

Phase III safety and efficacy study of long-term brinzolamide/timolol fixed combination in Japanese patients with open-angle glaucoma or ocular hypertension

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Background: The purpose of this study was to evaluate the safety and efficacy of a long-term, twice-daily brinzolamide 1%/timolol 0.5% fixed combination ophthalmic suspension (BRINZ/TIM-FC) in Japanese patients with open-angle glaucoma (primary open-angle, normal-tension, exfoliation, or pigmentary) or ocular hypertension.

Methods: This was a prospective, nonrandomized, multicenter, open-label, Phase III study of Japanese patients aged ≥ 20 years with diagnoses of open-angle glaucoma or ocular hypertension. Patients were treated with topical BRINZ/TIM-FC twice daily for 52 weeks. The primary endpoint was mean reduction from baseline in intraocular pressure. Data were analyzed using repeated-measures analysis of variance and *t*-tests. Adverse events and ophthalmic, physiologic, and laboratory parameters were measured throughout the study as safety endpoints. A total of 126 patients (mean \pm SD age, 63 \pm 12 years) were enrolled, and 125 received BRINZ/TIM-FC.

Results: Mean intraocular pressure was significantly reduced from baseline at weeks 4 through 52, with changes ranging from -4.1 mmHg to -5.7 mmHg ($P < 0.0001$, all time points). Adverse events related to BRINZ/TIM-FC treatment were observed in 22% of patients. No substantial changes from baseline were observed in ophthalmic, physiologic, or laboratory variables.

Conclusion: Long-term, twice-daily BRINZ/TIM-FC therapy produced and maintained significant intraocular pressure reductions and was generally well tolerated in Japanese patients with open-angle glaucoma or ocular hypertension.

Keywords: clinical trial, intraocular pressure, long-term safety, Japan

Introduction

Glaucoma is a progressive, vision-threatening disease characterized by functional and structural ocular abnormalities and is commonly associated with increased intraocular pressure (IOP). In the last few years, clinical perspectives have evolved to define glaucoma as a collection of diseases with varied etiologies leading to similar characteristic changes in the optic nerve disc and resulting defects of the visual field.¹ These changes occur in normotensive patients and in patients with elevated IOP.² Patients with ocular hypertension lack the optic disc pathology characteristic of glaucoma but are also at risk for visual impairment.³ Despite advances in diagnosis and treatment, glaucoma remains a leading global cause of visual impairment and irreversible blindness.^{4,5} In Japan, glaucoma is the leading cause of visual impairment

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and has an incidence of approximately 4% in patients aged ≥ 40 years.^{6,7} The prevalence of visual impairment in Japan is projected to increase to nearly 2 million people by 2050, and glaucoma accounts for approximately 24% of patients with impaired vision.⁷

The primary treatment approach for managing and preventing progression of glaucoma and ocular hypertension is lowering IOP.⁸ Maintaining sufficient reduction of IOP decreases the risk of vision loss and improves outcomes even in patients with normal-tension glaucoma.⁹ Large-scale clinical studies have demonstrated that $\geq 40\%$ of patients with glaucoma or ocular hypertension require two or more medications to maintain sufficient reductions in IOP after the first year of treatment; however, increasing the complexity of treatment decreases patient compliance with dosing regimens.^{10–12} Compared with use of multiple separate topical medications, use of fixed-combination therapies combining IOP-lowering medications may simplify drug administration, eliminate risk of drug washout, and decrease cumulative patient exposure to preservatives.^{12–15} Brinzolamide 1%, a reversible carbonic anhydrase inhibitor, and timolol 0.5%, a $\beta 1/\beta 2$ -blocker, effectively reduce IOP when used individually as topical monotherapy and exhibit increased efficacy when used in combination.¹⁶ A fixed combination of brinzolamide 1% and timolol 0.5% (BRINZ/TIM-FC) was demonstrated to be noninferior to a fixed-combination therapy of timolol plus an alternative carbonic anhydrase inhibitor, dorzolamide, and to be preferred over patients' previous monotherapies and combined therapies.^{17,18}

