a Novartis company

Short Title

Safety and Efficacy of SIMBRINZA BID as an Adjunctive to DUOTRAV

Long Title

Safety and Efficacy with Twice Daily Brinzolamide 1% / Brimonidine 0.2% (SIMBRINZA) as an Adjunctive Therapy to Travoprost 0.004% / Timolol 0.5% (DUOTRAV)

Protocol Number:	GLJ576-P001/ NCT02730871
Study Phase:	4
Sponsor Name and Address:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099
Investigational Product:	SIMBRINZA Brinzolamide 1% (10 mg/mL)/Brimonidine 0.2% (2 mg/mL) eye drops suspension
US IND# / EudraCT	**2016-000176-20**
Indication Studied:	Ocular Hypertension Open Angle Glaucoma

Investigator Agreement: I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements. Additionally, I will comply with all procedures for data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the Sponsor.

Principal Investigator:

Signature Date

Name:

Address:

1 SYNOPSIS

Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099	**Protocol Number:GLJ576-P001**
Investigational Product:	SIMBRINZA Brinzolamide 1%/ Brimonidine 0.2% eye drops suspension	**Study Phase:** ☐ 1 ☐ 2 ☐ 3 ☒ 4 ☐ N/A
Active Ingredient:	Brinzolamide 1% (10 mg/mL)//Brimonidine 0.2% (2 mg/mL)	
Protocol Title:	**Safety and Efficacy with Twice Daily Brinzolamide 1% / Brimonidine 0.2% (SIMBRINZA) as an Adjunctive Therapy to Travoprost 0.004% / Timolol 0.5% (DUOTRAV)**	
Investigator(s)/ No. of Sites:	Multicenter, approximately 40 sites	
Center Location(s)/	Europe, Asia, Latin America, and Canada	
No. of Subjects:	Approximately 300 subjects enrolled, 240 subjects randomized, 216 subjects evaluable	
Duration of Treatment:	Approximately 42 days	
Study Population:	Adults with open-angle glaucoma or ocular hypertension on DUOTRAV (Travoprost 0.004%/Timolol 0.5%) solution therapy who may benefit from further IOP lowering (IOP ≥ 19 and ≤28 mmHg in the study eye)	
Objective(s):	To demonstrate the additive IOP lowering effect of Brinzolamide 1%/Brimonidine 0.2% (dosed BID) when added to Travoprost 0.004%/Timolol 0.5% solution in subjects with open-angle glaucoma or ocular hypertension	
Methodology:	Multicenter, randomized, double-masked, parallel-group study	
Treatments:	**Investigational Product:**	SIMBRIMZA (Brinzolamide 1% (10 mg/mL)/ Brimonidine 0.2% (2 mg/mL))
	Route of Administration:	Topical ocular drops
	Duration of Treatment:	Approximately 42 days
	Dosage:	1 drop instilled 2 times per day in

Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099	**Protocol Number:GLJ576-P001**

affected eye(s) (09:00 and 21:00 hrs)

Background Medication:	DUOTRAV (Travoprost 0.004% (40 µg/mL)/ Timolol 0.5 % (5 mg/mL))
Route of Administration:	Topical ocular drops
Duration of Treatment:	Up to 10 days for eligibility and approximately 42 days after randomization
Dosage:	1 drop instilled once per day in affected eye(s) (09:00 or 21:00 hr)
Control Article:	Brinzolamide/Brimonidine Vehicle
Duration of Treatment:	Approximately 42 days
Dosage:	1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs)

Subject Selection:

Inclusion Criteria:

1. Subjects 18 years of age or older, of any race, diagnosed with either open-angle glaucoma (including pseudoexfoliation or pigment dispersion glaucoma) or ocular hypertension

2. Subjects currently on treatment with Travoprost 0.004% /Timolol 0.5% prescribed as approved in the country, on morning or evening dosing for at least 28 days prior to screening and that in the opinion of the Investigator may benefit from further IOP lowering. Subjects must remain on either their morning or evening dosing for the duration of the study.

3. Qualifying mean IOP measurements at both the Eligibility 1 and Eligibility 2 visits, in at least 1 eye (the same eye(s) ≥ 19 and ≤ 28 mmHg at 9:00 while on a Travoprost 0.004%/ Timolol 0.5% solution

4. Must be able to understand and sign an informed consent form that has been approved by an Institutional Review Board/Ethics Committee

5. Willing and able to attend all study visits.

Sponsor: Alcon Research, Ltd.
6201 South Freeway
Fort Worth, Texas
76134-2099

Protocol Number:GLJ576-P001

Exclusion Criteria:

1. Women of childbearing potential (WOCBP), defined as all women who are not postmenopausal for at least 1 year or less than 6 weeks since sterilization, are excluded from participation if:
    a. they are currently pregnant, or
    b. have a positive result on the urine pregnancy test at Screening, or
    c. intend to become pregnant during the study period, or
    d. are breast-feeding, or
    e. are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study.

All women of childbearing potential are required to use adequate birth control methods which are summarized as follows:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before Baseline. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to Baseline). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject

- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or

Sponsor: Alcon Research, Ltd.
6201 South Freeway
Fort Worth, Texas
76134-2099

Protocol Number:GLJ576-P001

transdermal hormone contraception

- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

2. Subjects with any form of glaucoma other than open-angle glaucoma or ocular hypertension.

3. Subjects with central cornea thickness (CCT) greater than 620 µm as measured by pachymetry in either eye (see MOP for further details).

4. Subjects with Schaffer angle Grade < 2 in either eye, as measured by gonioscopy (extreme narrow angle with complete or partial closure).

5. Subjects with cup/disc ratio greater than 0.80 (horizontal or vertical measurement) in either eye.

6. Subjects with severe central visual field loss in either eye or field loss threatening fixation in either eye.

7. Subjects with chronic, recurrent or severe inflammatory eye disease (eg, scleritis, uveitis, herpes keratitis) in either eye.

8. Subjects with ocular trauma in either eye within the past 6 months prior to the Screening visit.

9. Subjects with ocular infection or ocular inflammation in either eye within the past 3 months prior to the Screening visit.

10. Subjects with clinically significant or progressive retinal disease such as retinal degeneration, diabetic retinopathy, or retinal detachment in either eye.

11. Subjects with best-corrected visual acuity score worse than 55 ETDRS letters (equivalent to approximately 20/80 Snellen, 0.60 logMAR or 0.25 decimal) in either eye.

12. Subjects with other ocular pathology (including severe dry eye) in either eye that may, in the opinion of the Investigator, preclude the safe administration of any study medication.

Sponsor: Alcon Research, Ltd. **Protocol Number:GLJ576-P001**
6201 South Freeway
Fort Worth, Texas
76134-2099

13. Subjects with intraocular surgery in either eye within the past 6 months prior to the Screening visit.

14. Subjects with ocular laser surgery in either eye within the past 3 months prior to the Screening visit.

15. Subjects with any abnormality preventing reliable applanation tonometry in either eye.

16. Any other conditions including severe illness which would make the subject, in the opinion of the Investigator, unsuitable for the study.

17. Subjects with recent (within 4 weeks of the Eligibility 1 Visit) use of high dose (> 1 gm daily) salicylate therapy.

18. Subjects with history of active, severe, unstable or uncontrolled cardiovascular (eg, coronary insufficiency, hypertension, Raynaud's phenomenon, orthostatic hypotension, thromboangiitis obliterans), cerebrovascular (eg, cerebral insufficiency), hepatic, or renal disease that would preclude the safe administration of a topical alpha-adrenergic agonist or carbonic anhydrase inhibitor in the opinion of the Investigator

19. Subjects with current or anticipated treatment with any psychotropic drugs that augment an adrenergic response (eg, desipramine, amitriptyline).

20. Concurrent use of a monoamine oxidase inhibitor.

21. Study participants with asthma, history of asthma, or severe chronic obstructive pulmonary disease

22. Therapy with another investigational agent within 30 days prior to the Screening Visit.

23. Subjects with less than 30 days stable dosing regimen before the Screening Visit of any medications (excluding the IOP lowering treatments) or substances administered by any route and used on a chronic basis that may affect IOP (eg, β-adrenergic blocking agents). The dosing regimen of these

Sponsor: Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099

Protocol Number:GLJ576-P001

medications should not change during the study.

24. Subjects with hypersensitivity to alpha-adrenergic agonist drugs, topical or oral CAIs, PGAs, timolol, sulfonamide derivatives, or to any component of the study medications in the opinion of the Investigator.

25. Use of any additional topical or systemic ocular hypotensive medication in either eye during the study.

26. Subjects who cannot safely discontinue all glucocorticoids administered by any route prior to the Eligibility Visit 1 and continue to not use during the study.

    Steroid washout duration:

    a. Chronic therapy – 4 weeks
    b. Intermittent therapy - 2 weeks

27. Mean IOP > 28 mmHg at any time point in either eye during the Screening/Eligibility Phase.

The Medical Monitor may declare any subject ineligible for a valid medical reason.

Assessments:

Primary Efficacy:

Change from baseline in diurnal IOP (mean of changes at 09:00 and 11:00 time points) at Week 6.

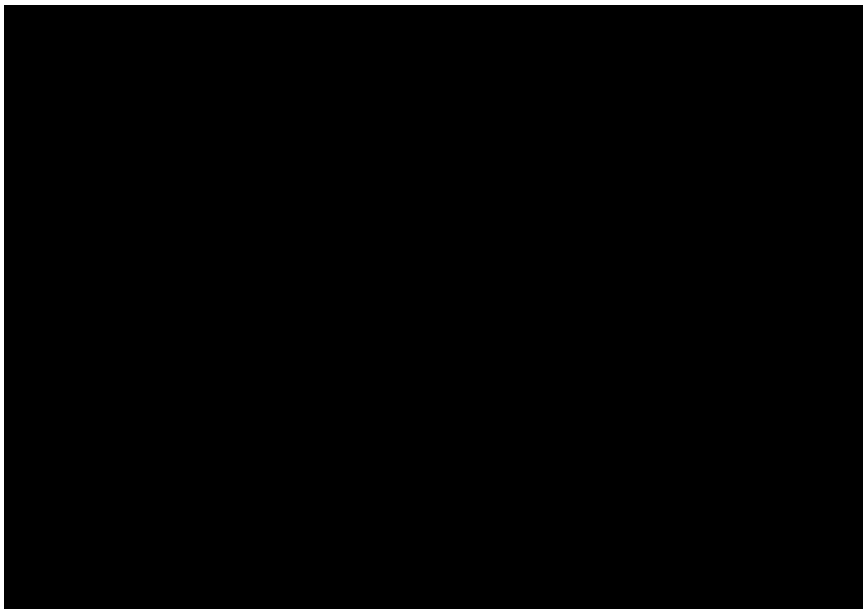
Secondary Efficacy:

- Diurnal IOP at Week 6
- Percentage change from baseline in diurnal IOP at Week 6
- IOP change from baseline at Week 6 at 11:00 hrs
- Percentage change from baseline in IOP at Week 6 at 11:00 hrs
- IOP change from baseline at Week 6 at 09:00 hrs
- Percentage change from baseline in IOP at Week 6 at 09:00

Sponsor: Alcon Research, Ltd.
6201 South Freeway
Fort Worth, Texas
76134-2099

Protocol Number:GLJ576-P001

hrs



Safety:

Automated perimetry, fundus parameters, best-corrected visual acuity (BCVA), slit-lamp exam, blood pressure, pulse rate and adverse events

Sponsor: Alcon Research, Ltd.
6201 South Freeway
Fort Worth, Texas
76134-2099

Protocol Number:GLJ576-P001

Statistical Methods: One eye from each patient will be chosen as the study eye and only the study eye will be used for analysis. If only 1 of a patient's eyes is dosed, the dosed eye will be selected as the study eye. If both eyes are dosed, the worse evaluable eye will be selected as the study eye. Worse eye is defined as the eye with the higher IOP at 9:00 averaged across the 2 eligibility visits. If both eyes are equal then the worse eye will be defined as the eye with the higher IOP at 11:00 averaged across the 2 eligibility visits. If both eyes are equal then the right eye will be selected for analysis.

