

# Combination of brinzolamide and brimonidine for glaucoma and ocular hypertension: critical appraisal and patient focus

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**Abstract:** Glaucoma is one of the leading causes of blindness and is characterized by optic nerve damage that results in visual field loss. Elevated intraocular pressure (IOP) has been associated with glaucoma progression; thus, IOP-lowering medications are the standard of care for glaucoma. Guidelines suggest monotherapy with IOP-lowering agents such as  $\beta$ -blockers (eg, timolol), prostaglandin analogs, carbonic anhydrase inhibitors (eg, brinzolamide), and  $\alpha_2$ -receptor agonists (eg, brimonidine). However, monotherapy may provide insufficient IOP reduction in some patients, thereby necessitating the use of multiple IOP-lowering medications. Multidrug regimens may be complex, may increase the risk of preservative-related ocular symptoms, and may potentially reduce overall drug exposure as a consequence of drug washout during closely timed sequential administrations; these difficulties may reduce overall drug efficacy and decrease patient persistence and adherence with multidrug treatment regimens. Fixed-combination medications that provide two IOP-lowering therapies within a single solution are available and may overcome some of these challenges. However, all currently available fixed combinations combine timolol with another IOP-lowering agent, indicating that additional fixed-combination alternatives would be beneficial. To meet this demand, a novel fixed combination of brinzolamide 1% and brimonidine 0.2% (BBFC) has recently been developed. In two randomized, double-masked, multinational clinical trials, BBFC had greater IOP-lowering efficacy than brinzolamide or brimonidine monotherapy after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension. In both studies, the overall safety profile of BBFC was consistent with that of brinzolamide and brimonidine. Comparative studies with BBFC versus other IOP-lowering monotherapy and fixed-combination medications are not available, but the IOP reductions observed with BBFC are similar to or greater than those reported in the literature for other glaucoma treatments; thus, BBFC provides an additional fixed-combination therapeutic option for patients who require further efficacious IOP reduction and improved convenience and tolerability versus concomitant administration of two separate medications.

**Keywords:** adherence, fixed combination, persistence, Simbrinza<sup>®</sup>, tolerability

## Introduction

In 2010, glaucoma accounted for over 8 million incidences of blindness worldwide and was one of the leading causes of blindness.<sup>1</sup> By 2020, an estimated 79 million individuals worldwide will have been diagnosed with glaucoma.<sup>1</sup> Glaucoma is characterized by elevated intraocular pressure (IOP), progressive optic neuropathy, and corresponding visual field loss.<sup>2,3</sup> Lowering IOP to an individualized target level (typically a  $\geq 25\%$  reduction from initial IOP) and maintaining that level reduces the risk of vision loss and improves outcomes,<sup>4-6</sup> even among patients with normal-tension

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glaucoma.<sup>4</sup> Reduction of elevated IOP is currently the only therapeutic approach effective for the prevention of glaucoma progression.<sup>7</sup>

A wide array of IOP-lowering agents with different mechanisms of action are available, including  $\beta$ -blockers (eg, timolol), prostaglandin analogs (eg, latanoprost), carbonic anhydrase inhibitors (CAIs; eg, brinzolamide), and  $\alpha_2$ -adrenergic agonists (eg, brimonidine).<sup>5,8</sup> These medications reduce IOP by decreasing aqueous production,<sup>5</sup> increasing aqueous outflow,<sup>5,9</sup> or both.  $\beta$ -blockers and CAIs reduce aqueous production by limiting blood flow to the iris root–ciliary body<sup>10</sup> or through inhibition of sulfonamide-susceptible carbonic anhydrase isozymes, respectively.<sup>11</sup> In contrast, prostaglandin analogs reduce IOP by increasing uveoscleral and trabecular meshwork outflow of aqueous humor,<sup>7,12</sup> and  $\alpha_2$ -adrenergic agonists reduce aqueous production and augment aqueous outflow through the uveoscleral pathway.<sup>13</sup>

Standard first-line treatment for glaucoma consists of treatment with a single IOP-lowering medication;<sup>5,14</sup> however, one prospective study showed that approximately 40% of patients require multiple IOP-lowering medications to reach and maintain their target IOP.<sup>15</sup> Unfortunately, persistence (ie, continued use of medication over time) with IOP-lowering medications is low.<sup>16–19</sup> A systematic review of 14 studies that evaluated persistence using survival analysis demonstrated that only 31% of patients remained on their initial therapy at the end of 12 months.<sup>16</sup> Persistence may be affected by the medication and regimen prescribed. A retrospective United States health claims database study showed that persistence with prostaglandins,  $\alpha_2$ -receptor agonists, and CAIs for 3 years was greater than that with  $\beta$ -blockers.<sup>18</sup> However, drug-related differences in persistence likely disappear within a specific drug class; for example, a retrospective, population-based review of a United States health claims database showed that a similar percentage of patients were persistent with their prescribed prostaglandin analog medication during a 1-year period regardless of the specific agent prescribed (ie, latanoprost [69.4%], travoprost [70.6%], or bimatoprost [68.1%]).<sup>19</sup> In addition to the specific medication given, the dosing regimen prescribed for an individual may affect persistence; patients with complex therapeutic regimens requiring separate administration of several therapeutic agents tend to have lower persistence.<sup>20,21</sup>