Fixed-combination ocular hypotensive therapies have consistently demonstrated IOP-lowering efficacy similar to or better than unfixed combinations of their component drugs.^{19–23} Concomitant therapy with multiple individual drugs is associated with decreased treatment compliance compared with single-drop therapy;^{12,15,20,24} therefore, fixed combinations are a desirable treatment option. A study of 162 Japanese patients treated with multiple drugs revealed that nearly 30% of the study population was treated with combinations including β -blockers and carbonic anhydrase inhibitors.²⁵ There are currently no published studies of long-term BRINZ/TIM-FC therapy in Japanese patients with open-angle glaucoma or ocular hypertension. The objective of this multicenter, open-label, Phase III study was to evaluate the safety and efficacy of 52 weeks of twice-daily BRINZ/TIM-FC therapy in adult Japanese patients with open-angle glaucoma (primary open-angle, normal-tension, exfoliation, or pigmentary) or ocular hypertension.

Patients and methods

Study design

This was a multicenter, open-label, 52-week, Phase III study. At the screening visit, IOP was assessed and use of ocular hypotensive therapies was discontinued. The baseline visit was scheduled at least 4–27 days after the screening visit according to the required drug washout duration for discontinued IOP-lowering drugs (β -blockers and prostaglandin analogs, >27 days; α and $\alpha\beta$ agonists, >13 days; miotics and carbonic anhydrase inhibitors, >4 days); when multiple medications were used (fixed or unfixed combinations), a longer washout period was used. These washout periods were similar to durations described in previous studies.^{26,27} Baseline ophthalmic assessments (IOP, best-corrected visual acuity, visual field test, slit-lamp examination, gonioscopy, ophthalmoscopy), physiologic assessments (resting blood pressure, pulse rate), and laboratory tests were performed at 9 am for the screening or baseline visit before administration of the investigational drug; IOP, blood pressure, and pulse were also assessed at 11 am, 2 hours post instillation. At the conclusion of the baseline visit, patients were instructed to instill one drop of BRINZ/TIM-FC in each eye at 9 am (± 30 minutes) and 9 pm (± 30 minutes) for the duration of the study. At the screening visit, patients were provided with a journal and requested to record the conditions of BRINZ/TIM-FC instillation (eg, time of instillation, missed doses) and changes in the use of concomitant drugs.

The study protocol was reviewed and approved by the institutional review board of each participating institution and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Patients

Study participants were Japanese patients aged ≥ 20 years with an existing diagnosis of open-angle glaucoma (primary open-angle, normal-tension, exfoliation, or pigmentary) or ocular hypertension at enrollment, and with IOP levels of 15–36 mmHg in both eyes at 9 am and 11 am at the baseline visit. Patients were eligible if they were receiving treatment with multiple IOP-lowering drugs (including combination drugs) at screening, or if they were treated with a single IOP-lowering drug and had insufficient IOP reduction at screening. Insufficient IOP reduction was defined as IOP >18 mmHg in at least one eye at the screening visit (primary open-angle, exfoliation, or pigmentary glaucoma)^{28,29} or IOP elevation $<30\%$ from the screening visit to the baseline visit (normal-tension glaucoma). In previous studies, reducing IOP

to <18 mmHg in patients with open-angle glaucoma or by $\geq 30\%$ in patients with normal-tension glaucoma resulted in slower rates of visual field progression.^{9,30,31} Patients were required to have been on a stable ocular hypotensive treatment regimen for ≥ 4 weeks before the screening visit and to be able to safely discontinue use of all ocular hypotensive medications before the baseline visit according to the washout schedule described above.

Key exclusion criteria included women who were pregnant, nursing, or planning to become pregnant during the study; current or previous (within 30 days of the screening visit) treatment with another investigational agent; inner eye surgery within 6 months or laser eye surgery within 3 months before screening; post-washout IOP ≥ 36 mmHg; best-corrected visual acuity worse than 0.2 (decimal acuity scale) in either eye; anterior angle grade below grade 2 in either eye; significant visual field defects as determined by the investigators; chronic or recurrent ocular inflammation, injury, or disease; and medical conditions or histories that could interfere with treatment, IOP and safety assessments, or data interpretation.

Treatment

Patients received BRINZ/TIM-FC (Azarga®, Alcon Laboratories, Fort Worth, TX, USA) ophthalmic solution.