Analysis sets:

Efficacy analyses will be based on the Full Analysis Set (FAS), defined as all randomized subjects who received a dose of study medication and had at least one of the two scheduled on-treatment visits. The Safety Analysis Set will consist of all who received a dose of study medication.

Primary Efficacy:

The primary efficacy analysis will be an assessment of differences between treatments in mean change from baseline in diurnal IOP at Week 6 (change in patient IOP averaged over the 09:00 and 11:00 time points). The null and alternative hypotheses for the primary analysis are:

$$\mathbf{H_0:}\ \mu_{\text{BrinzBrim+ DUOTRAV}} = \mu_{\text{Vehicle+ DUOTRAV}}$$

$$\mathbf{H_1:}\ \mu_{\text{BrinzBrim+ DUOTRAV}} \neq \mu_{\text{Vehicle+ DUOTRAV}}$$

where $\mu_{\text{BrinzBrim+ DUOTRAV}}$ refers to mean diurnal IOP change from baseline for subjects randomized to receive brinzolamide / brimonidine plus Travoprost 0.004%/ Timolol 0.5%, and $\mu_{\text{Vehicle+DUOTRAV}}$ refers to mean diurnal IOP change from baseline for subjects randomized to receive Vehicle plus Travoprost

Sponsor: Alcon Research, Ltd.
6201 South Freeway
Fort Worth, Texas
76134-2099

Protocol Number:GLJ576-P001

0.004%/ timolol 0.5%. The treatment difference in mean diurnal IOP change from baseline will be tested based on the least squares means derived from an analysis of covariance model. This model will include treatment as a fixed effect and baseline 09:00 IOP as a covariate.

Secondary efficacy:

Hypothesis tests of all secondary efficacy endpoints will use the same null and alternative hypotheses as above, with μ representing the mean for the variable being tested. Analyses of treatment differences in diurnal IOP and percent diurnal IOP change at Week 6 will use the same methods as those for the primary endpoint. Analyses of treatment differences in IOP change and percent IOP change at each Week 6 time point will utilize a repeated measures mixed model with fixed effects of treatment, time point, and the interaction of treatment and time point; and the baseline 09:00 IOP as a covariate.

A gate-keeping strategy will be employed to ensure overall control of the type I error rate. The secondary efficacy hypotheses will be relevant only if the primary efficacy null hypothesis is first rejected at the 5% level of significance (two-sided). Following the rejection of the primary efficacy null hypothesis, each secondary hypothesis will be tested following the order of the hypotheses as listed below. Each hypothesis will be relevant only if the preceding hypotheses have been rejected at the 5% level of significance (two-sided). The testing order (all based on IOP at Week 6) will be:

- Difference between treatments in mean change from baseline in diurnal IOP
- Difference between treatments in diurnal IOP
- Difference between treatments in percentage diurnal IOP change from baseline

Sponsor: Alcon Research, Ltd. **Protocol Number:GLJ576-P001**
6201 South Freeway
Fort Worth, Texas
76134-2099

- Difference between treatments in IOP change from baseline at 11:00 hrs
- Difference between treatments in percentage IOP change from baseline at 11:00 hrs
- Difference between treatments in IOP change from baseline at 09:00 hrs
- Difference between treatments in percentage IOP change from baseline at 09:00 hrs

Significance for a comparison will be claimed only if the null hypothesis is rejected ($p < 0.05$) for the previous endpoint in this series.

Descriptive statistics will be calculated for the primary and secondary endpoints at baseline and Week 6.

Only descriptive statistics will be calculated for the [redacted] variables.

This study will incorporate an interim analysis for efficacy assessment when 50% of the total planned subjects have completed or discontinued from the study. The objective of the interim analysis is to provide an opportunity for early rejection of the null hypothesis that there is no difference in diurnal IOP change from baseline between brinzolamide / brimonidine plus Travoprost 0.004%/ Timolol 0.5% and vehicle plus Travoprost 0.004%/ Timolol 0.5%. In order to ensure Type 1 error is adequately controlled at the 5% level of significance (two-sided), a p-value boundary will be employed, specifically, the Haybittle-Peto boundary (Haybittle 1971). The Haybittle-Peto boundary ensures that the study stops for efficacy only if there is overwhelming evidence of efficacy.

Sponsor: Alcon Research, Ltd.
6201 South Freeway
Fort Worth, Texas
76134-2099

Protocol Number:GLJ576-P001

Sample Size Justification:

With 108 evaluable subjects per treatment group in the primary efficacy analysis, there is at least 80% power to detect a difference in mean change from baseline in diurnal IOP at Week 6 IOP of 1.5 mmHg between the treatment groups. However, the required sample size to attain the same power is 28 subjects per arm if the difference is 3.0 mmHg between treatment groups as suggested by expert opinion. Both calculations are based on the assumption of a common standard deviation for mean of 3.9 mmHg and the use of a two-sample two-sided t-test performed at the α=0.05 level of significance.

Assuming a drop-out rate of 10%, approximately 120 subjects per treatment group will be enrolled to ensure the required number of evaluable subjects in the final efficacy analysis.

To mitigate the uncertainty about the expected treatment difference, a two-look design with Haybittle-Peto boundaries will be used. Thus, this study will incorporate an interim analysis for efficacy assessment when 50% of total planned subjects have completed or discontinued from the study. The power to reject the null hypothesis at the single interim analysis when 50% of subjects have completed or discontinued the study is 28.2% if the expected mean difference is 1.5 and 92.2% if the expected mean difference is 3.0.

Look #	Sample Size	Efficacy p-value	P-value Boundary	Exit Probabilities		
				$\delta = 0$	$\delta = 1.5$	$\delta = 3.0$
1	108	0.01	0.01	0.01	0.282	0.922
2	216	0.045	0.045	0.04	0.517	0.078
Sum of Exit Probabilities				0.050	0.799	1

1.1 Amendments

Amendment 1

1. Lower the qualifying IOP criteria at both the Eligibility 1 and Eligibility 2 visits from ≥ 21 and ≤ 28 mmHg at 09:00 to ≥ 19 and ≤ 28 mmHg at 09:00.

Rationale: Screen failures due to lower IOPs on Duotrav than the ≥21 mmHg cutoff is high. Reducing the entry IOP by 2 mmHg will allow more patients to be eligible for the study while maintaining an IOP baseline that will allow a reasonable efficacy effect to be observed. This lowering of inclusion IOP will not have a major effect on the study outcome parameters and the baseline IOP values will decrease proportionately. The study is powered appropriately to test for treatment effects between the study arms.

2. Remove the 15:00 IOP measurement time point at all study visits.

Rationale: The 12-hr trough and 2-hr peak effects of Simbrinza are seen at 09:00 and 11:00, respectively, and are the critical measurement time points for the study. The 15:00 time point provides further daytime data but is proving to be a major barrier to recruitment. Removing the late day 15:00 time point and reducing the patient commitment from ~ 7 hrs to ~ 3 hrs will facilitate recruitment. Removing this time point will not affect the scientific integrity of the study since the 12- hr trough (09:00 IOP) and 2-hr peak (11:00 IOP) are being captured and provide the key IOP fluctuation values. Further, the statistical design remains intact and valid since it is based on differences between treatment arms and the amendment affects measurements in both arms equally.

3. Allow subjects currently on treatment with Travoprost 0.004% /Timolol 0.5% for at least 28 days prior to screening in the morning or evening to be eligible for the study.

Rationale: There is broad variability globally on the Duotrav on label dosing schedule (morning vs. evening dosing). Allowing both, where on label, will allow for all Duotrav dosed patients to be considered. Additionally, studies have shown that the IOP lowering from Duotrav is similar statistically between AM and PM dosing and therefore the dosing time will not bias the study results. A planned descriptive analysis will be done (if patient numbers allow) to compare the effects of AM vs. PM dosing.

4. Incorporate an interim analysis for efficacy assessment when 50% of the total planned subjects have completed or discontinued form the study.

Rationale: The combination of Simbrinza + Duotrav has not been studied previously and as such, the study was powered to show a 1.5 mmHg difference between study arms. However, since the launch of Simbrinza, clinical experience has increased and expert opinion has suggested it may be more than 1.5 mmHg. To minimize unnecessary patient enrollment in the trial, an interim analysis has been added at 50% completion to test for statistical differences between treatments. If it is achieved, the study enrollment will stop and patients in the study will complete their visits. This analysis has no effect on patient safety nor does it change the assessments or study design.

5. Provide clarification to exclusion criteria # 27.

6. Allow for re-screening with defined criteria.

7. Update Statistical Analysis associated with the change in eligibility criteria.

8. Define procedure/assessment windows.

9. Update administrative information and correct minor errors from Protocol Version 1.0.

Current Study Phase: Execution Phase

Case Report Form Revision Required:	[X]	Yes	[ ]	No
Informed Consent Modifications Required:	[X]	Yes	[ ]	No
Applicable Investigators:	[X]	All	[ ]	Selected (list below)

Itemized Changes: Additions/modifications are noted in bold, italics. Deletions are noted with a strikethrough.

1. Lower the qualifying IOP criteria at both the Eligibility 1 and Eligibility 2 visits from ≥ 21 and ≤ 28 mmHg at 09:00 to ≥ 19 and ≤ 28 mmHg at 09:00.

- **Synopsis, Study Population**

  Adults with open-angle glaucoma or ocular hypertension on DUOTRAV (Travoprost 0.004%/Timolol 0.5%) solution therapy who may benefit from further IOP lowering (IOP ≥ ~~21~~ ***19*** and ≤28 mmHg in the study eye)

- **Synopsis, Subject Selection, Inclusion Criteria #3**

  Qualifying mean IOP measurements at both the Eligibility 1 and Eligibility 2 visits, in at least 1 eye (the same eye(s) ≥ ~~21~~ ***19*** and ≤ 28 mmHg at 9:00 while on a Travoprost 0.004%/ Timolol 0.5% solution

- **Synopsis, Assessments, [redacted], Baseline IOP**

  Baseline IOP: ~~21~~ ***19***-24 mmHg, >24-28 mmHg

- **Section 8 – Subject Population**

  To participate in the study, subjects must have a mean IOP measurement at 09:00 in at least 1 eye (***same eye***, study eye) ≥ ~~21~~ ***19*** and ≤ 28 mmHg at 2 consecutive visits (Eligibility 1 and Eligibility 2).

- **Section 10, Table 10-1, Study Plan by Treatment Group**

  Mean IOP for both Eligibility Visits must be: ≥ ~~21~~ ***19*** mmHg and ≤ 28 mmHg in at least 1 eye at 09:00 time point

- **Section 10.2.2., Visit 2 (Eligibility 1) and Visit 3 (Eligibility 2), Table 10-2**

  Mean IOP must be ≥ ~~21~~ ***19*** and ≤ 28 mmHg in at least one (same) eye(s) at 09:00.

