

**Appendix 1. Selection of study eye**

If both eyes were dosed, then the worse evaluable eye (defined as the eye with higher intraocular pressure (IOP) at 09:00 h averaged across the two eligibility visits) was selected as the study eye. If the IOP was the same in both eyes at 09:00 h, then the worse evaluable eye was defined as the eye with higher IOP at 11:00 h averaged across the 2 eligibility visits; if both eyes were still equal, the right eye was selected as the study eye.

**Appendix 2. Key exclusion criteria**

Key exclusion criteria were (1) Central corneal thickness  $>620$   $\mu\text{m}$  as measured by pachymetry in either eye; (2) Schaffer angle grade  $<2$  in either eye, as measured by gonioscopy; (3) Cup/disc ratio  $>0.80$  in either eye; (4) Best-corrected visual acuity (BCVA) score worse than 55 Early Treatment Diabetic Retinopathy Study letters (equivalent to  $\sim 20/80$  Snellen, 0.60 logarithm of the minimum angle of resolution, or 0.25 decimal) in either eye; (5) Severe central visual field loss in either eye or field loss threatening fixation in either eye. Severe central visual field loss was defined as a sensitivity of  $\leq 10$  dB in at least 2 of the 4 visual field test points closest to the point of fixation; (6) Hypersensitivity to  $\alpha$ -adrenergic agonists, carbonic anhydrase inhibitors, prostaglandins, sulfonamide derivatives, or to any component of the trial medications, in the opinion of the investigator.

**Appendix 3. Assessment of IOP, BCVA, perimetry, fundus and slit-lamp examination**

Two IOP measurements were taken for each eye. If the 2 measurements for the same eye differed by  $\leq 4$  mmHg, the average value was considered as the mean IOP for that eye. If the 2 measurements for the same eye differed by  $>4$  mmHg, a third measurement was taken and the two closest values were averaged. If the 3 measurements differed by equal amounts, all 3 measurements were averaged. BCVA assessments were performed at screening, eligibility, and on-therapy follow-up visits. Automated perimetry and dilated fundus examination were performed at screening and at the Week 6 follow-up visit. Automated perimetry was performed using either a Humphrey Field Analyzer or Octopus Perimeter, or other perimeters with prior approval of the Sponsor. The dilated fundus examination included assessments of vitreous, retina/macula/choroid, optic nerve, and cup/disc ratio (horizontal and vertical axis) for both eyes. Slit-lamp biomicroscopy examination

included assessment of the aqueous cells and flare and the lens and the examination was conducted prior to IOP measurements or instillation of fluorescein.

**Appendix 4:** Results for changes in blood pressure, visual acuity, perimetry, slit lamp biomicroscopy

Mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were small in the BBFC+PGA (SBP  $\leq$ 7.7 mmHg, DBP  $\leq$ 3.1 mmHg) and vehicle+PGA group (SBP  $\leq$ 3.1 mmHg, DBP  $\leq$ 1.6 mmHg). Mean changes in pulse in both treatment groups at any time point after dosing were also small ( $<$ 2.1 beats per minute).

Mean visual acuity at Eligibility 2 visit (baseline) was similar in both the groups (BBFC+PGA 81.5 letters; vehicle+PGA 81.6 letters). The mean change in visual acuity from baseline was also similar between BBFC+PGA and vehicle+PGA groups at Week 2 (both  $-1.2$  letters) and Week 6 ( $-0.9$  letters and  $-0.8$  letters respectively). At baseline, the mean defect (measured using an Octopus Field Analyzer) was 3.24 (BBFC+PGA) and 0.96 (vehicle +PGA), which decreased at Week 6 by 0.31 (BBFC+PGA) and 0.57 (vehicle+PGA). The two groups also showed a comparable change in mean deviation from baseline (BBFC+PGA  $-3.86$ ; vehicle+PGA  $-3.42$ ) to Week 6 (mean change: BBFC+PGA 1.308; vehicle+PGA 1.017) as measured with a Humphrey analyzer.

There were no differences between the groups for slit-lamp biomicroscopy (no worsening of slit lamp parameters like aqueous flare and status of lens in any patient). One patient experienced a faint aqueous flare on an unscheduled visit and withdrew from the treatment due to intolerable hyperemia.