Efficacy assessments

The primary efficacy endpoint was mean IOP change from baseline. Mean IOP over time was a secondary efficacy endpoint. IOP was measured at 9 am and 11 am at the baseline, week 26, and week 52 visits and at 11 am only at the week 4, 8, 13, 19, 32, 39, and 45 visits. Tonometry was performed at each study site using a Goldmann tonometer that was standard for that clinical practice; IOP was measured once at each time point.

Safety assessments

Safety endpoints were assessed throughout the study, and included adverse events, resting blood pressure and pulse rate, visual field (static perimetry; stages based on Greve's Modified Method of the Aulhorn Classification³²), best-corrected visual acuity (decimal), slit-lamp examination (cornea, eyelid/conjunctiva, iris/anterior chamber, and lens), anterior chamber angle grade (gonioscopy), cup-to-disc ratio, ophthalmoscopy (vitreous body, retina/macula lutea/choroid, and optic nerve), and laboratory tests (hematology, blood biochemistry, qualitative urine test). Solicited and unsolicited adverse events were recorded at each visit and coded using

the Medical Dictionary for Regulatory Activities (MedDRA), Japanese version 14.1.

Statistical analyses

Statistical analyses were performed when all patients completed the week 26 and week 52 visits. Least squares means of IOP change from baseline were estimated with 95% confidence intervals using repeated-measures analysis of variance. Significance of the primary endpoint, ie, reduction in IOP from baseline, was determined by paired *t*-tests at each time point. Descriptive statistics (eg, mean, standard deviation, percentage) were obtained for IOP change from baseline, IOP over time, and safety parameters.

Group sizes and statistical power were determined before initiation of the study. With an estimated standard deviation of 3.0 mmHg for IOP change from baseline, a sample size of ≥ 100 patients was determined. With a group size of 100 patients, mean scores were estimated within 0.6 mmHg (standard deviation 0.20 mmHg) using 95% two-sided confidence intervals based on a paired *t*-test with 99 degrees of freedom.

All study outcomes were analyzed using one eye (the target eye) from each patient. The target eye was defined as the eye satisfying the inclusion/exclusion criteria; if both eyes satisfied these criteria, the worse eye was selected. The worse eye was defined as the eye with higher IOP at 11 am on the baseline visit. If IOP was equal at 11 am, the eye with higher IOP at 9 am was selected. If both eyes had equal IOP at 9 am and 11 am, the right eye was selected for analysis. Efficacy was assessed in the intent-to-treat population (ie, all patients who received study medication and had available examinations/observation data) and the per-protocol population (ie, all patients who received study medication, had available examinations/observation data, and satisfied the protocol criteria). Safety variables were analyzed in the safety population (ie, all patients who received study medication).

Results

Patients

A total of 126 patients (mean \pm SD age, 63 \pm 12 years) were enrolled in the study. Demographic and disease characteristics from the intent-to-treat population at baseline are presented in Table 1. Most patients (n=98/125; 78%) had a diagnosis of open-angle glaucoma (primary open-angle, normal-tension, or exfoliation glaucoma), whereas 22% (n=27/125) had a diagnosis of ocular hypertension. No enrolled patients had pigmentary glaucoma. At screening, the glaucoma medications used included prostaglandin

Table 1 Patient demographics and diagnoses

	BRINZ/TIM-FC (n=125)
Sex, n (%)	
Men	62 (50)
Women	63 (50)
Age, years, mean \pm SD	63.0 \pm 12.0
Age group, years, n (%)	
<65	57 (46)
\geq 65	68 (54)
\geq 65 to <75	50 (40)
\geq 75 to <85	17 (14)
\geq 85 to <95	1 (1)
Diagnosis, n (%)	
Primary open-angle glaucoma	57 (46)
Normal-tension glaucoma	39 (31)
Exfoliation glaucoma	2 (2)
Pigmentary glaucoma	0 (0)
Ocular hypertension	27 (22)

Abbreviations: BRINZ/TIM-FC, brinzolamide 1%/timolol 0.5% fixed combination; SD, standard deviation.