- **Section 11.3 – Demographic and Baseline Characteristics**

  Subject characteristics summaries include tables and listings such as demographics (age, gender, race, iris color, and region) and baseline characteristics (baseline IOP by time point, baseline diurnal IOP, baseline IOP category (~~21~~ ***19***-24 mmHg, >24-28 mmHg), and diagnosis for all analysis sets (safety and FAS).

- **Section 11.3.2. – Baseline Characteristics**

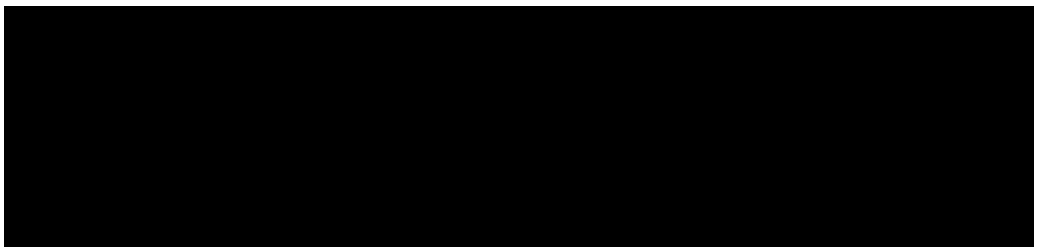
  Baseline IOP by time point and diurnal baseline IOP will be summarized as continuous variables. In addition, baseline IOP (~~21~~ ***19***-24 mmHg, >24-28 mmHg), will be summarized as a categorical variables.

- **Section 11.4.1.2.1. – Subgroup Analysis Methods**

  Subgroups of age category (< 50, 50-65, >65), sex, race (Caucasian, Black, Asian, Hispanic, Other), baseline IOP (~~21~~ ***19***-24 mmHg, >24-28 mmHg) and region (EMEA, Asia, ,LACAR,) will be summarized descriptively (N, mean, standard deviation) for the primary end point.

- **Section 11.4.2.2.1. – Subgroup Analysis Methods**

  Subgroups of age category (< 50, 50-65, > 65), sex, race (Caucasian, Black, Asian, Hispanic, Other), baseline IOP (~~21~~ ***19***-24 mmHg, >24-28 mmHg), and region (EMEA, Asia, LACAR) will be summarized descriptively (N, mean, standard deviation) for the secondary endpoints.

- 

2. Remove the 15:00 IOP measurement time point at all study visits.

   - **Synopsis, Assessments, Primary Efficacy**

     Change from baseline in diurnal IOP (mean of changes at 09:00 ***and*** 11:00 ~~and 15:00~~ time points) at Week 6.

   - **Synopsis, Statistical Methods, Primary Efficacy**

     The primary efficacy analysis will be an assessment of differences between treatments in mean change from baseline in diurnal IOP at Week 6 (change in patient IOP averaged over the 09:00 ***and*** 11:00~~, and 15:00~~ time points).

- **Section 2 – Overview of Study Plan**

  IOP (09:00, 11:00~~, 15:00~~)

- **Section 10.2.2., Visit 2 (Eligibility 1) and Visit 3 (Eligibility 2), Table 10-2**

  VISIT 2 (ELIGIBILITY 1) & VISIT 3 (ELIGIBILITY 2): [09:00 (+/-30 MIN), 11:00 (+/- 30 MIN~~), AND 15:00 (+/- 30 MIN)~~ EXAMINATIONS

- **Section 10.2.3., Visit 4 (Week 2) and Visit 5 (Week 6, Exit), Table 10-3**

  VISIT 4 (WEEK 2) & VISIT 5 (WEEK 6, EXIT): [09:00 (+/-30 MIN), 11:00 (+/- 30 MIN~~), AND 15:00 (+/- 30 MIN)~~ EXAMINATIONS

- **Section 11.4.1. Primary Efficacy**

  The primary efficacy analysis will be an assessment of differences between treatments in mean change from baseline in diurnal IOP at Week 6 (patient IOP change from baseline averaged over the 09:00 ***and*** 11:00~~, and 15:00~~ time points).

3. Allow subjects currently on treatment with Travoprost 0.004% /Timolol 0.5% for at least 28 days prior to screening in the morning or evening to be eligible for the study.

- **Synopsis, Background Medication, DUOTAV Dosage**

  1 drop instilled once per day in affected eye(s) ***(09:00 or*** 21:00 hr)

- **Synopsis, Subject Selection, Inclusion Criteria #2**

  Subjects currently on treatment with Travoprost 0.004% /Timolol 0.5% prescribed as approved in the country, ***on morning or*** evening dosing for at least 28 days prior to screening, and that in the opinion of the Investigator may benefit from further IOP lowering. ***Subjects must remain on either their morning or evening dosing for the duration of the study.***

- **Section 2. - Overview of Study Plan, footnote**

  * Visit 1 and 2 may be combined if the subject IOP was measured at 09:00, DUOTRAV taken on the previous ***morning at 09:00 ± 1hr or*** evening at 21:00 ± 1hr

- **Section 8 – Subject Population**

  To participate in the study, subjects must be on DUOTRAV (travoprost 0.004% / timolol 0.5 %) solution therapy for at least 4 weeks (28 days) ***dosing either in the morning or evening*** prior to screening.

- **Section 9 – Treatments Administered**

  At the Screening Visit, the PI will confirm that subjects have been on continuous ***morning*** or evening DUOTRAV (travoprost 0.004% / timolol 0.5 %) therapy for at least 28 days. If qualified, each subject will continue with open label study ***DUOTRAV, dosed at approximately the same time (evening or morning)*** for the duration of the study.

- **Section 9.2.1. – Route of Administration**

  During the time the subject is in the study, the supplied DUOTRAV will be used, ***according to the morning or evening regimen followed prior to Screening.*** One drop is to be applied topically to the eye***(s)*** daily ***in the morning (at 9:00± 30 min) or*** in the evening (at 21:00 ± 30 min)

- **Section 9.2.2. – Duration of Exposure**

  Subject's medical chart should confirm the use of the ***morning or*** evening dose of DUOTRAV (travoprost 0.004% / timolol 0.5 %) for at least 4 weeks (28 days) immediately prior to screening.

- **Section 10, Table 10-1, Study Plan by Treatment Group**

  Begin dosing with ***study supplied*** DUOTRAV at ~~09:00~~ ***21:00*** ±30min on the evening of the screening visit ***if subject dosed with Duotrav in the evenings prior to Screening, or begin dosing with study supplied DUOTRAV at 09:00 ±30min the following day after Screening if subject dosed with Duotrav in the mornings prior to Screening.***

At Screening Visit the investigator should document that the subject has been previously on ***morning or*** evening DUOTRAV solution therapy for at least 28 days prior to Screening Visit.

- **Section 10.2.1 – Visit 1 – Screening, Step #11, Step #15, Step #16**

    - Step 11. Perform Goldmann applanation tonometry OU

    *if subjects IOP was measured at 09:00, DUOTRAV taken on the previous ***morning at 09:00 ± 1 hr or*** evening at 21:00 ± 1 hr and all other study assessments can be completed as per protocol for Visit 1 (Screening) and Visit 2 (E1), then Visit 1 and Visit 2 can be combined

    - Step 15. Instruct each subject to instill DUOTRAV daily at ***either 09:00 or*** 21:00 ±30 min, OU.

    Reminder: Investigator must document that subjects are currently on ***morning or*** evening dosing for at least 28 days prior to the Screening Visit. ***The same DUOTRAV dosing schedule must be followed for the entire study (morning or evening dosing.)***

    - Step 16. Schedule the subject to return 1-5 days for the Eligibility 1 Visit (Visit 2).

    *if subjects IOP was measured at 09:00, DUOTRAV taken on the previous **morning at 09:00 ± 1 hr or** evening at 21:00 ± 1 hr and all other study assessments can be completed as per protocol for Visit 1 (screening) and Visit 2 (E1), then Visit 1 and Visit 2 can be combined.

- **Section 10.2.2., Visit 2 (Eligibility 1) and Visit 3 (Eligibility 2), Table 10-2**

    - Reconfirm that it is documented that the subject has administered ***morning or*** evening dose of DUOTRAV therapy daily for 28 days.

    - RESCHEDULE the visit if the subject did not dose the previous ***morning or*** evening.

- DUOTRAV – Daily dosing ***in the morning or*** in evening (***09:00 or*** 21:00 ± 30 min).

- The Visit 2 (Eligibility 1 Visit) should be conducted 1-5 days following the Screening Visit or can be combined if the subjects IOP was measured at 09:00±30 min, DUOTRAV was taken ***at 09:00 ±1 hr on the previous morning or*** at 21:00±1 hr on the previous evening and all other study assessments can be completed as per protocol for V1 (screening).

- Dosing instructions should be provided to the subject as follows:

- c) Continue with 1 drop of DUOTRAV in each affected eye daily at ***either 09:00 ± 30min or*** 21:00 ± 30min for approximately 6 weeks.

REMINDER: Contact the subject prior to the Week 2 and Week 6 Visits to remind the subject to:

- instill the dose of DUOTRAV at ***09:00 (± 30 minutes) or*** 21:00 (± 30 minutes) and masked study medication at 21:00 (± 30 minutes) the ~~night~~ ***day*** prior to the visit,

- DO NOT dose the masked IP ***or the DUOTRAV 09:00 morning dose*** the morning of the study visit. The morning dose ***of both the masked IP and DUOTRAV*** will be instilled in the office after the 09:00 IOP measurement.

- **Section 10.2.3, Visit 4 (Week 2) and Visit 5 (Week 6, Exit), Table 10-3**

  - RESCHEDULE the visit if the subject did not dose the previous evening or if the subject has already dosed the morning dose ***of DUOTRAV and/or the masked IP.***

  - Approximately 15 minutes after the IOP measurements, instill the masked IP ***and the DUOTRAV morning dose for subjects using the morning regimen*** in the office.

4. Incorporate an interim analysis for efficacy assessment when 50% of the total planned subjects have completed or discontinued form the study.

   - **Synopsis, Statistical Methods; Section 11.9**

This study will incorporate an interim analysis for efficacy assessment when 50% of the total planned subjects have completed or discontinued from the study. The objective of the interim analysis is to provide an opportunity for early rejection of the null hypothesis that there is no difference in diurnal IOP change from baseline between brinzolamide / brimonidine plus Travoprost 0.004%/ Timolol 0.5% and vehicle plus Travoprost 0.004%/ Timolol 0.5%. In order to ensure Type 1 error is adequately controlled at the 5% level of significance (two-sided), a p-value boundary will be employed, specifically, the Haybittle-Peto boundary (Haybittle 1971). The Haybittle-Peto boundary ensures that the study stops for efficacy only if there is overwhelming evidence of efficacy.

- **Synopsis, Sample Size Justification; Section 11.10**

With 108 evaluable subjects per treatment group in the primary efficacy analysis, there is at least 80% power to detect a difference in mean change from baseline in diurnal IOP at Week 6 IOP of 1.5 mmHg between the treatment groups. ***However, the required sample size to attain the same power is 28 subjects per arm if the difference is 3.0 mmHg between treatment groups as suggested by expert opinion***. ***Both*** calculations ***are*** based on the assumption of a common standard deviation for mean of 3.9 mmHg and the use of a two-sample two-sided t-test performed at the α=0.05 level of significance.