Medication adherence (ie, following the agreed-upon treatment regimen)<sup>18,22–37</sup> is also less than optimal among patients with glaucoma, even though reduced adherence with IOP-lowering medication has been linked with progressive visual field loss.<sup>22,38</sup> Rates of adherence to IOP-lowering

treatment among patients with glaucoma across multiple studies are shown in Table 1. Lack of patient adherence to their therapeutic regimen may ultimately decrease drug effectiveness. In a retrospective analysis of patient adherence in an ophthalmology clinic, 26.8% of patients did not achieve their target IOP as a result of nonadherence.<sup>39</sup> The reasons for patient nonadherence are diverse. Treatment complexity (eg, treatment with >1 IOP-lowering drug) and patients' attitude toward, and insufficient knowledge of, glaucoma have been associated with reduced adherence.<sup>23,24,26,28,32,36,40–42</sup> Other factors that may disrupt medication use by patients include cost and insurance coverage, forgetting to take the medication, difficulty with instillation of drops, higher number of daily doses, initial medication drug class, and poor tolerability.<sup>18,24,27,29,36,41,42</sup>

Patients who require multiple concomitant medications to achieve and maintain IOP control may be more likely to deviate from their prescribed medication regimen. In a retrospective, open-label database review, addition of a second medication to a monotherapy regimen increased the time between medication refills by >2 weeks in some patients.<sup>43</sup> Trouble remembering to take medication and having difficulty opening medication bottles were reported by more patients receiving multiple concomitant glaucoma treatments than those receiving one medication; these complaints were associated with reduced adherence.<sup>27</sup> The efficacy, cost, and tolerability of multidrug regimens may also affect persistence and adherence. Persistence can be related to treatment efficacy because lack of efficacy often results in a switch in treatment. With administration of multiple medications, administration of a second drug within 5 minutes of an initial medication may cause substantial reductions in the concentration of the first drug because of washout of the first drug,<sup>44</sup> thereby potentially reducing overall IOP-lowering efficacy.<sup>44</sup> In a survey of patients using topical glaucoma medications, 23.5% of patients administered a second drop of medication within 5 minutes of the first drop, and 14% waited less than 2 minutes before instilling the second drop.<sup>45</sup> Additionally, exposure to more than one preserved topical medication (and therefore a greater cumulative exposure to irritating preservatives) may increase ocular symptoms<sup>46,47</sup> and may predispose patients to discontinue their therapy. Cost may also be a significant burden<sup>42</sup> because each separate drug solution may be associated with an additional copay.<sup>48</sup>

To address the barriers to optimal adherence and persistence with IOP-lowering therapy, several fixed-combination medications, which allow instillation of two medications in a single solution, have been developed. Fixed-combination

Table 1 Treatment adherence rates among patients with glaucoma

Study	Patient population	Study setting	Study design	N	Assessment technique	Study dates	Duration	Rate (%)
Loon et al <sup>32</sup>	Adult patients with chronic glaucoma who were receiving topical glaucoma therapy for >3 months	National university hospital in Singapore	Prospective, cross-sectional	314	RAM adherence questionnaire	NR	NR	19.7 <sup>a</sup>
Rees et al <sup>33</sup>	Adult patients with glaucoma or ocular hypertension who had received $\geq 1$ topical medication for $\geq 6$ months	Tertiary referral ophthalmology hospitals in the US, Australia, and Singapore	Cross-sectional	475	Modified RAM adherence questionnaire	NR	NR	47.5–65.4 <sup>b</sup>
Ung et al <sup>28</sup>	Adult patients with primary open-angle glaucoma, primary angle-closure glaucoma, exfoliative glaucoma, low-tension glaucoma, or who were suspected as having glaucoma > 1 year who had filled a prescription for topical ocular hypertension medications	San Francisco General Hospital glaucoma clinic in the US	Retrospective, cross-sectional	126	Patient questionnaire	2011	1 year	50 <sup>c</sup>
Vandenbroeck et al <sup>29</sup>	Adult patients with glaucoma or ocular hypertension who were receiving topical glaucoma medication	Hospital and private practice ophthalmology centers in Belgium	Multicenter, cross-sectional	663	Self-report questionnaire	NR	2 weeks	58.5 <sup>d</sup>
Hong et al <sup>30</sup>	Adult patients with glaucoma	Medical university clinic in South Korea	Cross-sectional	125	Patient questionnaire	NR	NR	46.15–70.59 <sup>e</sup>
Rees et al <sup>26</sup>	Adult patients with glaucoma or ocular hypertension who had received $\geq 1$ topical medication for $\geq 6$ months	Public tertiary ophthalmic hospital	Cross-sectional	131	Modified RAM adherence questionnaire	NR	2 months	55 <sup>a</sup>
Djafari et al <sup>23</sup>	Adult patients with primary open-angle glaucoma, ocular hypertension, or who were suspected as having glaucoma for $\geq 2$ years and were covered by the Régie d'Assurance Maladie du Québec pharmaceutical insurance program	Medicare database in Quebec, Canada	Descriptive database	181	Pharmaceutical claims database search	2004	1 year	71.8 <sup>f</sup>
Olthoff et al <sup>31</sup>	Adult patients who were receiving treatment for primary open-angle glaucoma	the Netherlands	Cross-sectional	166	Patient questionnaire	NR	4 weeks	73.5 <sup>d</sup>
Nordstrom et al <sup>18</sup>	Adult patients with confirmed or suspected open-angle glaucoma who received $\geq 1$ topical ocular hypotensive medication and were continuously enrolled in the United Healthcare database for $\geq 365$ days	Ingenix Research Database in the US	Retrospective cohort	5,300	Prescription refill	1995–2001	36 months	15–58 <sup>g</sup>
Sleath et al <sup>27</sup>	Adult patients with glaucoma who were receiving $\geq 2$ IOP-lowering medications	Private ophthalmology clinics in the US	Cross-sectional survey	324	Patient questionnaire	2004	1 week	86 <sup>h</sup>

