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ORIGINAL RESEARCH

Safety of Fixed-Combination Bimatoprost 0.03%/Timolol 0.5% Ophthalmic Solution at 6 Months in Chinese Patients with Open-Angle Glaucoma or Ocular Hypertension

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ABSTRACT

Introduction: Fixed-combination bimatoprost 0.03%/timolol 0.5% ophthalmic solution (FCBT; Ganfort®, Allergan, an AbbVie company) effectively reduces intraocular pressure (IOP) via complementary mechanisms of action of the agents, but long-term (> 12 weeks) safety evaluations of FCBT remain limited. FCBT safety is evaluated herein, with particular focus on hyperemia and eyelash growth, at 24 weeks in Chinese patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Methods: In this multicenter, open-label, non-comparative, phase 4 study conducted in China, patients diagnosed with OAG or OHT having insufficient response to β-blocker- or prostaglandin analogue/prostamide (PGA)-based IOP-lowering monotherapy in one or both eyes were switched from their current IOP-lowering treatment to FCBT (one drop per eye every evening) without prior washout. Assessment visits were scheduled at baseline and weeks 4, 12, and 24 (or study exit). The primary outcome measure was adverse event (AE) incidence through 24 weeks.

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Results: Of 725 patients enrolled, 632 (87.2%) completed the study; 93 (12.8%) patients discontinued, including 29 (4.0%) due to AEs. Of 1326 FCBT-treated eyes (total), 594 (44.8%) experienced ≥ 1 ocular treatment-related AE during the study. Conjunctival hyperemia (the most common AE overall) and eyelash growth were reported in 269 (20.3%) and 54 (4.1%) FCBT-treated eyes, respectively. The incidence of other known PGA-related AEs (including blepharal pigmentation and erythema of eyelid) was < 10% each. Most conjunctival hyperemia reports were mild in severity (214/259; 82.6%) and only 1/259 (0.4%) was severe. Similarly, most cases of eyelash growth were mild (46/52; 88.5%); none were severe. One (< 0.1%) FCBT-treated eye had a serious ocular AE (OAG) considered FCBT-related.

Conclusions: The frequency and severity of FCBT-related AEs, including conjunctival hyperemia and eyelash growth, are consistent with previously published findings. No new safety concerns were raised. This prospective study reaffirms that once-daily FCBT is a safe and well-tolerated therapy for OAG and OHT.

ClinicalTrials.gov Identifier: NCT02571712.

Keywords: Bimatoprost; Fixed combination; Glaucoma; Intraocular pressure; Ocular hypertension; Safety; Timolol

Key Summary Points

Why carry out this study?
Studies evaluating the long-term (> 12 weeks) safety of fixed-combination bimatoprost 0.03%/timolol 0.5% ophthalmic solution (FCBT; Ganfort®) in Chinese patients remain limited, despite China being the most populous and one of the fastest ageing countries worldwide.
This Chinese study evaluated the safety of FCBT, with particular focus on the known bimatoprost side effects of hyperemia and eyelash growth, at 24 weeks in patients with open-angle glaucoma or ocular hypertension.
What was learned from the study?
No unexpected adverse events were reported.
As expected, conjunctival hyperemia (the most common adverse event overall) and eyelash growth were noted in 20.3% and 4.1% of FCBT-treated eyes, respectively, with > 99% of reports being mild or moderate.
FCBT is a safe and well-tolerated long-term therapy for open-angle glaucoma and ocular hypertension.

INTRODUCTION

Open-angle glaucoma (OAG) is a chronic disease characterized by progressive optic neuropathy and consequent visual field defects [1, 2]. It remains one of the leading causes of irreversible blindness worldwide [1–3], and because older age is a risk factor [2, 3], OAG is expected to affect a growing number of individuals as the global population ages.

In China, the prevalence of primary OAG (POAG—the most common form of glaucoma overall [3]) was estimated at 1.02% nationally in 2015, with a projected increase of approximately 27% by 2050 [4]. In addition, blindness (unilateral or bilateral) reportedly affects 2.7–74.5% of patients with POAG in China, depending on the region [5–11]. These findings, along with the fact that the humanistic and economic burdens of glaucoma have been shown to increase with disease severity [12–19], highlight the importance of adequately managing the disease.

For patients with OAG or ocular hypertension (OHT), fixed-combination bimatoprost 0.03%/timolol 0.5% (corresponding to 0.68% timolol maleate in the formulation, and referred to as "timolol 0.5%" hereafter) ophthalmic solution (FCBT; Ganfort®, Allergan, an AbbVie company) can effectively reduce intraocular pressure (IOP) [20, 21] via complementary mechanisms of action of the combined agents. FCBT has indeed demonstrated superior IOP

lowering when evaluated against its individual components [22, 23], and noninferiority when compared with concomitant instillation of bimatoprost and timolol [24]. These studies [22–24] supported the approval of FCBT for IOP reduction in patients with OAG or OHT who are insufficiently responsive to monotherapy with topical β-blockers or prostaglandin analogues/prostamide (PGAs). However, introduction of two or more drugs can exacerbate adverse events (AEs) in certain patient populations, and studies evaluating the long-term (> 12 weeks) safety of FCBT remain limited [22]. This phase 4, 24-week study of the safety of FCBT, conducted in patients with OAG or OHT who were insufficiently responsive to topical/ocular IOP-lowering monotherapy containing a β-blocker or PGA, provides prospective data to address this gap.