To mitigate the uncertainty about the expected treatment difference, a two-look design with Haybittle-Peto boundaries will be used. Thus, this study will incorporate an interim analysis for efficacy assessment when 50% of total planned subjects have completed or discontinued from the study. The power to reject the null hypothesis at the single interim analysis when 50% of subjects have completed or discontinued the study is 28.2% if the expected mean difference is 1.5 and 92.2%, if the expected mean difference is 3.0.

Look #	Sample Size	Efficacy p-value	P-value Boundary	Exit Probabilities		
				$\delta = 0$	$\delta = 1.5$	$\delta = 3.0$
1	108	0.01	0.01	0.01	0.282	0.922
2	216	0.045	0.045	0.04	0.517	0.078
Sum of Exit Probabilities				0.050	0.799	1

- **Section 10.5, Clinical Study Termination**

  Added text:

  Reasons for the closure of an investigational site or termination of a study may include:

  Interim analysis results met pre-specified stopping rule

- **Section 14, References**

  Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983. 70(3):659-63.

5. Provide clarification to exclusion criteria # 27

   - **Synopsis, Subject Selection, Exclusion Criteria # 27**

     Mean IOP > 28 mmHg at any time point ***in either eye*** during the Screening/Eligibility Phase.

6. Allow for re-screening with defined criteria.

   - **Section 8 – Subject Population**

     A subject may be re-screened if they screen failed due to eligibility criteria defined in the original version of the protocol. Refer to the CRF Completion Guidelines for further information on EDC documentation guidance.

7. Update Statistical Analysis associated with the change in eligibility criteria:

   - **Synopsis, Assessments, Secondary Efficacy**

     Changed from:

- Diurnal IOP at Week 6
- Percentage change from baseline in diurnal IOP at Week 6
- IOP change from baseline at Week 6 for each time point (09:00, 11:00, 15:00 hrs)
- Percentage change from baseline in IOP at Week 6 for each time point

Changed to:

- Diurnal IOP at Week 6
- Percentage change from baseline in diurnal IOP at Week 6
- IOP change from baseline at Week 6 ~~for each time point (09:00,~~ ***at*** 11:00 ~~15:00~~ hrs
- Percentage change from baseline in IOP at Week 6 ~~for each time point~~ ***at 11:00 hrs***
- ***IOP change from baseline at Week 6 at 09:00 hrs***
- ***Percentage change from baseline in IOP at Week 6 at 09:00 hrs***

- **Synopsis, Statistical Methods, Secondary Efficacy**

Changed from:

The testing order (all based on IOP at Week 6) will be:

- Difference between treatments in mean change from baseline in diurnal IOP
- Difference between treatments in diurnal IOP
- Difference between treatments in percentage diurnal IOP change from baseline
- Difference between treatments in IOP change from baseline for each time point
- Difference between treatments in percentage IOP change from baseline for each time point (09:00, 11:00, 15:00)

Changed to:

The testing order (all based on IOP at Week 6) will be:

- Difference between treatments in mean change from baseline in diurnal IOP
- Difference between treatments in diurnal IOP
- Difference between treatments in percentage diurnal IOP change from baseline
- Difference between treatments in IOP change from baseline ~~for each time point~~ ***at 11:00 hrs***
- Difference between treatments in percentage IOP change from baseline ***at 11:00 hrs*** ~~for each time point (09:00, 11:00, 15:00)~~
- ***Difference between treatments in IOP change from baseline at 09:00 hrs***
- ***Difference between treatments in percentage IOP change from baseline at 9:00 hrs***

- **Section 11.4, Efficacy Analysis**

  Changed from:

  Unless otherwise specified, all statistical analyses will be two-sided at the 5% level.

  Changed to:

  Unless otherwise specified, all ~~statistical analyses~~ ***significance testing*** will be ***at the 5% significance level*** two-sided~~ at the 5% level.~~

- **Section 11.4.2. – Secondary Efficacy**

  Changed from:

  The secondary endpoints are:

  - Diurnal IOP at Week 6
  - Percentage change from baseline in diurnal IOP at Week 6
  - Change from baseline in IOP for each time point (09:00, 11:00, 15:00) at Week 6
  - Percentage change from baseline in IOP for each time point (09:00, 11:00, 15:00) at Week 6

  Changed to:

  The secondary endpoints are:

  - Diurnal IOP at Week 6
  - Percentage change from baseline in diurnal IOP at Week
  - Change from baseline in IOP ~~for each time point (09:00,~~ ***at*** 11:00 ***hrs*** ~~15:00)~~ at Week 6
  - Percentage change from baseline in IOP ~~for each time point (09:00, 11:00, 15:00)~~ at ***11:00 hrs at*** Week 6

- ***Change from baseline in IOP at 09:00 hrs at Week 6***
- ***Percentage change from baseline in IOP at 09:00 hrs at Week 6***

- **Section 11.6 – Multiplicity**

  Changed from:

  The testing order (all based on IOP at Week 6) will be:

  - Difference between treatments in mean change from baseline in diurnal IOP
  - Difference between treatments in diurnal IOP
  - Difference between treatments in percentage diurnal IOP change from baseline
  - Difference between treatments in IOP change from baseline for each time point
  - Difference between treatments in percentage IOP change from baseline for each time point (09:00, 11:00, 15:00)

  Significance for a comparison will be claimed only if the null hypothesis is rejected ($p < 0.05$) for the previous endpoint in this series. Success for the last two endpoints will be defined as
  $p< 0.05$ for at least 2 of the 3 time points.

  Changed to:

  The testing order (all based on IOP at Week 6) will be:

  - Difference between treatments in mean change from baseline in diurnal IOP
  - Difference between treatments in diurnal IOP
  - Difference between treatments in percentage diurnal IOP change from baseline
  - Difference between treatments in IOP change from baseline ~~for each time point~~ ***at 11:00 hrs***

- Difference between treatments in percentage IOP change from baseline ~~for each time point (09:00, 11:00, 15:00)~~ ***at 11:00 hrs***

- ***Difference between treatments in IOP change from baseline at 09:00 hrs***

- ***Difference between treatments in percentage IOP change from baseline at 09:00 hrs***

Significance for a comparison will be claimed only if the null hypothesis is rejected ($p < 0.05$) for the previous endpoint in this series. ~~Success for the last two endpoints will be defined as p< 0.05 for at least 2 of the 3 time points.~~

8. Define procedure/assessment windows:

- **Section 2. - Overview of Study Plan, Procedure/Assessment**

IOP (09:00, 11:00~~, 15:00~~***)*** ***± 30 minutes***

9. Update administrative information and correct minor errors from Protocol Version 1.0:

- **Synopsis, No. of Sites:**

Multicenter, approximately ~~30~~ ***40*** sites

- **Section 8 - Subject Population**

The study population includes approximately 240 subjects to be randomized at approximately ~~30~~ ***40*** sites globally.

- **Section 9.4 – Subject Confidentiality and Methods Used to Minimize Bias**

Changed From:

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. At the end of the clinical study, the Sponsor will collect a copy of the enrollment log without any identifying subject information.

All documents submitted to the Sponsor will identify the subjects exclusively by number and demographic information. No other personally identifying information should be transmitted to the Sponsor.

Changed To:

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep ~~an enrollment~~ ***a subject*** log with confidential identifying information that corresponds to the subject number***, subject name and medical ID number*** ~~s and initials~~ of each study participant. At the end of the clinical study, the Sponsor will collect a copy of the ~~enrollment~~ ***subject*** log without any identifying subject information. All documents submitted to the Sponsor will identify the subjects exclusively by number ~~and demographic information~~. No other personally identifying information should be transmitted to the Sponsor.

- **Section 10.2.3. Visit 4 (Week 2), Table 10-3, Activities for Week 2 and Week 6 (Exit) Visits**

Error Correction - Removal of 11:00 assessments from Visit 4 (Week 2); assessments not collected at 11:00 at Visit

2 OVERVIEW OF STUDY PLAN

	Nominal Time ± Visit Window Limits						
Procedure/ Assessment	**Visit 1*** ***Screening***	**Visit 2*** ***Eligibility 1*** ***1-5 days after Screening***	**Visit 3** ***Eligibility 2*** **(Randomization)** ***3-5 days from E1***	**Visit 4** ***Day 14± 3 Days from E2***	**Visit 5** ***Exit*** ***Day 42 ± 5 Days from E2***	**Unscheduled Visit**	**Early Exit[a]**
Informed Consent [b]	X						
Demographics	X						
Medical History	X						
Concomitant Medications	X						
Changes in concomitant meds		X	X	X	X	X	X
Inclusion/Exclusion	X						
Urine Pregnancy Test [c]	X				X		X
BCVA	X	X[1]	X[1]	X[1]	X[1]	X	X
Slit-Lamp Biomicroscopy	X	X[1]	X[1]	X	X[1]	X	X
Corneal thickness (packymetry)	X						
Angle width screening (Gonioscopy)	X						
Dilated Fundus Exam	X				X	X	X
Visual field assessment (Automated perimetry)	X[d]				X[e]		X[e]
IOP	X			X[2]		X	X
IOP (09:00, 11:00) +/- 30 minutes		X	X		X		
Blood Pressure	X			X[2]		X	X
Blood Pressure (09:00, 11:00)		X	X		X		
Pulse rate	X			X[2]		X	X
Pulse Rate (09:00, 11:00)		X	X		X		
Dispense study meds	X		X				
Instill Meds in office				X	X		

	Visit 1* ***Screening***	**Visit 2*** ***Eligibility 1***	**Visit 3** ***Eligibility 2*** **(Randomization)**	**Visit 4**	**Visit 5** ***Exit***	**Unscheduled Visit**	**Early Exit[a]**
Adverse Events (Both Volunteered and Elicited)	X	X	X	X	X	X	X
Collect Study Meds					X		X
Exit patient & Complete Exit Form					X		X

* Visit 1 and 2 may be combined if the subject IOP was measured at 09:00, DUOTRAV taken on the previous morning at 09:00 ± 1hr or evening at 21:00 ± 1hr and all other study assessments can be completed as per protocol

[1] morning only
[2] 09:00 ± 2 hrs
[a] Perform assessments on subjects who discontinue study participation prior to Week 6 visit.
[b] Must be signed/dated before study procedures are performed.
[c] Required on all female subjects of childbearing potential.
[d] VF can have been performed 30 days before Screening to E2 visit
[e] May be conducted anytime during the visit.