**Notes:** <sup>a</sup>Patients who reported a full adherence score on the RAM questionnaire; <sup>b</sup>patients who disagreed or strongly disagreed in response to the questions "I sometimes forget to take my eye drops" and "I sometimes alter the dose or miss a dose of my eye drops to suit my own needs"; <sup>c</sup>and who reported "never" in answer to the questions "Some people I have talked to say that they miss out on a dose of their eye drops or adjust the doses to suit their own needs. How often do you do that?" and "Sometimes people forget to take their eye drops. How often does this happen to you?"; <sup>d</sup>patients who reported >80% adherence in response to the question "We understand that many individuals who have been prescribed glaucoma medication find it very difficult to take them regularly and often miss doses. On a scale from 0 to 100, with 0% being you never take your medications to 100% being you always take your medications and never miss a dose, how often did you take your medications?"; <sup>e</sup>patients who reported no missed doses; <sup>f</sup>patients who reported missing fewer than 1–2 doses per month; <sup>g</sup>patients who received  $\geq 75\%$  of their medication doses based on comparison of the number of days the patient had pharmaceutical coverage for medication versus the number of days the patient's medical chart indicated medication was to be taken; <sup>h</sup>patients who had a current refill of their initially prescribed medication; <sup>i</sup>patients who reported taking 100% of their medication.

**Abbreviations:** IOP, intraocular pressure; NR, not reported; RAM, reported adherence to medication.

medications reduce the number of medication bottles required, may reduce costs, and provide a simplified dosing regimen, all of which may increase persistence<sup>20,21,49</sup> and adherence.<sup>20,21</sup> In a 2008–2009 United States study, Kaplan–Meier survival analysis of a prescription database demonstrated increased persistence with fixed-combination IOP-lowering medications compared with concomitant administration of two separate drugs (Figure 1).<sup>21</sup> The same study reported greater adherence with fixed combinations (40.6%–42.7%) than separate administration of two medications (23.3%–34.9%) after 1 year of treatment.<sup>21</sup>

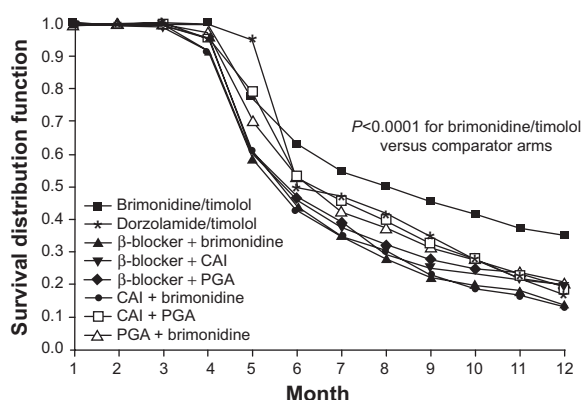
Prospective trials have shown that switching from concomitant administration of multiple separate medications to a fixed-combination therapy increases patient adherence.<sup>50,51</sup> For example, when patients were switched from separate administration of latanoprost 0.005% and timolol 0.5% to a fixed combination of latanoprost 0.005%/timolol 0.5%, the percentage of patients who reported never missing a dose was significantly greater after the switch (71.0%) compared with before the switch (59.3%;  $P=0.0115$ ).<sup>51</sup> Because adherence relies on patients' willingness to take their medication, it is important that patients prefer the medication they are prescribed over other equally efficacious alternatives. A reduction in ocular symptoms associated with the prescribed medication may have beneficial effects on patient preference and may increase adherence. Fixed combinations may have a better tolerability profile than concomitant administration of two agents with regard to ocular symptoms because cumulative exposure to irritating preservatives is reduced;<sup>52</sup> therefore, the reduced ocular

symptoms associated with fixed-combination medications may improve overall adherence.

A fixed-dose combination of a CAI, brinzolamide 1%, and an  $\alpha_2$ -adrenergic agonist, brimonidine 0.2% (BBFC; Simbrinza®; Alcon Laboratories, Inc., Fort Worth, TX, USA), has recently been developed to provide improved IOP-lowering efficacy, with a safety profile similar to its individual components. BBFC is approved for 3-times-daily dosing in the United States and is indicated for the reduction of elevated IOP in patients with primary open-angle glaucoma or ocular hypertension. This review highlights the efficacy and safety of this new fixed-combination medication and discusses its practical implications for patients.

## Efficacy of BBFC

In clinical trials, BBFC administered three times daily (in accordance with the approved dosing regimens of brinzolamide and brimonidine in the United States) had a greater IOP-lowering effect than brinzolamide 1% or brimonidine 0.2% after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension.<sup>53–56</sup> In these trials, baseline IOP values were similar among all treatment groups. Between-group differences in IOP from baseline were based on prespecified analyses of least squares (LS) means instead of arithmetic means. LS means differ from arithmetic mean values in that they account for covariates (eg, correlated IOP measurements within patients) and are less sensitive to missing data; therefore, LS means may be better estimates of the overall average IOP within this patient population. In a randomized, Phase III, double-masked clinical trial of BBFC versus brinzolamide or brimonidine in patients with open-angle glaucoma or ocular hypertension, the LS mean IOP after 3 months of treatment was significantly lower with BBFC (17.0–20.5 mmHg) than with brinzolamide (20.0–21.6 mmHg;  $P\leq 0.002$  for all time points) or brimonidine (18.8–23.3 mmHg;  $P<0.001$  for all time points) throughout the day (ie, 8 am, 10 am, 3 pm, and 5 pm; Table 2).<sup>53</sup> Mean IOP reductions from baseline and percentage change in IOP from baseline were also greater with BBFC (5.7–8.8 mmHg; percentage reduction, 24.1%–34.9%) than with brinzolamide (4.1–6.2 mmHg; percentage reduction, 16.9%–22.6%) or brimonidine (3.5–6.5 mmHg; percentage reduction, 14.3%–25.8%).<sup>53</sup> Similar results were observed in a separate randomized, double-masked Phase III trial with a 3-month safety extension (LS mean IOP at 3 months: BBFC, 17.2–21.1 mmHg; brinzolamide, 20.4–22.0 mmHg,  $P\leq 0.005$  versus [vs] BBFC; brimonidine, 18.9–23.2 mmHg,  $P<0.0001$  vs BBFC; Figure 2) and a pooled



**Figure 1** Kaplan–Meier analysis of treatment persistence among fixed and unfixed glaucoma medications.

**Notes:** Treatment persistence was evaluated from a medication database as medication possession ratio during a 1-year period after the index prescription date. Reproduced from Schwartz GF, Burk C, Bennett T, Patel VD. Adherence and persistence with glaucoma therapy: brimonidine/timolol versus dorzolamide/timolol and various two-bottle combinations. *J Clin Exp Ophthalmol*. 2012;3(8):1–6.<sup>21</sup> Copyright © 2012 Schwartz GF, et al.