METHODS

Study Design

This multicenter, open-label, noncomparative, 24-week safety study (ClinicalTrials.gov Identifier: NCT02571712) was conducted in China between November 10, 2015 and June 21, 2018, in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and/or other applicable local regulations, guidance documents, or laws, depending on which provided greater protection to the individuals. For each center, the study protocol was approved by an institutional review board or independent ethics committee before study start. Written informed consent was obtained from all patients before initiation of study treatment.

Participants

Patients were enrolled if they met the following key inclusion criteria at baseline: at least 18 years of age, diagnosis of OAG or OHT (in at least one eye) that was insufficiently responsive to topical/ocular IOP-lowering monotherapy containing a β-blocker or PGA (per investigator judgement), and willingness to switch from their current IOP-lowering medications to FCBT as a single therapy in the affected eye(s).

The key exclusion criteria were hypersensitivity to the active substances or any of the excipients; reactive airway disease (including bronchial asthma, or a history of bronchial asthma or severe chronic obstructive pulmonary disease); sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricular block not controlled with a pacemaker, overt cardiac failure, or cardiogenic shock; current or recent (within 30 days of entry in this study) enrollment or participation in an investigational drug or device study; and any condition or situation that, in the investigator's opinion, may have put the patient at significant risk, confounded the study results, or interfered significantly with the patient's participation in the study.

During the study, any use or change in use of medications or treatment was captured, including ocular (unilateral or bilateral) and nonocular dietary supplements/nutraceuticals, homeopathic preparations, and traditional medications.

Treatment

No washout of prior IOP-lowering medications was required. Patients were instructed to begin once-daily instillation of one drop of FCBT in the study eye(s) at 8 PM (± 1 h) on day 1 (baseline). Treatment continued for approximately 24 weeks, with follow-up visits scheduled at weeks 4 (± 7 days), 12 (± 7 days), and 24 (± 14 days, or exit in case of early discontinuation of the study treatment). The last FCBT dose was to be administered in the evening preceding the week-24 (or exit) visit. FCBT was provided by Allergan (an AbbVie company) and dispensed at study visits, each bottle providing one month's supply. Reminders to use the study treatment as instructed were provided by the study centers as needed.

Fellow eyes that did not receive FCBT during the study are referred to as untreated eyes throughout the manuscript.

Safety Assessments

Macroscopic conjunctival hyperemia (an AE of special interest due to the presence of bimatoprost in FCBT) was graded under consistent lighting across visits, using the Allergan Bulbar Hyperemia Grading Guide, which is based on a 5-point photographic grading scale: 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). Findings were reported as conjunctival hyperemia and ocular hyperemia (preferred terms of the Medical Dictionary for Regulatory Activities [MedDRA] version 21.0). Assessment of eyelash growth (the second AE of special interest due to the presence of bimatoprost in FCBT) was at the discretion of the investigators, based on clinical examination, and findings were reported as eyelash growth and eyelash thickening (preferred terms of the aforementioned MedDRA).

Slit lamp biomicroscopy was used to examine the eyelids/eyelid margins/lashes, bulbar/palpebral conjunctiva, anterior chamber, and iris/pupil. Erythema and edema of the eyelids/eyelid margins/lashes, conjunctival edema, and corneal edema/punctate epithelial staining were each graded using a 5-point scale: 0 (none), 0.5 (trace), 1 (mild), 2 (moderate), and 3 (severe). Anterior chamber cells were graded using a 6-point scale: 0 (0 cells), 0.5 (1–5 cells), 1 (6–15 cells), 2 (16–25 cells), 3 (26–50 cells), and 4 (> 50 cells), whereas anterior chamber flare was categorized as 0 (none), 1 (faint), 2 (moderate—iris and lens details clear), 3 (marked—iris and lens details hazy), and 4 (intense—fibrin or plastic aqueous) [25]. The iris/pupil was evaluated for pathology findings.

IOP and visual acuity (in Snellen equivalents) were evaluated in both eyes according to standard practice at each study center, using the same instrument type across visits for an individual patient. Whenever possible, IOP was assessed at the same time of day across visits. The cup/disc ratio was measured in both eyes (undilated) per the Allergan Cup-Disc Ratio Guide and reported using a 0–1.0 scale.

Assessments were performed at all visits, except visual acuity (evaluated at baseline and week 24 [or exit]) and cup/disc ratio (measured at baseline, week 12, and week 24 [or exit]).

Outcome Variables and Analyses

Safety outcome variables included the incidence of AEs (primary outcome measure), as well as changes from baseline in (1) visual acuity (expressed in letter lines and determined through standard calculations after the logarithmic values obtained at each visit were rounded to the nearest tenth), (2) conjunctival hyperemia severity grade, (3) eyelash growth, (4) biomicroscopy findings (i.e., at least one severity grade increase/worsening from baseline, or a status change from absence at baseline to presence at a post-baseline visit for other pathology findings not associated with severity grades), (5) cup/disc ratio, and (6) IOP.

The safety population included all patients who received at least one dose of FCBT in the treated eye(s), without imputation of missing values (unless otherwise stated). An overall summary of treatment-emergent AEs (TEAEs) was provided on a per-patient basis (including exacerbation of a pre-existing condition and onset of a new symptom, treatment-related AEs, serious AEs, deaths, and AEs leading to discontinuation). Ocular and nonocular safety variables were then analyzed on a per-eye and per-patient basis, respectively. If more than one severity grade was reported for any given AE and patient, the worst severity grade was used for analysis; if severity was missing, the event/patient was categorized as severity unknown.