**Supplementary Table 1.** Mean IOP and mean reduction in IOP (mmHg) from baseline at each visit by time point and mean diurnal IOP at Week 6 in patients with 16:00 h data (full analysis set)

Visit	Time point	BBFC+PGA		Vehicle+PGA	
		N=95		N=92	
		IOP	IOP Reduction	IOP	IOP Reduction
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<sup>a</sup> Baseline	09:00	23.9 (1.99)	–	24.0 (1.99)	–
	11:00	22.7 (2.54)	–	23.0 (2.60)	–
	16:00	21.9 (2.44)	–	22.1 (2.85)	–
Week 2	09:00	19.1 (3.90)	4.7 (3.25)	22.4 (3.25)	1.5 (2.47)
	11:00	16.4 (3.27)	6.3 (3.12)	21.1 (3.55)	1.9 (2.56)
	16:00	16.7 (3.01)	5.2 (2.88)	20.5 (3.63)	1.6 (2.56)
Week 6	09:00	19.3 (3.51)	4.6 (3.02)	21.1 (3.68)	2.9 (3.02)
	11:00	15.7 (3.69)	7.0 (3.37)	20.3 (3.62)	2.7 (2.91)
	16:00	17.2 (3.06)	4.9 (2.75)	19.9 (3.87)	2.2 (3.19)
		Diurnal IOP	Diurnal IOP reduction	Diurnal IOP	Diurnal IOP reduction
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<sup>b</sup> Baseline	–	22.7 (2.02)	–	22.9 (2.26)	–
Week 6	–	17.4 (3.06)	5.3 (2.46)	20.4 (3.48)	2.4 (2.59)

<sup>a</sup>Baseline is defined as the average of the 9:00-h, 11:00-h and 16:00-h values at both eligibility visits for 09:00-h, 11:00-h and 16:00-h calculations, respectively.

<sup>b</sup>Baseline is defined as the average of the 9:00-h and 11:00-h values at both eligibility visits.

BBFC, brinzolamide 1%/brimonidine 0.2% fixed-dose combination; N, number of patients; PGA, prostaglandin analog; SD, standard deviation.

**Supplementary Table 2.** Mean change from baseline in ocular perfusion pressure (mmHg) at individual time points and at Week 6 (full analysis set)

Visit	Time point	BBFC+PGA		Vehicle+PGA	
		N=95		N=92	
		OPP	Increase in OPP	OPP	Increase in OPP
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<sup>a</sup> Baseline	09:00	48.4 (6.53)	–	49.5 (7.07)	–
	11:00	48.4 (7.00)	–	49.5 (6.86)	–
Week 6	09:00	51.0 (7.32)	2.5 (5.22)	50.2 (7.72)	0.6 (4.40)
	11:00	49.9 (7.84)	1.4 (4.76)	49.5 (7.79)	0.2 (4.52)
		OPP	Increase in OPP	OPP	Increase in OPP
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<sup>b</sup> Baseline	–	48.2 (6.52)	–	49.4 (6.72)	–
Week 6	–	50.7 (7.11)	2.4 (4.30)	50.1 (7.49)	0.6 (3.74)

<sup>a</sup>Baseline is defined as the average of the 09:00-h, 11:00-h values at both eligibility visits for 09:00-h, 11:00-h calculations, respectively

<sup>b</sup>Baseline is defined as the average of the 09:00-h and 11:00-h values at both eligibility visits

At each time point, only subjects with a value at both baseline and that time point are included in the calculation of change

BBFC, brinzolamide 1%/brimonidine 0.2% fixed-dose combination; N, total number of patients; PGA, prostaglandin analog; SD, standard deviation.