**Abbreviations:** CAI, carbonic anhydrase inhibitor; PGA, prostaglandin analog.

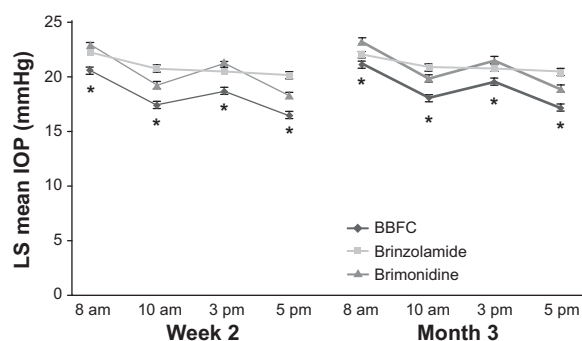
Table 2 Intraocular pressure across visits and time points<sup>a</sup>

Drug	Baseline				Week 2			
	8 am	10 am	3 pm	5 pm	8 am	10 am	3 pm	5 pm
<b>BBFC</b>								
Number	209	209	209	209	209	205	205	204
Mean (SD), mmHg	26.9 (2.6)	25.3 (2.8)	23.7 (3.0)	23.2 (3.1)	19.7 (3.4)	16.4 (3.0)	17.8 (3.0)	15.9 (2.9)
LS, mean (SE), mmHg	NA	NA	NA	NA	20.4 (0.3)	17.1 (0.3)	18.4 (0.3)	16.6 (0.3)
<b>Brinzolamide</b>								
Number	224	224	224	224	223	221	220	220
Mean (SD), mmHg	27.1 (2.6)	25.4 (2.7)	23.8 (3.2)	23.6 (3.4)	21.3 (3.7)	19.9 (3.4)	19.7 (3.6)	19.1 (3.3)
LS, mean (SE), mmHg	NA	NA	NA	NA	22.0 (0.3)	20.5 (0.3)	20.4 (0.3)	19.7 (0.3)
<b>Brimonidine</b>								
Number	216	216	216	216	216	212	212	212
Mean (SD), mmHg	27.0 (2.6)	25.4 (2.8)	24.0 (3.3)	23.7 (3.3)	21.6 (4.1)	18.6 (3.6)	19.8 (3.9)	17.6 (3.2)
LS, mean (SE), mmHg	NA	NA	NA	NA	22.4 (0.3)	19.4 (0.3)	20.6 (0.3)	18.4 (0.3)
<b>P-value<sup>b</sup></b>								
BBFC vs brinzolamide	NA	NA	NA	NA	<0.001	<0.001	<0.001	<0.001
BBFC vs brimonidine	NA	NA	NA	NA	<0.001	<0.001	<0.001	<0.001
<b>6 wk</b>								
<b>3 mo</b>								
<b>BBFC</b>								
Number	198	197	196	196	189	189	189	189
Mean (SD), mmHg	19.7 (3.9)	16.8 (3.4)	18.3 (3.6)	16.4 (3.4)	19.8 (4.2)	16.5 (3.6)	18.0 (3.7)	16.3 (3.7)
LS, mean (SE), mmHg	20.4 (0.3)	17.5 (0.3)	18.9 (0.3)	17.0 (0.3)	20.5 (0.3)	17.2 (0.3)	18.7 (0.3)	17.0 (0.3)
<b>Brinzolamide</b>								
Number	215	214	214	214	213	213	212	212
Mean (SD), mmHg	21.2 (4.3)	19.5 (3.7)	19.5 (3.3)	19.0 (3.5)	20.9 (4.2)	19.7 (4.0)	19.7 (3.7)	19.3 (3.7)
LS, mean (SE), mmHg	21.9 (0.3)	20.2 (0.3)	20.2 (0.3)	19.7 (0.3)	21.6 (0.3)	20.4 (0.3)	20.4 (0.3)	20.0 (0.3)
<b>Brimonidine</b>								
Number	203	201	200	199	192	192	192	190
Mean (SD), mmHg	21.8 (4.3)	18.6 (3.4)	20.2 (3.9)	17.7 (3.2)	22.5 (4.4)	18.9 (3.7)	20.5 (3.8)	17.9 (3.3)
LS, mean (SE), mmHg	22.6 (0.3)	19.5 (0.3)	21.1 (0.3)	18.6 (0.3)	23.3 (0.3)	19.7 (0.3)	21.3 (0.3)	18.8 (0.3)
<b>P-value<sup>b</sup></b>								
BBFC vs brinzolamide	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	<0.001	<0.001
BBFC vs brimonidine	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

**Notes:** <sup>a</sup>Intraocular pressure was analyzed using the intent-to-treat population. <sup>b</sup>Pairwise t-test on LS means. Reprinted with permission from Katz G, Dubiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol*. 2013;131(6):724–730. <sup>33</sup> Copyright © 2013 American Medical Association. All rights reserved.