Statistical analyses were conducted using Statistical Analysis System (SAS®) software version 9.1 or higher. For continuous variables, summary statistics included the mean, standard deviation (SD), and median. For categorical variables, summary statistics included the frequency and percentage. The sample size was determined empirically; assuming a dropout rate of 20%, enrollment of approximately 750 patients was planned to ensure that 600 patients completed the study.

RESULTS

Of 750 patients enrolled at 15 centers, 725 received at least one dose of FCBT (safety population), and 632/725 (87.2%) completed the study; 93/725 (12.8%) patients discontinued the study early, including 29/725 (4.0%) who did so because of AEs (Fig. 1). Only 7/725 (1.0%) patients discontinued the study because of a lack of efficacy, as determined by investigator. Overall, 601 and 124 patients were treated in both eyes and one eye, respectively, for a total of 1326 FCBT-treated eyes analyzed.

Demographics and baseline characteristics of the safety population are summarized in Table 1; all patients were Asian, most had OAG, and mean age was 49.9 years. Patients were exposed to FCBT for a mean (SD) of 155.1 (44.5) days (median, 168; range, 1–283).

Overall, 475/725 (65.5%) patients had at least one TEAE, including 330/725 (45.5%) patients who had at least one treatment-related AE (Table 2), per investigator judgement. Ocular and nonocular FCBT-related AEs were reported in 325/725 (44.8%) and 13/725 (1.8%) patients, respectively; 8 patients had both ocular and nonocular FCBT-related AEs. Of 10 (1.4%) patients with a serious ocular TEAE (Table 2), only 1 (0.1%) experienced a serious ocular AE deemed treatment related. There were no deaths or unexpected TEAEs during the study.

Over the study duration, 594/1326 (44.8%) FCBT-treated eyes experienced at least one ocular treatment-related AE (Table 3). Among

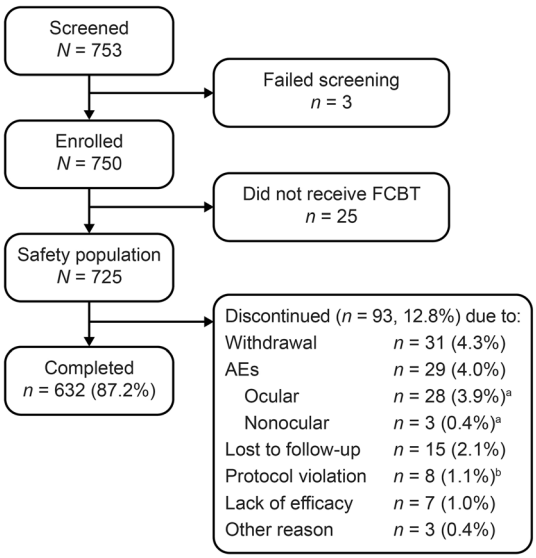

Fig. 1 Patient disposition. *AE* adverse event, *FCBT* fixed-combination bimatoprost 0.03%/timolol 0.5%. [a]Two (0.3%) patients had both ocular and nonocular AEs. [b]The most commonly reported protocol deviations leading to discontinuation were patients not undergoing protocol-specified assessments or procedures, and use of prohibited concomitant medications during the study

Table 1 Demographics and baseline characteristics (safety population)

Parameter	FCBT *N* = 725 patients/1326 eyes
Patient level	
Mean age (SD), years	49.9 (16.1)
Min, max	18, 87
≤ 65, *n* (%)	581 (80.1)
> 65, *n* (%)	144 (19.9)
Sex, *n* (%)	
Male	463 (63.9)
Female	262 (36.1)
Race, *n* (%)	
Asian	725 (100)
Eye level	
Diagnosis	
Open-angle glaucoma	1216 (91.7)
Ocular hypertension	106 (8.0)
Other diagnosis[a]	4 (0.3)
Mean IOP (SD), mmHg[b]	18.4 (5.4)

FCBT fixed-combination bimatoprost 0.03%/timolol 0.5%, *IOP* intraocular pressure, *min* minimum, *max* maximum, *SD* standard deviation

[a]One eye (one patient) had neovascular glaucoma and three eyes (two patients) had angle closure glaucoma

[b]Information was missing for one FCBT-treated eye. In FCBT-untreated contralateral eyes with available data (*n* = 112/124), mean (SD) baseline IOP was 16.8 (6.7) mmHg

Table 2 Summary of TEAEs reported in FCBT-treated patients

TEAEs[a]	FCBT (N = 725 patients) n (%)
Any	475 (65.5)
Ocular	384 (53.0)
Nonocular	207 (28.6)
Treatment-related	330 (45.5)
Ocular	325 (44.8)
Nonocular[b]	13 (1.8)
Serious	28 (3.9)
Ocular[c]	10 (1.4)
Nonocular[d]	18 (2.5)
Leading to discontinuations	29 (4.0)
Ocular	28 (3.9)
Nonocular[e]	3 (0.4)