3 ABBREVIATIONS

Abbreviation	Definition
AC	Anterior chamber
ADR	Adverse drug reaction
AE	Adverse event
AEF	Adverse event Form
AMP	Adenosine monophosphate
BAK	Benzalkonium chloride
BCVA	Best-corrected visual acuity
BID	Twice a day
BP	Blood pressure
CAI	Carbonic anhydrase inhibitor
CFR	Code of Federal Regulation
IB	Investigator's brochure
CIGTS	Collaborative Initial Glaucoma Treatment Study
Con Meds	Concomitant medications
CRF	Case report form
dB	Decibel
DUOTRAV	Travoprost (0.004% or 40µg/mL and Timolol (0.5 % or
E1	Eligibility 1
E2	Eligibility 2
CRF	Case report form
EDC	Electronic data capture
EMEA	European Medicines Agency
ETDRS	Early treatment diabetic retinopathy study
EudraCT	European clinical trials database
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good clinical practice
ICF	Informed consent form
ICH	International conference on harmonization
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IOP	Intraocular pressure
IP	Investigational Product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IUD	Intra-uterine device
LACAR	Latan America and Canada
logMAR	Log_{10} of the minimum angle of resolution
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
Med Hx	Medical history

Meds	Medications
mg	Milligram
mm	Millimeter
mmHg	Millimeters of mercury
MOP	Manual of procedures
N/A	Not applicable
NCR	Not clinically relevant
NDA	New Drug Application
OAG	Open-angle glaucoma
POAG	Primary Open-Angle Glaucoma
OC	Observed case
OD	Right eye
OHT	Ocular hypertension
OS	Left eye
OU	Both eyes
PI	Principal investigator
PQ	Polyquatemium-1
QA	Quality assurance
QD	Once a day
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	SAS statistical software, SAS Institute Inc., Cary, NC
SIMBRINZA	Brinzolamide (1% or 10mg/mL) and Brimonidine (0.2% or 2 mg/mL) eye drops suspension
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
VF	Visual Field

4 TABLE OF CONTENTS

5 INTRODUCTION

5.1 Study Rationale and Background

Glaucoma is a group of progressive optic neuropathies caused by the degeneration and death of retinal ganglion cells and the axons that form the optic nerve that may lead visual field deterioration if left untreated (Weinreb 2004).

The biological mechanisms of the retinal ganglion cell degeneration are not precisely known, but risk factors for glaucoma and disease progression have been identified, such as elevated intraocular pressure (IOP), race, age, vascular disease and family history. However, elevated IOP is the only modifiable risk factor hence all treatment is targeted towards lowering IOP.

Although uncontrolled glaucoma may lead to optic nerve atrophy and blindness, glaucoma is often associated with a reduced quality of life even before blindness occurs (Wilson 1998, Wu 2008). The primary goal of glaucoma treatment, therefore, is to preserve the subject's visual function and quality of life. Physicians often follow a stepwise management strategy that aims to maximize IOP lowering while minimizing adverse events.

Typically treatment is initiated with a topical monotherapy such as a prostaglandin analogue or beta blocker. If the initial therapy is inadequate or poorly tolerated, additional therapies can be added on or subjects can be switched to an alternate therapy. Among the various treatment options currently available, prostaglandin analogues (PGAs) are often preferred as initial monotherapy because of their IOP lowering efficacy, low frequency of systemic side effects, and lower frequency of instillation compared with older therapies. Indeed, PGAs have largely replaced topical beta-blockers as first-line monotherapy over the past 10 years (Nasser 2006, Stewart 2008, Stewart 2005).

Despite the efficacy of the PGAs, a significant proportion of patients will fail on monotherapy and will require more than one medication to reach a target IOPs (IOP at which optic nerve damage will not progress). In the Ocular Hypertension Treatment Study (OHTS) by year five almost 40% of subjects needed two or more medications to achieve their target IOP (Kass 2002), and in the Collaborative Initial Glaucoma Treatment Study (CIGTS) after year two, more than 75% of subjects needed two or more medications to reach their target IOP (Lichter 2001). As such, clinicians often add on therapy or, switch to fixed dose combinations to better manage the disease

One of the commonly used topical IOP lowering combination drugs used to treat elevated IOP is DUOTRAV. A fixed dose combination eye drop containing a topical prostaglandin analogue, travoprost 40 µg/mL, and a topical beta-adrenergic receptor blocking agent, timolol

5 mg/mL, which lower lOP by complementary mechanisms of action. The safety and efficacy of both travoprost and timolol have been established as single and adjunctive therapy in well-controlled clinical studies in thousands of patients diagnosed with open-angle glaucoma or ocular hypertension. A summary of the known and potential risks and benefits associated with DUOTRAV can be found in the Summary of Product Characteristics (SmPC) or Product Information equivalent.

SIMBRINZA is a fixed dose combination eye drop suspension comprised of a carbonic anhydrase Inhibitor (CAI), brinzolamide (1% or 10mg/mL), and an Alpha agonist, brimonidine (0.2% or 2 mg/mL) which lower lOP by complementary mechanisms of action. In July 2014, brinzolamide/brimonidine fixed combination received marketing approval in the EU-27 member states with a 2 times per day (BID) dosing regimen under the trade name of SIMBRINZA. Earlier, in April 2013, brinzolamide/brimonidine fixed combination received marketing approval in the United States with 3 times per day (TID) dosing under the trade name of SIMBRINZA. A summary of the known and potential risks and benefits associated with SIMBRINZA can be found in the Summary of Product Characteristics (SmPC) or Product Information equivalent

The fixed dose combination of both DUOTRAV and SIMBRINZA, are effective, subjects may require further IOP lowering because of disease progression. However, the complexity of treatments (doses per day, number of bottles) has been shown to affect patient adherence to medications and often precludes adding further therapies; indeed, clinicians often plan for a surgical intervention when a third bottle is added to the treatment regime.

With the approval of SIMBRINZA, clinicians have the option of managing glaucoma with all 4 classes of medications (PGAs, beta blockers, CAIs and alpha agonists) thereby providing maximal medical therapy in 2 bottles with 3 drops/day. However, as some of these medications have a similar mechanism of action (inhibit production or increase flow), the IOP lowering that may be achieved as monotherapy, may be even lower when used together. This study will therefore investigate the additive IOP lowering effect achieved when SIMBRINZA is used adjunctively to DUOTRAV in patients with OAG or OH after 6 weeks of treatment.

5.2 Known and Potential Risks

SIMBRINZA (brinzolamide 1%/brimonidine 0.2%)

The most common ocular adverse drug reactions (ADRs) reported in clinical studies with the use of the fixed combination SIMBRINZA were hyperemia, visual disturbances, ocular discomfort, and the development of ocular allergic type reactions (Aung 2014, Gandolfi 2014).

These types of ADRs are known nonserious risks associated with the use of one or both of the individual components. Common systemic ADRs reported included dysgeusia, oral dryness, and fatigue/drowsiness. Like common ocular ADRs, these systemic events are known class effects of one or both of the individual components. While a bitter taste and dry mouth may be unpleasant, neither adverse reaction poses a safety issue for the use of SIMBRINZA. The development of fatigue/drowsiness may impair a person's ability to operate a motor vehicle or machinery. Subjects should be advised of this possible risk while using SIMBRINZA.

Decreased blood pressure and/or pulse rate have also been identified as systemic risks associated with the use of an alpha-2 adrenergic agonist (Kable 2000, Kamibayashi 2000). The use of brimonidine tartrate 2 mg/mL has been associated with minimal decreases in blood pressure. Some subjects who dosed with SIMBRINZA experienced decreases in blood pressure similar to those observed with the use of brimonidine as monotherapy.

With topical ocular carbonic anhydrase inhibitors (CAI) such as brinzolamide, there is an increased potential for developing corneal edema in subjects with low endothelial cell counts. No reports of corneal edema have been reported to date in clinical trials with the use of SIMBRINZA (dosed BID or TID). Carbonic anhydrase inhibitors may also produce acid-base and electrolyte alterations. This is more likely with the use of an oral CAI (eg, acetazolamide); however, since brinzolamide is absorbed systemically, there is a potential risk for the development of acid-base and electrolyte alterations with the use of SIMBRINZA. This risk is higher in subjects concomitantly dosing with high dose salicylate therapy. No report of an acid-base or electrolyte alteration associated with the use of SIMBRINZA has been reported to date in clinical trials.

The brinzolamide component of the fixed combination is a sulfonamide and although it is administered as a topical ocular drug, it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical ocular administration of SIMBRINZA. Rare fatalities have occurred with systemic use of sulfonamides. Sulfonamide reactions have not been reported to date with the use of Simbrinza in clinical trials.

Simbrinza is preserved with benzalkonium chloride (BAK). BAK has been reported to cause punctate keratopathy and/or ulcerative keratopathy. Close monitoring is required with frequent or prolonged use in dry eye subjects, or in conditions where the cornea is compromised. The BAK concentration of SIMBRINZA is lower [redacted] relative to the BAK concentration in each of the individual components (0.1 mg for brinzolamide 10 mg/mL and 0.05 mg for brimonidine 2 mg/mL).

Pharmacokinetic data did not indicate a systemic pharmacokinetic drug-drug interaction between the individual active components in SIMBRINZA. Systemic concentrations of the individual active components after dosing with SIMBRINZA were similar to the systemic concentrations after dosing with the individual components.

Overall, no additional risks were identified with the use of SIMBRINZA relative to the known risks of the individual components.

DUOTRAV (Travoprost 0.004% / Timolol 0.5 %)

Like other topically applied IOP lowering medications, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic component of timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking medicinal products may occur. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

In clinical studies involving 2170 subjects treated with DUOTRAV the most frequently reported treatment-related adverse reaction was ocular hyperaemia

Other common adverse events associated with this class of medicinal product include: punctate keratitis, eye pain, visual disturbance, vision blurred, dry eye, eye pruritus, ocular discomfort and eye irritation.

Less common or rare adverse reactions include: keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, corneal erosion, meibomianitis, conjunctival hemorrhage, eyelid margin crusting, trichiasis, distichiasis. lacrimation increased, erythema of eyelid, growth of eyelashes eye allergy, conjunctival edema, eyelid edema, bradycardia, arrhythmia, heart rate irregular, hypertension, hypotension, dyspnea, postnasal drip, dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort, dermatitis contact, hypertrichosis, urticaria, skin discoloration, alopecia, skin hyperpigmentation (periocular), pain in extremity, chromaturia, thirst, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased, hypersensitivity, nervousness, dizziness, and headache.

No specific drug interaction studies have been performed with travoprost or timolol. There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine. The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

Potentiated systemic beta-blockade (eg, decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (eg, quinidine, fluoxetine, paroxetine) and timolol. Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally. Beta-blockers may increase the hypoglycaemic effect of antidiabetic medicinal products. Beta-blockers can mask the signs and symptoms of hypoglycemia.

5.3 Potential Benefits

SIMBRINZA

Results from clinical studies evaluating brinzolamide/brimonidine administered TID or BID show that the IOP lowering efficacy of the fixed combination is statistically superior to each of its individual components (Katz 2013, Nguyen 2013, Aung 2014). An additional multicenter clinical study has shown that the IOP lowering efficacy of the brinzolamide/brimonidine administered BID (fixed combination) is noninferior to the individual components administered concomitantly (unfixed combination) (Gandolfi 2014).

There are several potential benefits to SIMBRINZA fixed combination therapy such as:

- an IOP lowering effect of up to 35% (Aung 2014, Gandolfi 2014, Katz 2013, Nguyen 2013)
- a safety profile that is consistent with that of the individual components (Aung 2014, Gandolfi 2014, Katz 2013, Nguyen 2013, Whitson 2013)
- a lower exposure to preservatives versus the individual components
- the potential for increased subject adherence (Higgenbotham 2010, Schwartz 2010) versus the dosing the individual components concomitantly
- an alternative therapy option for subjects in whom therapy with beta-blockers is contraindicated.

DUOTRAV

DUOTRAV (travoprost 0.004% / timolol 0.5 %) is effective in lowering IOP and have often replaced β-blockers and PGAs. In some subjects however, target IOPs will not be reached and an adjunctive therapy will be required.

The approval of SIMBRINZA gives clinicians the option to manage the disease with 4 classes of medications (PGAs, beta blockers, CAIs and alpha agonists) using 3 drops/day.