**Abbreviations:** BBFC, brinzolamide 1%/brimonidine 0.2% fixed combination.





**Figure 2** LS mean IOP during a 3-month clinical trial with a 3-month safety extension.

**Notes:** Error bars represent SEs; \*BBFC versus brinzolamide or brimonidine,  $P < 0.001$ . Adapted from Nguyen QH, McMenemy MG, Realini T, Whitson JT, Goode SM. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther*. 2013;29(3):290–297.<sup>54</sup> The publisher for this copyrighted material is Mary Ann Liebert, Inc., publishers. Copyright © 2013.

**Abbreviations:** BBFC, brinzolamide 1%/brimonidine 0.2% fixed combination; IOP, intraocular pressure; LS, least squares; SE, standard error.

analysis of both Phase III trials (LS mean IOP at 3 months: BBFC, 17.1–20.8 mmHg; brinzolamide, 20.2–21.8 mmHg,  $P < 0.0001$  vs BBFC; brimonidine, 18.8–23.2 mmHg,  $P < 0.0001$  vs BBFC).<sup>54,55</sup> Greater reductions in mean IOP with BBFC compared with brinzolamide or brimonidine were observed at week 2 (the first post baseline evaluation day) in both Phase III trials<sup>53,54</sup> and continued for up to 6 months (mean reductions from baseline to month 6: 4.9–8.0 mmHg with BBFC, 4.1–5.8 mmHg with brinzolamide, and 3.0–6.3 mmHg with brimonidine).<sup>56</sup> Thus, the therapeutic benefit of BBFC occurs shortly after initial administration (ie, within the first 2 weeks) and continues for up to 6 months. Taken together, these data suggest that BBFC effectively lowers and maintains clinically relevant IOP reductions (ie, reductions  $\geq 1$  mmHg).<sup>57</sup> Although the IOP-lowering efficacy of some medications (eg,  $\beta$ -blockers, brimonidine) has been shown to fluctuate, often with decreased efficacy at night,<sup>58</sup> BBFC provides effective IOP reduction throughout the day. Some other fixed-combination glaucoma medications have also demonstrated 24-hour control of IOP. For example, fixed combinations of dorzolamide and timolol, and brimonidine and timolol both significantly decrease IOP from baseline (mean IOP reduction: 2.9 mmHg and 2.2 mmHg, respectively).<sup>59</sup> However, IOP reductions were greater during the night (6 pm and 2 am) with dorzolamide and timolol compared with brimonidine and timolol, which was to be expected given the decreased evening efficacy of both components.<sup>58,59</sup> Given that significant IOP reductions with BBFC are still seen at 8 am (10 hours after dosing), it is likely that the nocturnal IOP-lowering efficacy of BBFC is being conferred by the brinzolamide, not the

brimonidine, component.<sup>60,61</sup> However, 24-hour IOP control studies need to be conducted to confirm this.

The IOP reductions observed with BBFC in these clinical trials are similar to or greater than those observed with other monotherapy or fixed-combination treatments in other studies. Among IOP-lowering monotherapy treatments, prostaglandin analogs generally provide the greatest IOP-lowering efficacy (percentage IOP change from baseline at peak as determined in a meta-analysis of randomized clinical trials, 31%–33%), followed by  $\beta$ -blockers (23%–27%), an  $\alpha_2$ -adrenergic agonist (25%), and CAIs (17%–22%).<sup>62</sup> Similar trends in percentage IOP reduction from baseline have been observed among fixed-combination therapies combining timolol with prostaglandin analogs (peak IOP reduction as shown in a meta-analysis, 35%–36%), an  $\alpha_2$ -adrenergic agonist (32%), or CAIs (31%–34%).<sup>63</sup> With BBFC, peak percentage IOP reduction was approximately 32%–34%,<sup>53,54</sup> which is similar to that previously published for prostaglandin analogs and greater than reports with  $\alpha_2$ -adrenergic agonist and CAI monotherapy.<sup>62</sup> In addition, mean IOP reduction from baseline with BBFC at 3 months (5.4–8.8 mmHg) was similar to reductions observed with fixed-dose combinations containing timolol after 3 months of treatment (prostaglandin analogs plus timolol, 2.6–10.2 mmHg; CAIs plus timolol, 3.7–9.0 mmHg;  $\alpha_2$ -agonists plus timolol, ~5.5–7.5 mmHg; Table 3).<sup>53,54,64–75</sup>

## Safety and tolerability of BBFC

Similar to other fixed-combination therapies,<sup>48,64,66,69,72,74–76</sup> the overall safety profile of BBFC is consistent with that of its individual components (brinzolamide 1% and brimonidine 0.2%).<sup>53–56</sup> In clinical trials, ocular events were the most common treatment-related adverse events (TRAEs) associated with BBFC and occurred with similar frequency in the BBFC and brinzolamide or brimonidine groups (Tables 4 and 5).<sup>53,54,56</sup> In Phase III clinical trials, blurred vision (4.5%–6.1%) and eye irritation (2.8%–5.4%) were two of the most commonly reported ocular TRAEs with BBFC after 3 months of treatment.<sup>53,54</sup> Blurred vision was the most common ocular TRAE observed with brinzolamide (6.2%–6.8%) at 3 months.<sup>53,54</sup> The occurrence of blurred vision with BBFC and brinzolamide in some patients is unsurprising given that these medications are administered as ophthalmic suspensions. In contrast, the most frequently reported ocular TRAEs with brimonidine at 3 months were conjunctivitis (3.0%), dry eye (0.4%–2.7%), eye irritation (1.8%–2.6%), and ocular hyperemia (2.6%–4.1%).<sup>53,54</sup> In both trials, the incidence of ocular hyperemia was more