FCBT fixed-combination bimatoprost 0.03%/timolol 0.5%, *TEAE* treatment-emergent adverse event
[a]Some patients had both ocular and nonocular TEAEs
[b]Included headache (n = 4, 0.6%) and dizziness (n = 2, 0.3%), as well as dermatitis allergic, eczema, pruritus, rash, asthma, cough, and bradycardia (n = 1 each, 0.1%)
[c]Included cataract (n = 2, 0.3%), corneal degeneration (n = 1, 0.1%, fellow untreated eye), eye contusion (n = 1, 0.1%), glaucoma (n = 1, 0.1%), IOP increased (n = 2, 0.3%), macular fibrosis (n = 1, 0.1%), and open-angle glaucoma (n = 2, 0.3%). The AE (OAG) was deemed treatment-related in only one patient
[d]Included foot fracture (n = 2, 0.3%), as well as appendicitis, blood glucose fluctuation, bronchitis, cerebral arteriosclerosis, cholecystitis chronic, eczema, gastric polyps, hypertension, intervertebral disc protrusion, intestinal polyp, lipoma, pancreatitis acute, papillary thyroid cancer, rib fracture, subdural hematoma, type 2 diabetes mellitus, uterine leiomyoma, and uterine polyp (n = 1 each, 0.1%). None were deemed FCBT related
[e]Included headache, dizziness, and asthma (n = 1 each, 0.1%); all were considered to be treatment related and resolved without treatment

Table 3 Summary of treatment-related AEs reported in at least 1% of FCBT-treated eyes

Ocular FCBT-related AEs	FCBT (N = 1326 eyes) n (%)
Total	594 (44.8)
Conjunctival hyperemia	259 (19.5)
Blepharal pigmentation	84 (6.3)
Eye pain	73 (5.5)
Erythema of eyelid	62 (4.7)
Growth of eyelashes	52 (3.9)
Xerophthalmia	50 (3.8)
Eye pruritus	47 (3.5)
Dry eye	46 (3.5)
Vision blurred	35 (2.6)
Conjunctivitis	27 (2.0)
Intraocular pressure increased[a]	24 (1.8)
Keratitis	23 (1.7)
Eyelid edema	18 (1.4)
Eye irritation	17 (1.3)
Foreign body sensation in eyes	13 (1.0)

AE adverse event, *FCBT* fixed-combination bimatoprost 0.03%/timolol 0.5%
[a]Relative to baseline IOP

those, conjunctival hyperemia (n = 259, 19.5%), blepharal pigmentation (n = 84, 6.3%), and eye pain (n = 73, 5.5%) were most frequently reported, and the only treatment-related AEs with an incidence greater than 5%. Of 11 (0.8%) FCBT-treated eyes with a serious ocular TEAE (Table 4), only 2 (less than 0.2%, both eyes of one patient initially enrolled into the trial with a bilateral diagnosis of OAG) had a serious ocular AE, reported as OAG and considered treatment-related (per investigator judgement). One serious TEAE of corneal degeneration was reported in the untreated eye of a different patient and deemed not treatment related.

Of 261 eyes with treatment-related hyperemia (one of two AEs of special interest evaluated in this study), 259 had mild (n = 214), moderate (n = 44), and severe (n = 1)

Table 4 All serious ocular AEs reported in FCBT-treated eyes

Ocular serious AEs	FCBT (*N* = 1326 eyes) *n* (%)
Total	11 (0.8)
Cataract[a]	3 (0.2)
Open-angle glaucoma[b]	3 (0.2)
Intraocular pressure increased[c]	2 (0.2)
Eye contusion[d]	1 (0.1)
Glaucoma[d]	1 (0.1)
Macular fibrosis[a]	1 (0.1)

AE adverse event, *FCBT* fixed-combination bimatoprost 0.03%/timolol 0.5%

[a]The events (moderate in severity and not FCBT-related) did not result in a change in the study treatment regimen or discontinuation from the study

[b]Per investigator judgement, occurrence of open-angle glaucoma (mild in severity) was considered treatment related in both eyes of one patient (enrolled with a bilateral diagnosis of OAG). The events resolved with non-study treatment (trabeculectomy) and resulted in FCBT interruption and patient discontinuation from the study. The third event (moderate in intensity and not FCBT-related) resolved with non-study treatment and resulted in FCBT interruption in the affected eye, without study discontinuation

[c]Relative to baseline IOP. Both events (severe in intensity and not FCBT-related) resolved with non-study treatment and resulted in FCBT interruption, with study discontinuation in one case

[d]The event (severe in intensity and not FCBT-related) resolved with treatment and resulted in FCBT interruption but not study discontinuation

conjunctival hyperemia, while 2 had mild ocular hyperemia (Fig. 2A, B). Similarly, of 56 eyes with treatment-related eyelash growth (second AE of special interest evaluated herein), 52 had mild (n = 46) and moderate (n = 6) eyelash growth, while 9 had mild (n = 7) and moderate (n = 2) eyelash thickening (Fig. 2C, D); 5 eyes had both growth and thickening of their eyelashes. Of the ocular AEs that led to discontinuation of 50 eyes (3.8%; 28 patients) from the study, conjunctival hyperemia was the most common (n = 19 eyes, 1.4%), followed by eye pain (n = 8 eyes, 0.6%) (Table 5).