Nevertheless, as some of these medications have the same mechanism of action, the IOP lowering they may achieve as a monotherapy may be even lower when used together.

Alcon is investigating the effectiveness of SIMBRINZA, dosed twice daily, as an adjunctive therapy to DUOTRAV in subjects who require further IOP lowering. This combination of medications may expand the treatment options available to both clinicians and subjects in whom DUOTRAV alone does not provide sufficient IOP lowering.

6 ETHICS

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline and other regulations as applicable. The Investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

Before clinical study initiation, this protocol, the informed consent form (and assent form, if applicable), any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB). The Investigator must provide documentation of the IEC/IRB approval to the Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs, if any. The IEC/IRB must be provided with a copy of the Investigator's Brochure, any periodic safety updates, and all other information as required by local regulation and/or the IEC/IRB. At the end of the study, the Investigator will notify the IEC/IRB about the study's completion. The IEC/IRB also will be notified if the study is terminated prematurely. Finally, the Investigator will report to the IEC/IRB on the progress of the study at intervals stipulated by the IEC/IRB.

Voluntary informed consent will be obtained from every subject (and/or legal representative, as applicable) prior to the initiation of any screening or other study-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document

must meet all applicable local laws and will provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the investigational product, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also will be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent and must provide a duplicate copy to each subject.

7 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the IEC/IRB prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study may be required by the IRB/IEC to sign the approved, revised informed consent form.

8 SUBJECT POPULATION

The study population includes approximately 240 subjects to be randomized at approximately 40 sites globally. Enrollment will be competitive. To participate in the study, subjects must be on DUOTRAV (travoprost 0.004% / timolol 0.5 %) solution therapy for at least 4 weeks (28 days) either in the morning or evening prior to screening, have a mean IOP measurement at 09:00 in at least 1 eye (same eye, study eye) ≥ 19 and ≤ 28 mmHg at 2 consecutive visits (Eligibility 1 and Eligibility 2). A subject may be re-screened if they screen failed due to eligibility criteria defined in the original version of the protocol. Refer to the CRF Completion Guidelines for further information on EDC documentation guidance. The expected duration of subject participation in the study is approximately 8 weeks (42 days, 5 visits). The complete inclusion and exclusion criteria are presented in Section 1.

9 TREATMENTS ADMINISTERED

At the Screening Visit, the PI will confirm that subjects have been on continuous morning or evening DUOTRAV (travoprost 0.004% / timolol 0.5 %) therapy for at least 28 days. If qualified, each subject will continue with open label study DUOTRAV, dosed at approximately the same time (evening or morning) for the duration of the study.

For randomization into the study, subjects will be randomly assigned through IRT; a generated subject number will be automatically populated in the EDC system. Subjects will be randomized in a 1:1 manner to receive treatment with either SIMBRINZA or Vehicle adjunctively to their DUOTRAV therapy. Throughout the study, the Investigator will be responsible for the accounting of all study medications and will ensure they are not used in any unauthorized manner.

9.1 Identity of Study Treatments

Investigational Product (IP):	SIMBRINZA
Control Group:	Vehicle
Background Medication:	DUOTRAV

SIMBRINZA and Vehicle will be supplied in identical opaque DROP-TAINER bottles with masked labels indicating that the product is for investigational use only, and will be identified both by kit and protocol number. Each bottle will be filled to a volume of 5 mL with SIMBRINZA or Vehicle. Masked Investigational Products (SIMBRINZA or Vehicle) should be securely stored in accordance with the label. The Investigational and Vehicle Products will be provided in identical packaging with identical labels. The labels will include the protocol number, a statement that the products are for investigational use only and any other information required per local regulation

DUOTRAV will be provided open label by the Sponsor for the clinical trial following local country regulations.

A temperature log will be maintained at each investigational site documenting appropriate storage conditions of the investigational products and will be made available for the study monitor to inspect.

9.2 Usage

9.2.1 Route of Administration

During the time the subject is in the study, the supplied DUOTRAV will be used according to the morning or evening regimen followed prior to Screening. One drop is to be applied topically to the eye(s) daily in the morning (at 09:00 ± 30 min) or in the evening (at 21:00 ± 30 min).

One drop of masked IP is to be applied topically to the eye(s) at 09:00 (± 30 min) and 21:00 (± 30 min).

The study medications should be dosed in both eyes unless there is a potential safety issue to the subject (or is unnecessary) in the opinion of the Investigator. Subjects should be reminded to:

- Gently shake the masked IP prior to instillation,

- As evening instillation of both IOP-lowering medications occurs at the same time, instill the DUOTRAV first, wait 15 minutes, and then instill the masked IP.

9.2.2 Duration of Exposure

Subject's medical chart should confirm the use of the morning or evening dose of DUOTRAV (travoprost 0.004% / timolol 0.5 %) for at least 4 weeks (28 days) immediately prior to screening.

Masked IP (SIMBRINZA or Vehicle) will be received at Visit 3 (Eligibility 2 visit) following randomization for the 42 ± 5 days treatment phase.

9.2.3 Methods Used to Determine Dosage

The dosage and BID dosing regimen for SIMBRINZA in this study is based on the dosage and dosing regimen of the marketed product.

The dosage and QD dosing regimen for DUOTRAV is based on the dosage and dosing regimen of the marketed product.

9.3 Accountability Procedures

Upon receipt of masked IP from the Sponsor, the Investigator or designee will conduct an inventory of all products. Designated study staff will provide the study drugs to the subjects in accordance with their Electronic Data Capture (EDC) assigned subject numbers and the randomization schedule. During the study, the Investigator must maintain records of study treatment dispensation and collection of masked IP for each subject. This record must be made available to the study monitor for the purposes of verifying the accounting of clinical supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. At the conclusion of the study, the Investigator will be responsible for returning all used and unused study supplies unless otherwise instructed by the Sponsor.

9.4 Subject Confidentiality and Methods Used to Minimize Bias

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep a subject log with confidential identifying information that corresponds to the subject number, subject name and medical ID number of each study participant. At the end of the clinical study, the Sponsor will collect a copy of the subject log without any identifying subject information. All documents submitted to the Sponsor will identify the subjects exclusively by number. No other personally identifying information should be transmitted to the Sponsor.

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of end points, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the treatments by the Investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

This study is double-masked, with subjects randomized to use SIMBRINZA or Vehicle for the duration of approximately 42 days. However, DUOTRAV solution therapy is open labeled and will be dosed for the duration of the masked treatment period of approximately 42 days but also during the screening and Eligibility periods. The Investigator, subject, Sponsor, and monitors involved in reporting, obtaining, and/or reviewing the clinical evaluations will not be aware of the specific masked treatment (SIMBRINZA or Vehicle) being administered. This level of masking will be maintained throughout the conduct of the study. Both SIMBRINZA and Vehicle will be provided in identical masked bottles labeled with the protocol and kit numbers. Each kit will contain 1 bottle of masked IP.

The randomization scheme will be generated and maintained by the Sponsor. Only once all study data have been verified, validated and the database locked, will individual subjects be unmasked. In the event of a medical emergency where the knowledge of subject treatment is required, an individual Investigator will have the ability to unmask the treatment assignment for a specific subject.

10 STUDY PROCEDURES

10.1 Outline of Study

The study is a 6 week, multicenter, randomized, double-masked, 2-arm, parallel-group study in subjects with primary open-angle glaucoma and/or ocular hypertension on travoprost 0.004% /

timolol 0.5 % who may benefit from further IOP lowering medications. The study is divided into 2 sequential phases for a total of 5 visits. Phase I of the study is the open-labeled Screening/Eligibility Phase, which includes a Screening Visit followed by 2 Eligibility Visits (E1 and E2). Phase II of the study is the randomized, double-masked treatment phase (Masked Treatment Phase) which includes 2 on-therapy visits: Visit 4 (at Week 2) and Visit 5 (Week 6, Exit Visit) as shown in Table 10-1.

Table 10–1 Study Plan by Treatment Groups

<table>
<tr><td rowspan="2">Treatment Group</td><td colspan="2">Study Phase</td></tr>
<tr><td>Phase I
(Screening/Eligibility Phase)</td><td>Phase II
(Masked Treatment Phase)</td></tr>
<tr><td></td><td>Screening and Eligibility Visits</td><td>Week 2 and Week 6 (Exit) Visits</td></tr>
<tr><td>SIMBRINZA + DUOTRAV</td><td rowspan="2">Begin dosing with study supplied DUOTRAV at 21:00 ±30min on the evening of the screening visit if the subject dosed with DUOTRAV in the evenings prior to Screening, or begin dosing with study supplied DUOTRAV at 09:00 ±30min the following day after Screening if the subject dosed with DUOTRAV in the mornings prior to Screening.

Mean IOP for both Eligibility Visits must be:
≥ 19 mmHg and ≤ 28 mmHg
in at least 1 eye at
09:00 time point

The same eye(s) must qualify at both 09:00 time points.</td><td>SIMBRINZA BID (09:00 & 21:00)±30min and DUOTRAV QD 09:00±30min or 21:00±30min</td></tr>
<tr><td>Vehicle + DUOTRAV</td><td>Vehicle BID (09:00 & 21:00) ±30min and DUOTRAV QD 09:00±30min or 21:00±30min</td></tr>
</table>

At Screening Visit the investigator should document that the subject has been previously on morning or evening DUOTRAV solution therapy for at least 28 days prior to Screening Visit.

10.2 Visits and Examinations

All procedures and the correspondent scoring must be performed as detailed in the Manual of Procedures (MOP).

10.2.1 VISIT 1 (Screening)

Subjects who were previously on travoprost 0.004% / timolol 0.5 % for at least 28 days (documented) prior to Screening Visit and, in the opinion of the Investigator, may benefit from further IOP lowering are candidates to be screened (Visit 1/ Screening). If all other Inclusion/Exclusion criteria are met, the Eligibility 1 (Visit 2) may occur promptly (within ~1-5 days as convenient for site and subject).

1.	Explain the purpose, nature, and conduct of the study
2.	Complete the Informed Consent process before any screening procedures are performed
3.	Register the subject in EDC and obtain the subject number
4.	Screen the subject for protocol inclusion/exclusion criteria as per Section 1
5.	Document demographic information, medical history, and concomitant medications including information on all medications used within the past 30 days. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications
6.	Perform a urine pregnancy test if the subject is a woman of childbearing potential
7.	Perform pulse and blood pressure measurements
8.	Assess BCVA, OU
9.	Conduct visual field assessment (automated perimetry) OU
10.	Perform a slit-lamp examination (biomicroscopy), OU
11.	Perform Goldmann applanation tonometry, OU **if subjects IOP was measured at 09:00, DUOTRAV taken on the previous morning at 09:00 ± 1 hr or evening at 21:00 ± 1 hr and all other study assessments can be completed as per protocol for Visit 1 (Screening) and Visit 2 (E1), then Visit 1 and Visit 2 can be combined*
12.	Conduct gonioscopy, OU
13.	Perform pachymetry, OU

14.	Perform a dilated fundus examination (Fundoscopy), OU
15.	Instruct each subject to instill DUOTRAV daily at either 09:00 or 21:00 ±30 min, OU. **Reminder:** Investigator must document that subjects are currently on morning or evening dosing for at least 28 days prior to the Screening Visit. The same DUOTRAV dosing schedule must be followed for the entire study (morning or evening dosing).
16.	Schedule the subject to return in 1-5 days for the Eligibility 1 Visit (Visit 2) **if subjects IOP was measured at 09:00, DUOTRAV taken on the previous morning at 09:00 ± 1 hr or evening at 21:00 ± 1 hr and all other study assessments can be completed as per protocol for Visit 1 (screening) and Visit 2 (E1), then Visit 1 and Visit 2 can be combined.* Instruct Subjects who wear contact lenses to remove lenses before dosing, and reinsert lenses no sooner than 15 min post-instillation. Subjects should be reminded to wear or bring their glasses on study visit days.