**Table 3** Mean 3-month IOP reductions with currently available fixed-combination glaucoma medications

Fixed combination	N	Hours after dosing	Mean $\pm$ SD absolute IOP change from baseline <sup>a</sup> (mmHg)	Mean $\pm$ SD IOP change from baseline <sup>a</sup> (%)
Dorzolamide/timolol <sup>64</sup>	114	0	-7.7 $\pm$ 4.2	-27.4 $\pm$ 13.1
	112	2	-9.0 $\pm$ 4.3	-32.7 $\pm$ 12.9
Dorzolamide/timolol <sup>70</sup>	151	0	-4.2 $\pm$ 3.3	-16.3 $\pm$ 12.5
	151	2	-5.4 $\pm$ 3.1	-21.6 $\pm$ 12.3
Dorzolamide/timolol <sup>74</sup>	120	0	-3.6 $\pm$ 3.0	-13.8 $\pm$ 11.1
	119	2	-5.0 $\pm$ 3.5	-19.7 $\pm$ 12.9
	116	8	-3.7 $\pm$ 3.4	-14.9 $\pm$ 13.2
Brinzolamide/timolol <sup>75</sup>	171	0	-8.3 $\pm$ 3.8	30.6 <sup>c</sup>
	171	2	-8.7 $\pm$ 3.9	33.7 <sup>c</sup>
Brimonidine/timolol <sup>66</sup>	385	0	-7.0 <sup>b</sup>	NA
	385	2	-7.5 <sup>b</sup>	NA
	385	7	-5.5 <sup>b</sup>	NA
Brimonidine/timolol <sup>73</sup>	385	0	-7.0 <sup>b</sup>	NA
	NA	2	-7.5 <sup>b</sup>	NA
	NA	7	-5.5 <sup>b</sup>	NA
Latanoprost/timolol <sup>67</sup>	NA	Diurnal <sup>d</sup>	-3.6 <sup>b,c,e</sup>	NA
Latanoprost/timolol <sup>68</sup>	129	Diurnal <sup>f</sup>	-10.2 <sup>c</sup>	NA
Latanoprost/timolol <sup>71</sup>	170	Diurnal <sup>f</sup>	-10.0 <sup>c</sup>	NA
Latanoprost/timolol <sup>72</sup>	140	Diurnal <sup>d</sup>	-2.6 <sup>c,e</sup>	NA
Bimatoprost/timolol <sup>65</sup>	533	0	-9.2 $\pm$ 3.7	NA
	NA	2	-7.8 $\pm$ 4.0	NA
	NA	8	-7.4 $\pm$ 4.0	NA
Travoprost/timolol <sup>69</sup>	151	0	-8.7 $\pm$ 3.2	-34 $\pm$ 12
	151	2	-7.8 $\pm$ 3.0	-33 $\pm$ 11
	151	8	-7.4 $\pm$ 3.0	-32 $\pm$ 11
Brinzolamide/brimonidine <sup>54</sup>	196	0	-6.7 <sup>c</sup>	-24.6 <sup>b</sup>
	194	2	-8.3 <sup>c</sup>	-32.2 <sup>b</sup>
	194	7	-5.4 <sup>c</sup>	-22.1 <sup>b</sup>
Brinzolamide/brimonidine <sup>53</sup>	189	0	-7.1 <sup>c</sup>	-26.4 <sup>b</sup>
	189	2	-8.8 <sup>c</sup>	-34.8 <sup>b</sup>
	189	7	-5.7 <sup>c</sup>	-24.1 <sup>b</sup>

**Notes:** <sup>a</sup>When available; <sup>b</sup>approximate values (estimated from graphical data); <sup>c</sup>calculated means from values stated in article text or tables; <sup>d</sup>diurnal IOP was calculated as the mean of IOP measures at 8 am, 10 am, and 4 pm; <sup>e</sup>IOP assessed at 13 weeks; <sup>f</sup>mean IOP at 8 am, 10 am, and 4 pm or the mean of non-missing IOP measurements if a measurement was missing.

**Abbreviations:** IOP, intraocular pressure; NA, not available; SD, standard deviation.

prevalent with brimonidine (2.6%–4.1%) than BBFC (0.9%–3.3%) or brinzolamide (0.4%–0.9%) at 3 months.<sup>53,54</sup> After 6 months of treatment, eye irritation and eye allergy were the most common ocular TRAEs associated with BBFC (6.3% for both), whereas blurred vision (6.8%) and conjunctivitis (6.0%) were most frequent in the brinzolamide and brimonidine groups, respectively (Table 5).<sup>56</sup> Eye allergy rates were 0.4% with brinzolamide and 2.1% with brimonidine at 6 months.<sup>56</sup> The incidence of ocular hyperemia continued to be higher in the brimonidine group (3.8%) than the BBFC (2.7%) or brinzolamide (0.4%) groups after 6 months.<sup>56</sup> In the two Phase III clinical trials, discontinuations because of nonserious TRAEs were more common with BBFC (up to 11.3%) than with brinzolamide

(up to 2.1%) or brimonidine (up to 9.4%).<sup>53,54</sup> The slightly greater occurrence of some TRAEs and TRAE-related discontinuations with BBFC in these studies may be attributable to exposure to multiple therapeutic agents (ie, brinzolamide and brimonidine) versus monotherapy.