Among patients with visual acuity data available at week 24/exit, the proportions of FCBT-treated eyes with unchanged (less than 2 lines of improvement or worsening), improved (+ 2 lines or more), or worsened (− 2 lines or more) visual acuity from baseline were 77.4% (n = 923/1193), 11.7% (n = 140/1193), and 10.9% (n = 130/1193), respectively. Similarly, the proportions of untreated eyes with unchanged, improved, or worsened visual acuity from baseline were 76.2% (n = 64/84), 11.9% (n = 10/84), and 11.9% (n = 10/84), respectively. The proportions of FCBT-treated and untreated eyes with conjunctival hyperemia that was clinically worse than baseline (per macroscopic assessment) were also comparable at week 24/exit, i.e., 6.3% (n = 74/1167) vs 6.0% (n = 6/100), respectively. Clinically meaningful biomicroscopic findings were noted in 193/1326 (14.6%) FCBT-treated eyes and 21/124 (16.9%) untreated eyes; the most common findings were erythema of eyelid (6.7% vs 4.0%) and corneal staining (2.9% vs 3.2%), respectively. Over 96% of FCBT-treated eyes and at least 93% of untreated eyes had no change in cup/disc ratio, and there was no noticeable trend indicating worsening in either group during the study.

Patients were not washed out of their standard IOP-lowering medication prior to enrollment. Accordingly, among the 1326 FCBT-treated eyes, mean IOP reduction from medicated baseline was −2.6 mmHg at week 4 (n = 1307), −2.9 mmHg at week 12 (n = 1208), and −2.4 mmHg at week 24 (n = 1164). Among the 124 untreated (fellow) eyes, mean IOP change from unmedicated baseline was −0.4 mmHg at week 4 (n = 109), −0.8 mmHg at week 12 (n = 96), and −0.5 mmHg at week 24 (n = 89).

DISCUSSION

FCBT has been approved in China since 2013 and this multicenter, open-label, noncomparative, phase 4 study fulfilled a post-marketing commitment to the China Food and Drug Administration to further assess the long-term

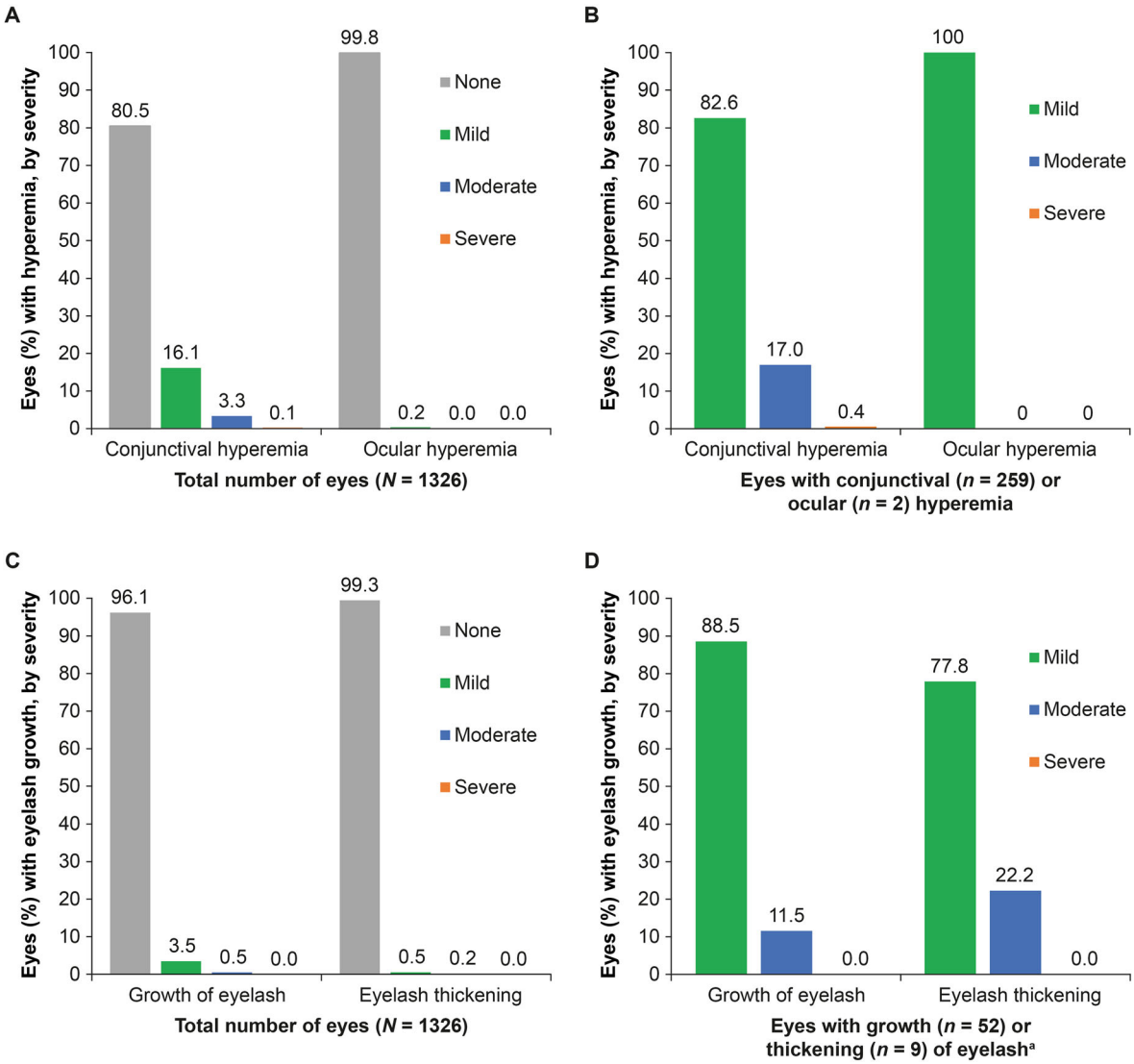

Fig. 2 Incidence of **A**, **B** conjunctival/ocular hyperemia and **C**, **D** eyelash growth as adverse events of special interest, by severity. [a]Five eyes had both growth and thickening of eyelash