and β -blocker monotherapies and prostaglandin/ β -blocker, prostaglandin/carbonic anhydrase inhibitor, β -blocker/carbonic anhydrase inhibitor, and prostaglandin/ β -blocker/carbonic anhydrase inhibitor combination therapies (fixed and unfixed). Mean IOP at screening ranged from 16.2 mmHg to 19.0 mmHg; after washout of glaucoma medications, mean increases in IOP from screening to baseline ranged from 1.0 mmHg to 6.6 mmHg (Table 2). Mean IOP increased from

Table 2 Intraocular pressure before and after washout of previous glaucoma medications

	Patients, n (%)	Mean \pm SD		Change from screening at baseline	
		Screening		9 am	
		9 am	11 am	9 am	11 am
	n=125	9 am	11 am	9 am	11 am
Monotherapy					
PG	42 (34)	16.8 \pm 2.8	16.9 \pm 2.4	2.9 \pm 2.0	3.0 \pm 2.0
β -blocker	22 (18)	19.0 \pm 3.4	19.2 \pm 3.5	1.9 \pm 1.9	1.4 \pm 2.5
Concomitant therapy with two drugs ^a					
PG/ β -blocker	34 (27)	17.4 \pm 3.5	17.4 \pm 3.6	3.5 \pm 2.3	4.0 \pm 3.0
PG/CAI	5 (4)	16.2 \pm 1.5	16.2 \pm 2.2	5.2 \pm 1.9	6.0 \pm 0.7
β -blocker/CAI	10 (8)	16.3 \pm 3.5	16.5 \pm 3.5	3.1 \pm 3.5	3.4 \pm 2.2
Concomitant therapy with three drugs ^a					
PG/ β -blocker/CAI	8 (6)	17.6 \pm 1.1	18.3 \pm 1.4	6.5 \pm 2.6	6.6 \pm 3.7
Other	4 (3)	16.5 \pm 2.6	17.0 \pm 2.6	1.8 \pm 2.2	1.0 \pm 0.8

Note: ^aFixed or unfixed combinations.

Abbreviations: CAI, carbonic anhydrase inhibitor; PG, prostaglandin analog; SD, standard deviation.

screening levels after washout of all classes of previously used glaucoma drugs.

One patient was discontinued from the study after screening but before receiving BRINZ/TIM-FC because the inclusion criteria were not met. A total of 125 patients were treated with BRINZ/TIM-FC and included in the intent-to-treat and safety populations. Eleven patients discontinued the study during treatment. Five patients discontinued because of adverse events (hospitalization and treatment for unrelated conditions [n=2], ocular complications [n=2], and insufficient IOP reduction [n=1]). The other cases of discontinuation were because of patient request (n=4) and investigator decision (n=2).

Efficacy

Mean IOP and efficacy results for the intent-to-treat and per-protocol populations were similar throughout the study; therefore, efficacy data are presented only for the intent-to-treat population. Mean \pm SD baseline IOP values at 9 am and 11 am were 20.5 \pm 3.3 mmHg and 20.8 \pm 3.3 mmHg, respectively. With BRINZ/TIM-FC treatment, least squares mean IOP reductions from baseline were significant at all time points assessed (range -4.1 to -5.7 mmHg; all $P < 0.0001$). Descriptive statistics (mean \pm standard deviation) for IOP reductions from baseline are shown in Figure 1. At treatment weeks 4 through 52, mean IOP ranged from 15.1 mmHg to 16.4 mmHg (Figure 2).

Safety

Overall, adverse events were reported in 66% of patients (n=82/125); adverse events for which a causal relationship with BRINZ/TIM-FC could not be ruled out were observed in 22% of patients (n=28/125, Table 3). All potentially treatment-related adverse events were mild (n=26/28) or moderate (n=2/28). There were six serious adverse events reported in five patients (n=1 each of malignant lung neoplasm, cholelithiasis, epilepsy/sudden hearing loss, cerebral artery occlusion, and hemorrhagic enterocolitis); none were considered to be related to BRINZ/TIM-FC treatment. The most frequently observed treatment-emergent adverse events (occurring in \geq 5% of patients) were rhinopharyngitis (21% [n=26]), punctate keratitis (10% [n=13]), and eye irritation (6% [n=7]). Treatment-related adverse events with an incidence \geq 2% included punctate keratitis, eye irritation, keratitis, and dysgeusia (Table 3). Adverse events were cited as a cause of study discontinuation for five patients.