The lack of head-to-head comparative studies of BBFC and other IOP-lowering monotherapies and fixed-combination medications prevents the assessment of BBFC tolerability in terms of other IOP-lowering therapies, and differences in study design preclude direct comparisons between IOP-lowering medications evaluated in different clinical trials. However, the incidence of eye burning/stinging/irritation (which are often associated with  $\beta$ -blockers) appeared to be similar with BBFC compared

**Table 4** Treatment-related adverse events (incidence  $\geq 1\%$  in any group) from a 3-month Phase III trial

Adverse event	BBFC, n (%) (n=214)	Brinzolamide 1%, n (%) (n=226)	Brimonidine 0.2%, n (%) (n=220)
Ocular			
Blurred vision	13 (6.1)	14 (6.2)	1 (0.5)
Ocular hyperemia	7 (3.3)	2 (0.9)	9 (4.1)
Eye irritation	6 (2.8)	2 (0.9)	4 (1.8)
Allergic conjunctivitis	4 (1.9)	1 (0.4)	2 (0.9)
Eye pain	3 (1.4)	4 (1.8)	2 (0.9)
Conjunctival hyperemia	3 (1.4)	4 (1.8)	3 (1.4)
Foreign body sensation in eyes	3 (1.4)	2 (0.9)	1 (0.5)
Dry eye	2 (0.9)	2 (0.9)	6 (2.7)
Eye pruritus	2 (0.9)	2 (0.9)	3 (1.4)
Eye allergy	1 (0.5)	0	3 (1.4)
Punctate keratitis	1 (0.5)	1 (0.4)	3 (1.4)
Eye discharge	1 (0.5)	3 (1.3)	0
Nonocular			
Dysgeusia	8 (3.7)	14 (6.2)	0
Dry mouth	7 (3.3)	0	6 (2.7)

**Notes:** Reproduced with permission from Katz G, Dubiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol.* 2013;131(6):724–730.<sup>53</sup> Copyright © 2013 American Medical Association. All rights reserved.

**Abbreviation:** BBFC, brinzolamide 1%/brimonidine 0.2% fixed combination.

with previous reports for timolol at 3 months (up to 5.4% with BBFC vs up to 18.1% [burning and stinging] with timolol) and slightly greater with BBFC than timolol at 6 months (6.3% with BBFC vs 4.5% [burning and stinging] with timolol).<sup>53,54,56,64,66,75</sup> The incidence of other AEs (eg, blurred vision, which is commonly associated

with CAIs) was slightly greater at month 3 with BBFC (up to 6.1%) than that previously reported with dorzolamide (4.0%).<sup>53,54,64</sup> In general, the safety profile of BBFC appears to be similar to other currently marketed fixed-combination medications. Emergence or worsening of hyperemia was reported in up to 3.3% of patients receiving BBFC in

**Table 5** Treatment-related adverse events (incidence  $\geq 1\%$  in either group) from a 3-month clinical trial with a 3-month safety extension

TRAЕ	3 months			6 months		
	BBFC, n (%) (n=221)	Brinzolamide, n (%) (n=234)	Brimonidine, n (%) (n=235)	BBFC, n (%) (n=221)	Brinzolamide, n (%) (n=234)	Brimonidine, n (%) (n=235)
Ocular						
Eye irritation	12 (5.4)	4 (1.7)	6 (2.6)	14 (6.3)	3 (1.3)	8 (3.4)
Blurred vision	10 (4.5)	16 (6.8)	0	10 (4.5)	16 (6.8)	0
Eye allergy	10 (4.5)	0	2 (0.9)	14 (6.3)	1 (0.4)	5 (2.1)
Eye pain	6 (2.7)	4 (1.7)	3 (1.3)	6 (2.7)	4 (1.7)	3 (1.3)
Eye pruritus	5 (2.3)	3 (1.3)	0	7 (3.2)	2 (0.9)	3 (1.3)
Allergic conjunctivitis	4 (1.8)	1 (0.4)	5 (2.1)	8 (3.6)	1 (0.4)	10 (4.3)
Conjunctival hyperemia	4 (1.8)	1 (0.4)	2 (0.9)	5 (2.3)	1 (0.4)	3 (1.3)
Dry eye	4 (1.8)	2 (0.9)	1 (0.4)	4 (1.8)	2 (0.9)	2 (0.9)
Conjunctivitis	4 (1.8)	0	7 (3.0)	11 (5.0)	0	14 (6.0)
Increased lacrimation	3 (1.4)	1 (0.4)	1 (0.4)	3 (1.4)	1 (0.4)	2 (0.9)
Ocular hyperemia	2 (0.9)	1 (0.4)	6 (2.6)	6 (2.7)	1 (0.4)	9 (3.8)
Conjunctival follicles	1 (0.5)	0	3 (1.3)	1 (0.5)	0	4 (1.7)
Nonocular						
Dysgeusia	9 (4.1)	24 (10.3)	1 (0.4)	9 (4.1)	24 (10.3)	1 (0.4)
Dry mouth	6 (2.7)	0	5 (2.1)	7 (3.2)	0	5 (2.1)
Fatigue	1 (0.5)	0	4 (1.7)	1 (0.5)	0	4 (1.7)

**Notes:** 3 months data adapted with permission from Nguyen QH, McMenemy MG, Realini T, Whitson JT, Goode SM. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther.* 2013;29(3):290–297.<sup>54</sup> The publisher for this copyrighted material is Mary Ann Liebert, Inc. publishers. Copyright © 2013. 6 months data is adapted with permission of Dove Medical Press Ltd., from Six-month results from a phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension, Whitson JT, Realini T, Nguyen QH, McMenemy MG, Goode SM, 7, 2013.<sup>56</sup> Copyright © 2013.