safety of FCBT in a large population of patients with OAG or OHT. The study was designed to evaluate the safety of FCBT at 6 months, focusing on two AEs of special interest: conjunctival hyperemia and eyelash growth. The treatment-related ocular AEs reported are consistent with the established safety profile of FCBT [26], and are known to be associated with the use of IOP-lowering monotherapy containing timolol or bimatoprost [27, 28]. As expected, the treatment-related ocular AE most frequently reported in FCBT-treated eyes was conjunctival hyperemia, a recognized AE associated with use of ophthalmic solutions containing bimatoprost (and PGAs in general). Conjunctival hyperemia is indeed the most common adverse reaction listed in the bimatoprost product label, hence its designation as an AE of special interest herein. Eyelash growth is similarly known to be a side effect of bimatoprost use, and bimatoprost remains the only PGA approved to treat eyelash hypotrichosis [29]. In this study, eyelash growth was also evaluated as an AE of special interest. Considering that recently

Table 5 Summary of discontinuations from the study due to ocular AEs

AEs	FCBT (N = 1326 eyes) n (%)
Total	50 (3.8)
Conjunctival hyperemia	19 (1.4)
Eye pain	8 (0.6)
Intraocular pressure increased	5 (0.4)
Blepharal pigmentation	4 (0.3)
Eyelid edema	4 (0.3)
Conjunctivitis	2 (0.2)
Conjunctivitis allergic	2 (0.2)
Corneal exfoliation	2 (0.2)
Dry eye	2 (0.2)
Dyschromatopsia	2 (0.2)
Foreign body sensation in eyes	2 (0.2)
Keratitis	2 (0.2)
Open-angle glaucoma	2 (0.2)
Photophobia	2 (0.2)
Visual acuity reduced	2 (0.2)
Eye pruritus	1 (0.1)
Eyelid retraction	1 (0.1)
Vision blurred	1 (0.1)

AE adverse event, *FCBT* fixed-combination bimatoprost 0.03%/timolol 0.5%

approved IOP-lowering ophthalmic solutions containing one or two active components were associated with conjunctival hyperemia rates of at least 47% in studies conducted over up to 6 months [30–33], our results confirm the low incidence of treatment-related conjunctival hyperemia (19.5%) following use of FCBT for a similar duration. Moreover, the incidence rates of conjunctival hyperemia and eyelash growth (3.9%) reported herein are consistent with those of previously published registration studies in which 533 patients instilled FCBT for 3 or 12 months [22, 23]. In those studies, the incidence of treatment-related conjunctival hyperemia and eyelash growth was 22.7% and 3.6% at 3 months [23], and 25.7% and 7.3% at 12 months [22], respectively.

These findings are of clinical interest because they substantiate the overall safety of FCBT in patients with OAG and OHT, while providing prospective data on the long-term use of FCBT. No unexpected AEs were reported; only 1 (0.1%) ocular serious TEAE was considered FCBT-related (OAG in both eyes of one patient), and there were no clinically significant changes in visual acuity, biomicroscopy findings, or cup/disc ratio. Our findings are also in line with a recently published multicenter, observational survey study that was conducted in China to evaluate satisfaction with FCBT at 1–3 months in 500 patients with glaucoma [34]. With 87% of patients using FCBT alone as a replacement for another IOP-lowering medication (β-blocker, 32%; PGA, 21%; carbonic anhydrase inhibitor, 13%; α-adrenergic agonist, 11%; miotics, 4%; combination therapy, 6%), and 13% adding it to their preexisting regimen of IOP-lowering medications, the study results indicated that 82% of patients agreed or very much/strongly agreed that FCBT provided better tolerability and comfort than their previous treatment. The mean satisfaction score was statistically significantly higher with FCBT than with previous treatment, regardless of age ($P < 0.0001$), medical insurance coverage ($P < 0.0011$), employment status ($P < 0.0001$), annual household income ($P \leq 0.0481$), and duration of FCBT treatment ($P < 0.0001$) [34]. Another multicenter, observational, 3-month study conducted in Greece evaluated the efficacy and tolerability of FCBT in 785 patients with OAG or OHT and insufficient IOP lowering on their previous therapy [35]. Of patients who completed the study (n = 766), 96.0% rated the tolerability of FCBT as good or very good [35]. In a combined analysis of five multicenter, observational studies conducted throughout Europe (excluding the aforementioned study for which data were not yet available), 5556 patients were included and, of those with available data at 3 months, 4102 (88.0%) rated the tolerability of FCBT as good or very good [36]. Moreover, in a survey of 606 German

patients with POAG or OHT, the tolerability of FCBT at 3 months was rated as excellent or good by 96.7% of patients [37]. Although these studies did not evaluate long-term tolerability and were observational in nature, they support the findings of the current interventional study.

CONCLUSION

Evaluation of the safety of FCBT at 6 months in this large population of patients with OAG or OHT who were insufficiently responsive to IOP-lowering monotherapy containing a β-blocker or PGA reaffirms that long-term use of once-daily FCBT in one or both eyes is safe and well tolerated. The incidence of conjunctival hyperemia and eyelash growth was in line with that of the registration studies [22, 23], these AEs were typically mild in nature, and eyelash growth could even be considered a benefit to some patients.

