Society guidelines,[4] and patients' prescriptions should be updated/changed if the potential for more effective IOP control and good tolerability warrants it. Although future studies should evaluate the efficacy of bim/tim in a homogenous population of patients with pseudoexfoliation glaucoma, our findings suggest that bim/tim is effective at lowering IOP in these patients. This is clinically relevant considering that our screening of 313 abstracts (identified in PubMed using glaucoma, pseudoexfoliation, and IOP as search terms) revealed only one study in which 19/36 patients had pseudoexfoliation glaucoma and 10/36 patients received bim/tim.[19]

Potential limitations of the study include the open-label design[53] and absence of a predefined washout period, which could also have impacted outcomes. However, the study was designed to reflect typical clinical settings. In addition, outcomes were reported at 8–12 weeks after initiation of study treatment, hence precluding residual carryover effects from previous treatments, as evidenced in other published studies.[54–57] The fact that patients with pseudoexfoliation or pigmentary glaucoma were included in the analyses should also be considered, although it provided valuable information.

## Conclusion

In this prospective, multicenter, observational study conducted in the Turkish clinical setting, PGA/P-containing medications, including fixed-combination bim/tim used by the majority of patients, significantly reduced IOP in patients with OAG or OHT who were previously treated. More than 78% of patients reached the prespecified target IOP or had an even lower IOP than the target, and >89% reported good or very good tolerability. PGA/P-containing medications such as fixed-combination bim/tim should be considered as a safe and effective therapeutic option for Turkish patients who exhibit poor response, tolerance, or adherence to their previous therapy.

## Acknowledgments

We thank the following researchers (institutions) for their participation in the study: Nevbahar Tamçelik (National Coordinator, Scientific Consultant, İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi), Belgin İzgi (İstanbul Üniversitesi Capa Tıp Fakültesi), Ahmet Temel (Marmara Üniversitesi Pendik EAH), Altan Ozcan (Çukurova Üniversitesi Tıp Fakültesi), Nurşen Yüksel (Kocaeli Üniversitesi Tıp Fakültesi), Çiğdem Altan (Beyoglu Eye Training and Research Hospital), Nilgun Yildirim (Osmangazi Üniversitesi Tıp Fakültesi), Ufuk Elgin (Ankara Ulucanlar Göz EAH), and Mehmet Okka (Necmettin Erbakan Üniversitesi Hastanesi).

This study was sponsored by Allergan plc (Marlow, UK). Writing and editorial assistance was provided to the authors by Michele Jacob, PhD, CMPP, of Evidence Scientific Solutions (Philadelphia, PA, USA), and funded by Allergan plc (Irvine, CA, USA). All authors met the International Committee of Medical Journal Editors (ICMJE) authorship criteria. Neither honoraria nor payments were made for authorship.

## Disclosure

Baris Ozer is an employee of Allergan plc. The other authors report no conflicts of interest in this work.

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