**Abbreviations:** BBFC, brinzolamide 1%/brimonidine 0.2% fixed combination; TRAЕ, treatment-related adverse event.



two clinical trials,<sup>53,54</sup> an incidence similar to that reported with prostaglandin analog/timolol fixed combinations across multiple studies (up to 2.8%).<sup>68,71,72</sup> Additionally, the incidence of blurred vision with BBFC (up to 6.1%)<sup>53,54</sup> was only slightly greater than that previously observed with CAI fixed combinations (brinzolamide/timolol, 3.4%; dorzolamide/timolol, 4%).<sup>64,75</sup>

As with all fixed-combination medications, BBFC increases IOP-lowering efficacy by providing two medications with different mechanisms of action in a single drop, with a potential decrease in cumulative exposure to preservatives. Preservatives, particularly benzalkonium chloride (BAK), have been associated with a variety of ocular symptoms, including dry eye,<sup>47,77,78</sup> foreign body sensation in the eye,<sup>77</sup> stinging/burning,<sup>77,78</sup> tearing,<sup>77</sup> reduced tear production,<sup>78</sup> and hyperemia;<sup>77</sup> thus, limiting exposure to preservatives by using fixed-combination medications instead of multiple individual medications may improve overall tolerability. For example, a recent systematic review and meta-analysis of randomized trials comparing fixed combinations of prostaglandins and timolol with concomitant administration of both medications showed that the relative risk of hyperemia was lower with the fixed combination than with the unfixed combinations (relative risk, 0.70; 95% confidence interval, 0.43–1.14).<sup>79</sup> In a pooled analysis of two 3-month clinical trials, ocular symptoms that have been associated with preservatives (eg, dry eye and ocular hyperemia) occurred at a similar rate with BBFC (1.4% and 2.1% for dry eye and ocular hyperemia, respectively) compared with individual administration of brinzolamide (0.9% and 0.7%) or brimonidine (1.5% and 3.3%).<sup>55</sup> Although it is possible that punctate keratitis, which was reported in only one of the Phase III trials (0.5%, 0.4%, and 1.4% with BBFC, brinzolamide, and brimonidine, respectively),<sup>53</sup> may have contributed to the incidence of these ocular symptoms, this association remains unclear. These data suggest that despite exposure to additional medications (ie, two therapeutic agents instead of one), BBFC does not elicit any greater risk of ocular symptoms than its individual components. This observation may be explained by the reduced exposure to preservatives with BBFC versus administration of two separate preservative-containing medications.

Some IOP-lowering agents (eg, topical  $\beta$ -blockers and  $\alpha_2$ -receptor agonists) have been associated with significant alterations in blood pressure.<sup>80,81</sup> For example, in a head-to-head trial in 27 patients with newly diagnosed primary open-angle glaucoma, brimonidine and timolol, but not dorzolamide or latanoprost, significantly reduced systolic and

diastolic blood pressure from baseline;<sup>82</sup> however, the clinical significance of these alterations is unknown. Interestingly, diastolic ocular perfusion pressure was low with timolol and brimonidine (53.0 mmHg and 46.2 mmHg, respectively), whereas values with dorzolamide (55.9 mmHg) and latanoprost (56.4 mmHg)<sup>82</sup> exceeded the threshold associated with progression of primary open-angle glaucoma (ie, <55 mmHg).<sup>83</sup> With BBFC, a slight decrease in mean systolic and diastolic blood pressure was observed in clinical studies; similar reductions were reported with brinzolamide and brimonidine and none were considered to be of clinical concern.<sup>53–56</sup> Furthermore, individual blood pressure and pulse rate remained relatively stable (<1.5 bpm decrease in the BBFC, brinzolamide, and brimonidine groups).<sup>53–56</sup> Some clinical studies of other available fixed-combination therapies, all of which contain timolol, have also reported no clinically significant changes in blood pressure from baseline.<sup>65,69</sup> However, small but statistically significant mean alterations in heart rate and blood pressure from baseline have been reported with certain fixed-combination medications (eg, brimonidine/timolol<sup>66,73</sup> and latanoprost/timolol).<sup>67</sup>

## Additional considerations for BBFC

BBFC provides IOP-lowering efficacy greater than instillation of either of its components (brinzolamide or brimonidine), with potentially improved adherence and tolerability compared with concomitant administration of the separate medications. The increased convenience of dosing with one bottle instead of two may improve adherence and persistence and allow patients to achieve greater IOP control than dosing with separate components. IOP lowering may also be augmented with BBFC because it eliminates the potential of drug washout from sequential instillations of concomitant medications. In addition, reduced overall exposure to preservatives may increase patient comfort (and, as a result, potentially increase adherence to medication) and reduce the need for discontinuation or switching of therapies.

All currently available fixed-combination IOP-lowering medications provide similar IOP-lowering efficacy.<sup>53,54,63</sup> However, all of these medications, except BBFC, contain the  $\beta$ -blocker timolol. Because glaucoma incidence increases with age,<sup>84</sup> patients with glaucoma or ocular hypertension tend to have comorbid conditions or therapeutic regimens (eg, systemic  $\beta$ -blockers)<sup>85</sup> that make them vulnerable to adverse drug reactions (eg, depression of systemic cardiovascular function observed with  $\beta$ -blockers).<sup>86–90</sup> By providing effective IOP reduction with brinzolamide and brimonidine instead of timolol, BBFC expands the available fixed-combination

options for patients who require efficacious IOP lowering and for those in whom use of  $\beta$ -blockers is contraindicated.

## Conclusion

Glaucoma affects millions of individuals worldwide and is a leading cause of blindness.<sup>1</sup> Reduction of IOP may prevent or delay visual field loss in patients with glaucoma or ocular hypertension;<sup>4,6</sup> thus, monotherapy with IOP-lowering medications is standard-of-care treatment. However, many patients require multiple IOP-lowering therapies to reach their target IOP.<sup>15,91</sup> Drug washout during concomitant administration of multiple medications<sup>44</sup> and low adherence and persistence with complex glaucoma therapeutic regimens<sup>22,24,27</sup> may reduce the effectiveness of multidrug regimens. Fixed-combination medications prevent drug washout, simplify dosing regimens, and may reduce costs,<sup>92</sup> thereby potentially increasing medication adherence<sup>21,51,93,94</sup> and persistence.<sup>20,21</sup> BBFC provides IOP-lowering efficacy greater than or similar to various monotherapy and fixed-combination medications, with potentially improved convenience and better tolerability.

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