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Conflict of Interest. Financial arrangements of the authors with companies whose products may be related to the present report follow, as declared by the authors. Xinghuai Sun, Ke Yao, Qinghuai Liu, Hong Zhang, Xiaoli Xing, Aiwu Fang, Xuanchu Duan, and Minbin Yu have nothing to disclose. Jingyuan Yang and Margot L. Goodkin are employees of AbbVie. Michelle Y. Chen is an employee of Perfuse Therapeutics, Inc., and was an employee of Allergan (an

AbbVie company) when the study was conducted.

Compliance with Ethics Guidelines. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and/or other applicable local regulations, guidance documents, or laws, depending on which provided greater protection to the individuals. For each center, the study protocol was approved by the following institutional review board or independent ethics committee prior to study start: Clinical Trial Ethics Committee of Huazhong University of Science & Technology (2015 Ethics Review No. 198; Hong Zhang); Ethics Committee of Beijing Hospital (2016BJYYEC-002; Hong Dai); Ethics Committee of Beijing Tongren Hospital Capital Medical University (TREC2016-04; Tao Wang); Ethics Committee of Eye & ENT Hospital of Fudan University (2015 Ethics No. 2015032; Xinghuai Sun); Ethics Committee of Eye Hospital of Wenzhou Medical University (2015 Drug Ethics Review No. 7; Aiwu Fang); Ethics Committee of Henan Provincial Eye Hospital (HNEEC-2015-13; Yangzeng Dong); Ethics Committee of The First Hospital of Nanjing Medical University (2015-MD-200; Qinghuai Liu); Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine (2016 Drug Ethics Review No. 79; Ke Yao); Ethics Committee of Second Xiangya Hospital of Central South University (2015 Drug Ethics Review No. 112; Xuanchu Duan); Ethics Committee of Tianjin Eye Hospital (TJYYLL-2017-02; Jin Yang); Ethics Committee of Tianjin Medical University Eye Hospital (201610; Xiaoli Xing); Ethics Committee of West China Hospital, Sichuan University (2016 Clinical Trial [Postmarketing] Review No. 5; Li Tang); Ethics Committee of Xuanwu Hospital Capital Medical University (Clinical Drug Review No. [2016] 019; Dachuan Liu); Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-Sen University (2016YWNL002; Minbin Yu); Peking University Third Hospital Medical Science Research Ethics Committee (2015 Drug Ethics Review No. 61; Chun Zhang). Written informed consent was obtained from all patients before initiation of study treatment.

Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. For more information on the process, or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

REFERENCES

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–11.

2. Gedde SJ, Vinod K, Wright MM, et al; American Academy of Ophthalmology Preferred Practice Pattern Glaucoma Panel. Primary open-angle glaucoma preferred practice pattern. Ophthalmology. 2021;128(1):71–150.

3. European Glaucoma Society. Terminology and guidelines for glaucoma, 5th edn. Br J Ophthalmol. 2021;105:1–169.

4. Song P, Wang J, Bucan K, Theodoratou E, Rudan I, Chan KY. National and subnational prevalence and burden of glaucoma in China: a systematic analysis. J Glob Health. 2017;7(2):020705.

5. He J, Zou H, Lee RK, et al. Prevalence and risk factors of primary open-angle glaucoma in a city of Eastern China: a population-based study in Pudong New District, Shanghai. BMC Ophthalmol. 2015;15:134.

6. Li H, Zhang YY, Liu SC, et al. Prevalence of open-angle glaucoma in southwestern China: the Yongchuan Glaucoma Study. J Huazhong Univ Sci Technol Med Sci. 2014;34(1):137–41.

7. Zhong H, Li J, Li C, et al. The prevalence of glaucoma in adult rural Chinese populations of the Bai nationality in Dali: the Yunnan Minority Eye Study. Invest Ophthalmol Vis Sci. 2012;53(6):3221–5.

8. Sun J, Zhou X, Kang Y, et al. Prevalence and risk factors for primary open-angle glaucoma in a rural northeast China population: a population-based survey in Bin County, Harbin. Eye (Lond). 2012;26(2):283–91.

9. Liang YB, Friedman DS, Zhou Q, et al. Prevalence of primary open angle glaucoma in a rural adult Chinese population: the Handan eye study. Invest Ophthalmol Vis Sci. 2011;52(11):8250–7.

10. Song W, Shan L, Cheng F, et al. Prevalence of glaucoma in a rural northern China adult population: a population-based survey in Kailu County, Inner Mongolia. Ophthalmology. 2011;118(10):1982–8.

11. Xu L, Chen JH, Li JJ, et al. [The prevalence and its screening methods of primary open angle glaucoma in defined population-based study of rural and urban in Beijing]. Zhonghua Yan Ke Za Zhi. 2004;40(11):726–32.

12. Beal B, Shih V, Campbell J, Veenstra D, Devine B. Comparing healthcare resource utilization and costs for patients with normal tension glaucoma across levels of severity: a retrospective cohort study. Clin Ophthalmol. 2021;15:453–60.

13. Shih V, Parekh M, Multani JK, et al. Clinical and economic burden of glaucoma by disease severity: a United States claims-based analysis. Ophthalmol Glaucoma. 2021;4(5):490–503.