Alcon - Business Use Only Protocol - Clinical
Document: TDOC-0051572 Version: 2.0; Most-Recent; Effective; CURRENT Effective Date: 4/10/2017 10:03:07 AM
Status: Effective
Printed By:
Print Date:

10.2.2 VISIT 2 (ELIGIBILITY 1) & VISIT 3 (ELIGIBILITY 2): [09:00 (+/-30 MIN), 11:00 (+/- 30 MIN) EXAMINATIONS]

Table 10–2 Activities for Eligibility 1 and Eligibility 2 Visits

Activity	Visit 2 -Eligibility 1 (E1)		Visit 3- Eligibility 2 (E2)	
	09:00	11:00	09:00	11:00
Reconfirm that it is documented that the subject has administered morning or evening dose of DUOTRAV therapy daily for 28 days.	X			
Document date and time of last instillation. RESCHEDULE the visit if the subject did not dose the previous morning or evening	X		X	
Update Medical History /Concomitant Medications	X	X	X	X
Obtain Blood Pressure and Pulse Rate	X	X	X	X
Perform BCVA, OU	X		X	
Perform slit-lamp exam (Aqueous cells, aqueous flare, lens, status of lens), OU	X		X	
Measure IOP (Goldmann), OU *Mean IOP must be ≥ 19 and ≤ 28 mmHg in at least one (same) eye(s) at 09:00.* *Mean IOP must be less than 28 mmHg in either eye at **all** time points.* *(The mean IOP is defined as the average of two or more IOP readings in the same eye).*	X	X	X	X
Schedule the subject to return for Visit 3-Eligibility 2 (E2) in 3-5 days following E1 Visit prior to 09:00				
Verify inclusion/exclusion criteria. ***Only subjects meeting all requirements can be randomized***				
Randomize the subject upon confirmation of eligibility.				X
Dispense to the subject the corresponding masked study medication, document in the dispensing logs.				X
For subjects wearing contact lenses, instruct them to remove the lenses before the instillation of the study medication & wait approximately 15 minutes after dose before inserting the lenses again. DUOTRAV – Daily dosing in the morning or evening (09:00 or 21:00± 30 min). Masked IP – BID dosing at 09:00 ± 30 min and 21:00 ± 30 min				X
Schedule the successfully randomized subject to return for Visit 4 (Week 2 Visit) in 14 ±3 days following E2 Visit **prior to 09:00 (± 30 min)**				X

NOTE:

• The Visit 2 (Eligibility 1 Visit) should be conducted 1-5 days following the Screening Visit or can be combined if the subjects IOP was measured at 09:00±30 min, DUOTRAV was taken at 09:00 ±1 hr on the previous morning or 21:00±1 hr on the previous evening and all other study assessments can be completed as per protocol for V1 (screening)

• The Visit 3 (Eligibility 2 Visit) should be conducted 3-5 days following the Eligibility 1 Visit.

• DUOTRAV and Masked IP should be dosed in both eyes unless there is a potential safety issue (or is unnecessary) to the subject in the opinion of the Investigator.

At the end of the Eligibility 2 Visit, if the subject qualifies to continue in the study, use EDC to randomize the subject. The IRT system will return the assigned kit numbers for the masked study treatment to be dispensed to the subject. Once the EDC/IRT assigns kit numbers, dispense the kit numbers assigned to the subject.

Dosing instructions should be provided to the subject as follows:

a) Subjects wearing contact lenses should remove the lenses before instillation of either medication. Following instillation of the study medications, the subject should wait approximately 15 minutes after the last dose before re-inserting lenses.

b) MUST gently shake masked IP before use. Instill 1 drop of masked study medication in each affected eye daily at 09:00 (± 30 min) and 21:00 (± 30 min) for approximately 6 weeks.

c) Continue with 1 drop of DUOTRAV in each affected eye daily at either 09:00 ± 30min or 21:00 ± 30min for approximately 6 weeks.

d) If instillation of DUOTRAV and masked IP occurs at approximately the same time;

    i. Instill DUOTRAV first

    ii. Wait approximately 15 minutes before instilling masked IP

    iii. Attempt to instill study medications at the same time each evening

At the Eligibility 2 Visit, schedule the subject to return in 14 days (± 3 days) in the morning prior to 09:00 (± 2 hours) for Visit 4 (Week 2 Visit).

REMINDER: *Contact the subject prior to the Week 2 and Week 6 Visits to remind the subject to:*

- *instill the dose of DUOTRAV at 09:00 (± 30 minutes)or 21:00 (± 30 minutes) and masked study medication at 21:00 (± 30 minutes) the day prior to the visit,*
- *remove contact lenses prior to instillation of study medications and wait 15 minutes before inserting the lenses again*
- ***DO NOT dose the masked IP or the DUOTRAV 09:00 morning dose the morning of the study visit****. The morning dose of both the masked IP and DUOTRAV will be instilled in the office after the 09:00 IOP measurement.*
- ***DO NOT*** *discard any unused or empty bottles,*
- *bring all masked IP study medication bottles to the study visit,*
- *bring contact lenses or glasses with them to the study visit if they wear them*

10.2.3 VISIT 4 (WEEK 2) & VISIT 5 (WEEK 6, EXIT): [09:00 (+/-30 MIN), 11:00 (+/- 30 MIN) EXAMINATIONS]

Table 10–3 Activities for Week 2 and Week 6 (Exit) Visits

Activity	Visit 4 (Week 2)	Visit 5 (Week 6)/(Exit)	
	09:00	09:00	11:00
Document date and time of last instillation. RESCHEDULE the visit if the subject did not dose the previous evening **or** if the subject has already dosed the morning dose.	X	X	
Document any changes in Medical History and Concomitant Medications	X	X	X
Perform a urine pregnancy test if subject is female of child bearing age			X
Obtain Blood Pressure and Pulse Rate	X	X	X
Perform BCVA, OU	X	X	
Perform slit-lamp exam (Aqueous cells, aqueous flare, lens, status of lens), OU	X	X	

Activity	Visit 4 (Week 2)	Visit 5 (Week 6)/(Exit)	
	09:00	**09:00**	**11:00**
Perform Goldmann applanation tonometry, OU. Record time of IOP measurements	**X**	**X**	**X**
For subjects who wear contact lenses: remind them to remove contact lenses before dosing and re-insert lenses no sooner than 15 minutes following instillation of the study medication.	**X**	**X**	
Approximately 15 minutes after the IOP measurements, instill the masked IP and the DUOTRAV morning dose for subjects using the morning regimen in the office. Record the time of instillation by the site.	**X**	**X**	
Perform visual field assessment (automated perimetry), OU			[X]
Perform dilated fundus exam. *Assess vitreous, retina/macula/choroid, and optic nerve, including cup/disc ratio, OU*			X
Complete Adverse Event Forms if applicable. *Report all serious events to Alcon within 24 hours of the Investigator's knowledge of the event and to the IRB, according to their requirements.*	**X**	**X**	**X**
Schedule the subject to return for the next planned visit approximately 09:00 (± 30 min before the morning instillation)	X		
Collect the study medications. Complete subject's drug dispensing log.			X
Complete the Exit Form and exit the subject from the study			X

[X]: Any time

NOTE:
The visit 4 (Week 2 Visit) should be conducted 14 days (± 3 days) following the Eligibility 2 Visit.
The visit 5 (Week 6 Visit) should be conducted 42 days (± 5 days) following the Eligibility 2 Visit

10.3 Unscheduled Visits

Any visit that occurs between the regularly scheduled visits must be documented in the Unscheduled Visit pages of the CRF. During all unscheduled visits, the following procedures should be conducted if at all possible:

1. Obtain information on any changes in medical health and/or the use of concomitant medications.

2. Obtain blood pressure and pulse rate.

3. The following, if conducted, must be completed in the order they are listed in both eyes:

    a. BCVA,

    b. Slit-lamp exam,

    c. IOP, and

    d. Dilated Fundus exam.

4. Assess and document adverse events reported or observed.

5. The unmasked site staff will dispense extra kits as necessary.

Other assessments may be done at the discretion of the Investigator to appropriately treat the subject. Any additional assessments will be documented at the unscheduled visit and medical records. If the subject is discontinuing at the unscheduled visit, the **Early Exit** CRFs should be completed rather than the CRFs for the Unscheduled Visit and the appropriate Exit procedures should be completed (see sections 10.4 and 10.5).

10.4 Discontinued Subjects

Discontinued subjects are those who withdraw or are withdrawn from the study after being successfully randomized into the study. Subjects may discontinue from the study at any time for any reason. Subjects may also be discontinued from the study at any time if, in the opinion of the Investigator, their continued participation poses a risk to their health. Discontinued subjects will not be replaced (ie, their subject numbers will not be re-assigned/re-used).

Should a subject exhibit any clinically relevant signs, symptoms, or other clinical observations that possibly could be associated with suspected sensitivity or intolerance to one of the study treatments, the Investigator must document those observations on an Adverse Event (AE) Form.

Any subject who exits early from the study must undergo all procedures outlined at Week 6. Additionally, the Exit Form must be completed and one of the following reasons for discontinuation must be identified:

- Discontinued Study due to Adverse Event
- Discontinued Study due to Death
- Discontinued Study due to Lack of Efficacy

- Discontinued Study due to Lost to Follow Up
- Discontinued Study due to Non-Compliance with Study Drug
- Discontinued Study due to Physician Decision
- Discontinued Study due to Pregnancy
- Discontinued Study due to Protocol Violation
- Discontinued Study due to Study Terminated by Sponsor
- Discontinued Study due to Withdrawal by Subject
- Discontinued Study due to Other Reasons

10.4.1 Screen Failure Subjects

Screen failures are those subjects who, after ICF is signed, do not qualify for the study and therefore are NOT randomized. Only available information from screening and E1 & E2 Visits are collected in EDC for those subjects

10.5 Clinical Study Termination

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulatory authorities of the termination/ suspension and the reason(s) for the termination/suspension. The Investigator should promptly notify the IEC/IRB of the termination or suspension and of the reasons. The Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause. Reasons for the closure of an investigational site or termination of a study may include:

- Successful completion of the study
- The study's enrollment goals are met
- The Investigator fails to comply with the protocol or GCP guidelines
- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of subjects by the Investigator
- Interim analysis results met pre-specified stopping rule

The Investigator also may terminate the study at his/her site for reasonable cause. If the Sponsor terminates the study for safety reasons, it will immediately notify the Investigator(s)

by telephone and subsequently will provide written confirmation of and instructions for study termination.

11 ANALYSIS PLAN

11.1 Subject Evaluability

The final subject evaluability will be determined prior to breaking the code for masked treatment assignment and locking the database.

11.2 Analysis Data Sets

11.2.1 Full Analysis Set

The full analysis set (FAS) is the primary analysis set for the study; all primary, secondary [redacted] analyses will be based on the FAS.