Fundus examination via ophthalmoscopy revealed no cases of score aggravation from baseline for vitreous,

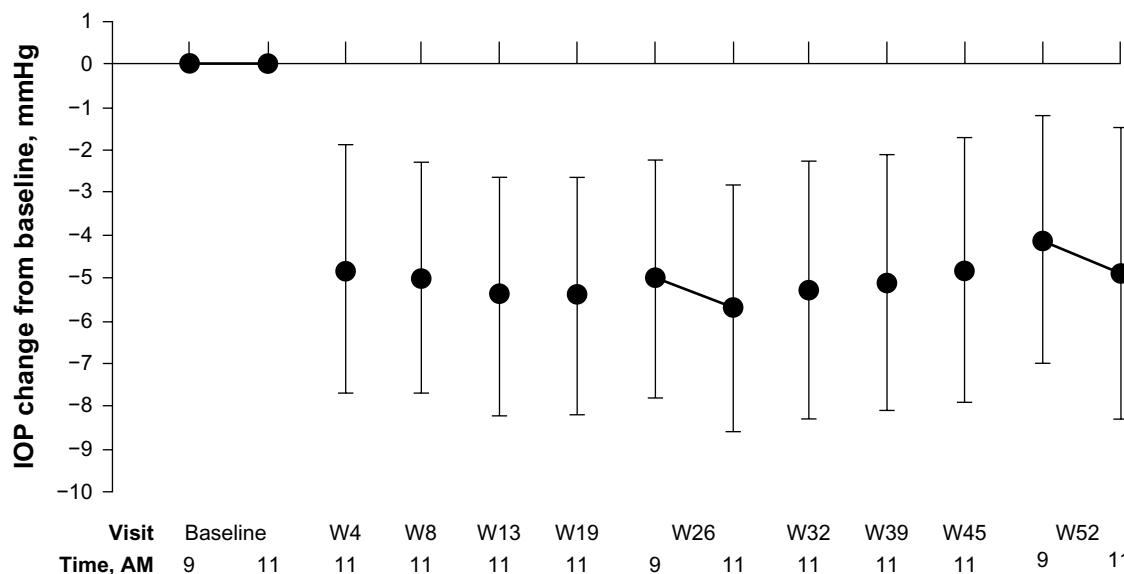


Figure 1 Mean IOP reduction from baseline at 9 am (preinstillation) and 11 am (2 hours post instillation) with BRINZ/TIM-FC. Data points represent the mean \pm standard deviation; n=125 at baseline and 11 am time points; n=118 at week 26 and week 52 9 am time points.
Abbreviations: BRINZ/TIM-FC, brinzolamide 1%/timolol 0.5% fixed combination; IOP, intraocular pressure; W, week.

retina, macula, choroid, or optic nerve; no patient showed substantial changes in cup-to-disc ratio, and there was no change in anterior chamber angle grade in any patient (data not shown). Of the 123 patients with complete baseline and follow-up data, worsening of more than one stage in visual field testing from baseline to week 52 was observed in nine patients (7%); changes in visual field were mild in all cases. Slit-lamp examination showed that 11/125 patients (9%) developed conjunctival or eyelid aggravation during the study, but all cases resolved by the exit visit. Corneal score

aggravation was observed in 18/125 patients (14%) during the study; 7/125 patients (6%) continued to have corneal score aggravation at the exit visit.

Few cases of altered visual acuity were observed. Declines in best-corrected visual acuity ≥ 3 steps on the logMAR scale (ie, ≥ 0.5 decrease in decimal visual acuity) occurred in 2/125 cases (2%), both of which resolved by the exit visit. At the exit visit, 3/125 patients (2%) had a best-corrected visual acuity decrease of two lines, 10/125 (8%) had a decrease of one line, and 1/125 (1%) had an increase of one line.