14. Varma R, Lee PP, Goldberg I, Kotak S. An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol. 2011;152(4):515–22.

15. Thygesen J, Aagren M, Arnavielle S, et al. Late-stage, primary open-angle glaucoma in Europe: social and health care maintenance costs and quality of life of patients from 4 countries. Curr Med Res Opin. 2008;24(6):1763–70.

16. McKean-Cowdin R, Varma R, Wu J, Hays RD, Azen SP. Severity of visual field loss and health-related quality of life. Am J Ophthalmol. 2007;143(6):1013–23.

17. Lee PP, Walt JG, Doyle JJ, et al. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. Arch Ophthalmol. 2006;124(1):12–9.

18. Traverso CE, Walt JG, Kelly SP, et al. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. Br J Ophthalmol. 2005;89(10):1245–9.

19. Vicente C, Walker J, Buys Y, Einarson TR, Covert D, Iskedjian M. Association between mean intraocular pressure, disease stability and cost of treating glaucoma in Canada. Curr Med Res Opin. 2004;20(8):1245–51.

20. Lou H, Wang H, Zong Y, Cheng JW, Wei RL. Efficacy and tolerability of prostaglandin-timolol fixed combinations: an updated systematic review and meta-analysis. Curr Med Res Opin. 2015;31(6):1139–47.

21. Hommer A, Wickstrom J, Friis MM, et al. A cost-effectiveness analysis of fixed-combination therapies in patients with open-angle glaucoma: a European perspective. Curr Med Res Opin. 2008;24(4):1057–63.

22. Lewis RA, Gross RL, Sall KN, Schiffman RM, Liu CC, Batoosingh AL. The safety and efficacy of bimatoprost/timolol fixed combination: a 1-year double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension. J Glaucoma. 2010;19(6):424–6.

23. Brandt JD, Cantor LB, Katz LJ, Batoosingh AL, Chou C, Bossowska I. Bimatoprost/timolol fixed combination: a 3-month double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension. J Glaucoma. 2008;17(3):211–6.

24. Ling Z, Zhang M, Hu Y, et al. Safety and efficacy of bimatoprost/timolol fixed combination in Chinese patients with open-angle glaucoma or ocular hypertension. Chin Med J (Engl). 2014;127(5):905–10.

25. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509–16.

26. Allergan. Package leaflet: information for the user—Ganfort®. Irvine, CA, USA: Allergan; 2008. https://allergan-web-cdn-prod.azureedge.net/allerganindia/allerganindia/media/allergan-india/products/ganfort.pdf. Accessed Oct 14, 2022.

27. Bausch + Lomb. TIMOPTIC® 0.25% and 0.5% (Timolol maleate ophthalmic solution). Bridgewater, NJ, USA: Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC; 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018086s076lbl.pdf. Accessed Oct 14, 2022.

28. Allergan, an AbbVie company. LUMIGAN® (bimatoprost ophthalmic solution) 0.01% [highlights of prescribing information]. Irvine, CA, USA: Allergan; 2022. http://www.allergan.com/assets/pdf/lumigan_pi.pdf. Accessed Oct 14, 2022.

29. Allergan, an AbbVie company. Highlights of prescribing information—LATISSE® (bimatoprost ophthalmic solution) 0.03%. Irvine, CA, USA: Allergan; 2017. https://media.allergan.com/actavis/actavis/media/allergan-pdf-documents/product-prescribing/20170829-LATISSE-USPI-72303US17.pdf. Accessed Oct 14, 2022.

30. Singh IP, Fechtner RD, Myers JS, et al. Pooled efficacy and safety profile of netarsudil ophthalmic solution 0.02% in patients with open-angle glaucoma or ocular hypertension. J Glaucoma. 2020;29(10):878–84.

31. Walters TR, Ahmed IIK, Lewis RA, et al. Once-daily netarsudil/latanoprost fixed-dose combination for elevated intraocular pressure in the randomized phase 3 MERCURY-2 study. Ophthalmol Glaucoma. 2019;2(5):280–9.

32. Khouri AS, Serle JB, Bacharach J, et al. Once-daily netarsudil versus twice-daily timolol in patients with elevated intraocular pressure: the randomized phase 3 ROCKET-4 study. Am J Ophthalmol. 2019;204:97–104.

33. Serle JB, Katz LJ, McLaurin E, et al. Two phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure: Rho kinase elevated IOP treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). Am J Ophthalmol. 2018;186:116–27.

34. Sun X, Lin M, Duan X, Zhang C, Ming J. Patient satisfaction with fixed-combination bimatoprost/timolol ophthalmic solution: a survey study in patients with glaucoma in China. Patient Prefer Adherence. 2017;11:845–52.

35. Rotsos TG, Kliafa VG, Asher KJ, Papaconstantinou D. Bimatoprost/timolol fixed combination (BTFC) in patients with primary open angle glaucoma or ocular hypertension in Greece. Int J Ophthalmol. 2016;9(1):69–75.

36. Pfennigsdorf S, de Jong L, Makk S, et al. A combined analysis of five observational studies evaluating the efficacy and tolerability of bimatoprost/timolol fixed combination in patients with primary open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2013;7:1219–25.

37. Feuerhake C, Buchholz P, Kimmich F. Efficacy, tolerability and safety of the fixed combination of bimatoprost 0.03% and timolol 0.5% in a broad patient population: multicenter, open-label observational study. Curr Med Res Opin. 2009;25(4):1037–43.