**Supplementary Table 3: Treatment-related AEs (safety set)**

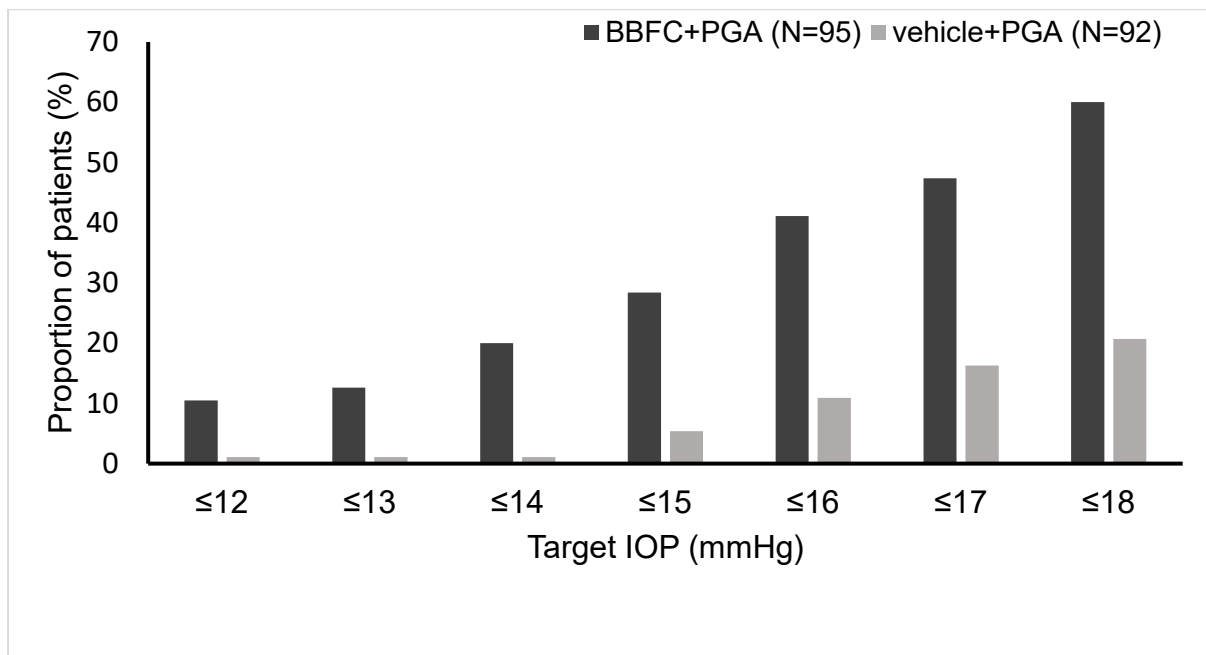
Preferred term	BBFC+PGA N=95	Vehicle+PGA N=92
<b>Any event, n (%)</b>	22 (23.2)	4 (4.3)
Dry mouth	5 (5.3)	0 (0.0)
Conjunctival hyperemia*	4 (4.2)	1 (1.1)
Ocular hyperemia*	4 (4.2)	0 (0.0)
Eye irritation	3 (3.2)	0 (0.0)
Ocular discomfort	3 (3.2)	0 (0.0)
Vision blurred	2 (2.1)	2 (2.2)
Dry eye	2 (2.1)	0 (0.0)
Fatigue	2 (2.1)	0 (0.0)
Eye allergy	1 (1.1)	1 (1.1)
Blepharitis	1 (1.1)	0 (0.0)
Conjunctivitis allergic	1 (1.1)	0 (0.0)
Eye pruritus	1 (1.1)	0 (0.0)
Eyelid edema	1 (1.1)	0 (0.0)
Punctate keratitis	1 (1.1)	0 (0.0)
Dizziness	1 (1.1)	0 (0.0)
Dysgeusia	1 (1.1)	0 (0.0)
Headache	1 (1.1)	0 (0.0)
Lacrimation increased	0 (0.0)	1 (1.1)

The AEs are arranged in decreasing order of incidence in the BBFC+PGA group

\*Based on the judgement of the investigator

AE, adverse event; BBFC, brinzolamide 1%/brimonidine 0.2% fixed-dose combination; N, total number of patients; PGA, prostaglandin analog

**Supplementary Figure 1.** Percentage of patients reaching IOP (mmHg) target at Week 6 (full analysis set)



IOP target categories are cumulative

BBFC, brinzolamide 1%/brimonidine 0.2% fixed-dose combination; IOP, intraocular pressure; N, total number of patients; PGA, prostaglandin analog