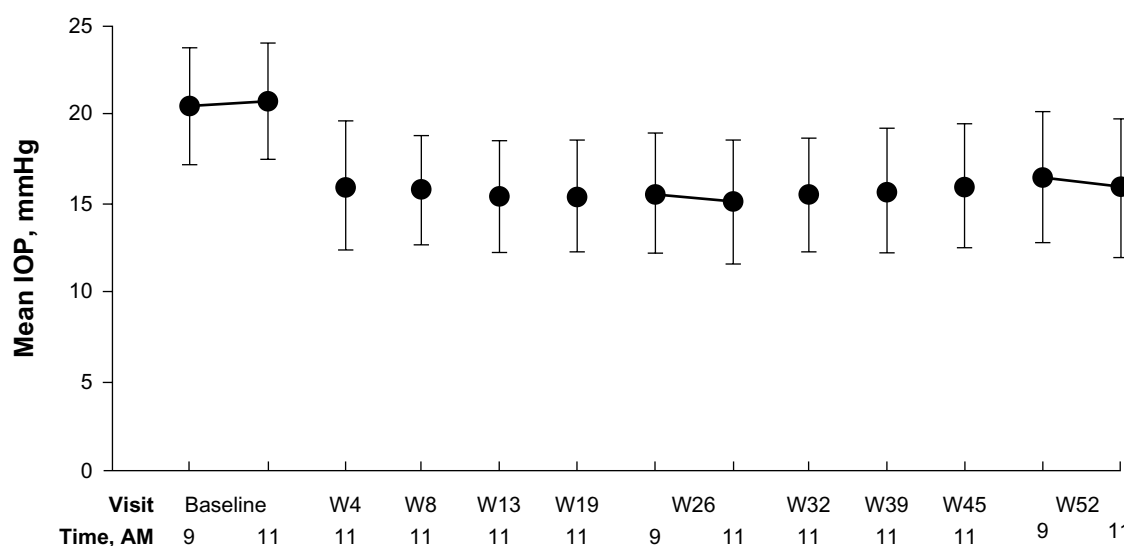


Figure 2 Mean IOP over time from baseline to week 52 with BRINZ/TIM-FC. Data points represent mean \pm standard deviation; n=125 at baseline and 11 am time points; n=118 at week 26 and week 52 9 am time points.
Abbreviations: BRINZ/TIM-FC, brinzolamide 1%/timolol 0.5% fixed combination; IOP, intraocular pressure; W, week.

Table 3 Adverse events

	BRINZ/TIM-FC (n=125)
Total AEs, n (%)	82 (66)
Potential treatment-related AE ^a , n (%)	28 (22)
Punctate keratitis	12 (10)
Eye irritation	7 (6)
Keratitis	4 (3)
Dysgeusia	4 (3)
Conjunctival hyperemia	1 (1)
Dry eye	1 (1)
Photophobia	1 (1)
Blurred vision	1 (1)
Positional vertigo	1 (1)
Allergic rhinitis	1 (1)
Cough	1 (1)
Discomfort	1 (1)
Malaise	1 (1)
Leukocytopenia	1 (1)
AE incidence according to age in years, n/N (%)	
<65	36/57 (63)
≥65	46/68 (68)
AE incidence according to sex, n/N (%)	
Men	38/62 (61)
Women	44/63 (70)
AE severity, n (treatment-related/total)	
Mild	26/77
Moderate	2/13
Severe	0/2

Note: ^aAEs for which a causal relationship with the investigational drug could not be ruled out.

Abbreviations: AE, adverse event; BRINZ/TIM-FC, brinzolamide 1%/timolol 0.5% fixed combination; n/N, number of patients reporting AEs/total group size.

No clinically significant changes in blood biochemistry, hematology, or urinalysis were observed, and in most cases, changes from baseline remained within the range of physiologic variation (data not shown). Eleven abnormal laboratory values in four patients were reported as adverse events; no causal relationship with BRINZ/TIM-FC was found for any of these adverse events, except one case of leukocytopenia. All changes in mean pulse rate, systolic blood pressure, and diastolic blood pressure from baseline over 52 weeks were within the predetermined normal ranges (ie, pulse rate, 60–100 beats per minute; systolic blood pressure 100–140 mmHg; diastolic blood pressure 60–90 mmHg). There were no adverse events related to pulse rate or blood pressure.

Discussion

Reducing IOP is currently the only therapeutic approach effective in preventing progression of open-angle glaucoma and ocular hypertension.^{8,33} Topical ophthalmic pharmacotherapies are commonly employed to manage IOP in

patients with these conditions.⁸ Chronic treatment with a single IOP-lowering agent is often insufficient to maintain IOP reduction in the long term;^{10,11} as a result, concomitant pharmacotherapies may be required to achieve additional IOP reduction.^{10,16} A trend toward increasing use of multiple medications to manage IOP has been observed in Japanese patients.³⁴ Fixed-combination therapies enable instillation of multiple agents from one bottle, providing additive effects on IOP reduction compared with single agents and simplifying administration compared with multiple medications.^{15,16} Whereas several studies of short-term (up to one month) safety and efficacy of BRINZ/TIM-FC have been reported,^{35–37} long-term (≥12 months) clinical studies of BRINZ/TIM-FC ocular hypotensive therapy are limited.¹⁷ The goal of the current study was to evaluate the long-term safety and efficacy of BRINZ/TIM-FC in Japanese patients with open-angle glaucoma (primary open-angle, normal-tension, exfoliation, or pigmentary) or ocular hypertension. Treatment with BRINZ/TIM-FC significantly reduced IOP from baseline by 4 weeks, and IOP reductions were maintained through 52 weeks. Long-term treatment with BRINZ/TIM-FC was generally well tolerated, with no serious adverse events associated with instillation. Additionally, no pathologic worsening of visual field, best-corrected visual acuity, optic nerve aspect, or cup-to-disc ratio was observed, and no clinically significant effects on resting pulse rate, blood pressure, or blood biochemistry were reported.

BRINZ/TIM-FC has been shown to reduce IOP effectively in patients with open-angle glaucoma and ocular hypertension and to be noninferior to an alternative fixed-combination therapy comprising dorzolamide 2% and timolol 0.5%.^{16–18} In a double-masked, 52-week clinical trial comparing BRINZ/TIM-FC with a fixed combination of dorzolamide/timolol in patients with glaucoma or ocular hypertension, both fixed-combination agents decreased IOP and had safety profiles similar to those observed in the current study.¹⁷ Furthermore, long-term (12–24 months) treatment with other topical fixed-combination therapies (timolol with the α_2 -adrenoceptor agonist brimonidine or the prostaglandin analog latanoprost) showed sustained reductions in IOP, with generally good safety and tolerability in patients with glaucoma or ocular hypertension.^{38,39} In the current study, long-term treatment with BRINZ/TIM-FC decreased IOP by 4.1 mmHg to 5.7 mmHg, which translated to a mean IOP reduction of approximately 25%.

Studies of patient preference and safety profiles comparing BRINZ/TIM-FC with dorzolamide 2%/timolol 0.5% demonstrated that BRINZ/TIM-FC therapy was favored by

a majority of patients with a treatment preference, possibly because BRINZ/TIM-FC was associated with less ocular discomfort.^{36,40} In the present study, with up to 52 weeks of treatment with BRINZ/TIM-FC, no serious treatment-related adverse events were observed. The most frequently reported treatment-related adverse event was punctate keratitis, which was mild in all cases and did not impede patient compliance. These findings are consistent with clinical studies of 18 months of brinzolamide monotherapy and 60 months of BRINZ/TIM combination therapy.^{41,42} Similar to the current study, these studies demonstrated that long-term brinzolamide, both alone and in combination with timolol, maintained significant IOP reductions from baseline and had a favorable safety profile.

A potential limitation of this study is the lack of a placebo or active control; however, given that uncontrolled IOP is a significant risk factor for disease progression and vision loss,^{3,9} long-term placebo-controlled studies in patients with glaucoma or ocular hypertension may not be feasible.

Conclusion

Long-term ocular hypotensive therapy with twice-daily BRINZ/TIM-FC is efficacious in producing and maintaining significant IOP reductions in Japanese patients with open-angle glaucoma or ocular hypertension. BRINZ/TIM-FC was generally safe and well tolerated over 52 weeks of treatment. In general, visual field, cup-to-disc ratio, angle grade, and visual acuity were stable throughout the study, and no serious adverse events were observed, indicating that BRINZ/TIM-FC can be used safely for long-term reduction of IOP.

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Disclosure

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