All randomized subjects who receive study medication and who complete at least 1 scheduled on-therapy study visit will be evaluated in the full analysis set.

11.2.2 Safety Analysis Set

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. The safety analysis set will be used for each of the safety parameters and adverse events (AEs) occurring after exposure to investigational products administered during this study.

Safety data is to be collected for each subject beginning at the time of informed consent. Should any AEs occur prior to investigational products exposure, these AEs will be presented separately from those treatment-emergent AEs considered in the safety analysis.

11.3 Demographic and Baseline Characteristics

Subject characteristics summaries include tables and listings such as demographics (age, gender, race, iris color, and region) and baseline characteristics (baseline IOP by time point, baseline diurnal IOP, baseline IOP category (19-24 mmHg, >24-28 mmHg), and diagnosis for all analysis sets (safety and FAS). All descriptive summary statistics will be displayed with n and % for categorical data, and with mean, standard deviation, median, minimum, and maximum for continuous data. Tables will be presented by treatment and overall.

11.3.1 Demographic Characteristics

Age will be summarized as a continuous variable as well as categorically (<65, ≥65 and furthermore as <50, 50-64, ≥65). In addition, sex, race, iris color and region will be summarized as categorical variables.

11.3.2 Baseline Characteristics

Baseline IOP by time point and diurnal baseline IOP will be summarized as continuous variables. In addition, baseline IOP (19-24 mmHg, >24-28 mmHg), will be summarized as a categorical variables.

DUOTRAV type (PQ or BAK formulations) will be also collected at baseline for each individual subject.

11.4 Efficacy Analysis

Unless otherwise specified, all significance testing will be at the 5% significance level two-sided.

Efficacy analyses will be based on the Full Analysis Set (FAS), defined as all randomized subjects who received a dose of study medication and had at least one of the two scheduled on-therapy visits.

One eye from each patient will be chosen as the study eye and only the study eye will be used for analysis. If only 1 of a patient's eyes is dosed, the dosed eye will be selected as the study eye. If both eyes are dosed, the worse evaluable eye will be selected as the study eye. Worse eye is defined as the eye with the higher IOP at 09:00 averaged across the 2 eligibility visits. If both eyes are equal then the worse eye will be defined as the eye with the higher IOP at 11:00 averaged across the 2 eligibility visits. If both eyes are equal then the right eye will be selected for analysis.

11.4.1 Primary Efficacy

The primary objective of this study is to demonstrate the additive effect of brinzolamide 1% /brimonidine 0.2% in subjects with either open-angle glaucoma or ocular hypertension who are currently on DUOTRAV (travoprost 0.004% / timolol 0.5 %).

The primary endpoint is:

- Change from baseline in diurnal IOP at Week 6

The primary efficacy analysis will be an assessment of differences between treatments in mean change from baseline in diurnal IOP at Week 6 (patient IOP change from baseline averaged over the 09:00 and 11:00 time points).

11.4.1.1 Statistical Hypotheses

The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu_{BrinzBrim+\ DUOTRAV} = \mu_{Vehicle+\ DUOTRAV}$$

$$H_1: \mu_{BrinzBrim+\ DUOTRAV} \neq \mu_{Vehicle+\ DUOTRAV}$$

where $\mu_{BrinzBrim+\ DUOTRAV}$ refers to mean diurnal IOP change from baseline for subjects randomized to receive brinzolamide / brimonidine plus DUOTRAV, and $\mu_{Vehicle+\ DUOTRAV}$ refers to mean diurnal IOP change from baseline for subjects randomized to receive Vehicle plus DUOTRAV.

Thus, success reflects a greater reduction in mean diurnal IOP from baseline at Week 6 for the adjunctive therapy (brinzolamide / brimonidine plus DUOTRAV) relative to Vehicle plus DUOTRAV.

11.4.1.2 Analysis Methods

The treatment difference in mean diurnal IOP change from baseline at Week 6 will be tested based on the least squares means derived from an analysis of covariance model. This model will include treatment as a fixed effect and the baseline 9:00 IOP as a covariate;

Descriptive statistics will also be presented for the primary endpoint at Week 6.

11.4.1.2.1 Subgroup Analysis Methods

Planned subgroup analyses will assess the impact of sites and demographic subgroups on overall study results and assess the efficacy in each subgroup. Subgroups of age category (< 50, 50-65, >65), sex, race (Caucasian, Black, Asian, Hispanic, Other), baseline IOP (19-24 mmHg, >24-28 mmHg) and region (EMEA, Asia, ,LACAR,) will be summarized descriptively (N, mean, standard deviation) for the primary end point.

11.4.2 Secondary Efficacy

The secondary endpoints are:

- Diurnal IOP at Week 6
- Percentage change from baseline in diurnal IOP at Week 6

- Change from baseline in IOP at 11:00 hrs at Week 6
- Percentage change from baseline in IOP at 11:00 hrs at Week 6
- Change from baseline in IOP at 09:00 hrs at Week 6
- Percentage change from baseline in IOP at 09:00 hrs at Week 6

11.4.2.1 Statistical Hypotheses

The null and alternative hypotheses for analysis of the secondary endpoints are:

H_0: $\mu_{BrinzBrim+\ DUOTRAV} = \mu_{Vehicle+\ DUOTRAV}$

H_1: $\mu_{BrinzBrim+\ DUOTRAV} \neq \mu_{Vehicle+\ DUOTRAV}$

where $\mu_{BrinzBrim+\ Duotrav}$ refers to the mean of each secondary endpoint for subjects randomized to receive brinzolamide / brimonidine plus DUOTRAV, and $\mu_{Vehicle+\ DUOTRAV}$ refers to the mean of the same endpoint in the corresponding group of subjects randomized to receive Vehicle plus DUOTRAV.

11.4.2.2 Analysis Methods

Analyses of treatment differences in diurnal IOP and percent diurnal IOP change at Week 6 will use the same methods as those for the primary endpoint. Analyses of treatment differences in IOP change and percent IOP change at each Week 6 time point will utilize a repeated measures mixed model with fixed effects of treatment, time point, and the interaction of treatment and time point, and the baseline 09:00 IOP as a covariate.

Descriptive statistics will also be reported for each of the secondary endpoints.

11.4.2.2.1 Subgroup Analysis Methods

Planned subgroup analyses will assess the impact of sites and demographic subgroups on overall study results and assess the efficacy in each subgroup. Subgroups of age category (< 50, 50-65, > 65), sex, race (Caucasian, Black, Asian, Hispanic, Other), baseline IOP (19-24 mmHg, >24-28 mmHg), and region (EMEA, Asia, LACAR) will be summarized descriptively (N, mean, standard deviation) for the secondary endpoints.

[redacted]

11.5 Handling of Missing Data

The primary, secondary, [redacted] efficacy analyses will be based on an observed case (OC) analysis. The statistical model that will be employed and its associated analysis is one that is robust to data that are missing at random (MAR).

11.6 Multiplicity

A gate-keeping strategy will be employed to ensure overall control of the type I error rate. The secondary efficacy hypotheses will be relevant only if the primary efficacy null hypothesis is first rejected at the 5% level of significance (two-sided). Following the rejection of the primary efficacy null hypothesis, each secondary hypothesis will be tested following the order of the hypotheses as listed below. Each hypothesis will be relevant only if the preceding hypotheses have been rejected at the 5% level of significance (two-sided). The testing order (all based on IOP at Week 6) will be:

- Difference between treatments in mean change from baseline in diurnal IOP

- Difference between treatments in diurnal IOP
- Difference between treatments in percentage diurnal IOP change from baseline
- Difference between treatments in IOP change from baseline at 11:00 hrs
- Difference between treatments in percentage IOP change from baseline at 11:00 hrs
- Difference between treatments in percentage IOP change from baseline at 11:00 hrs
- Difference between treatments in IOP change from baseline at 09:00 hrs
- Difference between treatments in percentage IOP change from baseline at 09:00 hrs

Significance for a comparison will be claimed only if the null hypothesis is rejected ($p < 0.05$) for the previous endpoint in this series.

11.7 Safety Analysis

The safety endpoints in this study are visual field (automated perimetry), fundus parameters, best-corrected visual acuity (BCVA), slit-lamp exam, blood pressure, pulse rate and adverse events.

The safety analyses will consist of descriptive summaries of the data as relevant to the scale of data, eg, frequencies and percentages for adverse events, and mean changes from baseline as appropriate

11.8 Health Economics

Not applicable

11.9 Interim Analyses

An interim analysis for efficacy assessment will be performed when 50% of total planned subjects have completed discontinued from the study. The objective of the interim analysis is to provide opportunity for early rejection of the null of hypothesis of no difference in mean change from baseline in diurnal IOP at Week 6 between treatment groups. In order to ensure Type 1 error is adequately controlled at the 5% level of significance (two-sided) a p-value boundary will be employed, in particular, the Haybittle-Peto boundary (Haybittle 1971). The Haybittle-Peto boundary ensures that the study stops for efficacy only if there is overwhelming evidence of efficacy.

11.10 Sample Size Justification

With 108 evaluable subjects per treatment group in the primary efficacy analysis, there is at least 80% power to detect a 1.5 mmHg difference in mean change from baseline in diurnal IOP at Week 6 between the treatment groups. However, the required sample size to attain the same power is 28 subjects per arm if the difference is 3.0 mmHg between treatment groups (as suggested by expert opinion). Both calculations are based on the assumption of a common standard deviation for mean of 3.9 mmHg and the use of a two-sample two-sided t-test performed at the α=0.05 level of significance.

Assuming a drop-out rate of 10%, approximately 120 subjects per treatment group will be randomized to ensure the required number of evaluable subjects in the final efficacy analysis.

To mitigate the uncertainty about the expected treatment difference, a two-look design with Haybittle-Peto boundaries will be used. Thus, this study will incorporate an interim analysis for efficacy assessment when 50% of total planned subjects have completed or discontinued from the study. The power to reject the null hypothesis at the single interim analysis when 50% of subjects have completed or discontinued the study is 28.2% if the expected mean difference is 1.5 and 92.2%, if the expected mean difference is 3.0.

Look #	Sample Size	Efficacy p-value	P-value Boundary	Exit Probabilities		
				$\delta = 0$	$\delta = 1.5$	$\delta = 3.0$
1	108	0.01	0.01	0.01	0.282	0.922
2	216	0.045	0.045	0.04	0.517	0.078
Sum of Exit Probabilities				0.050	0.799	1

12 ADVERSE EVENTS

12.1 General Information

An Adverse Event (AE) is any untoward medical occurrence in a subject who is administered a study treatment regardless of whether or not the event has a causal relationship with the treatment. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment, whether or not related to the treatment. In clinical studies, an AE can include an untoward medical occurrence occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The determination of clinical relevance is based upon the medical judgment of the Investigator.

12.2 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the standard questions:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change, as determined by the Investigator, in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health.

Changes from baseline in any protocol-specific ocular or systemic parameter evaluated during the study are to be reviewed by the Investigator. In addition, the subject's responses to any questionnaire utilized during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant, in the opinion of the Investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

12.3 Procedures for Recording and Reporting AEs and SAEs

Subsequent to signing an informed consent form, all untoward medical occurrences that occur during the course of the study must be documented on an Adverse Event Form (AEF). A separate AEF must be filled out for each event. When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (ie, severity), any action with study treatment taken as a result of the event, and an assessment of the adverse event's relationship to the study treatment.

Nonserious Adverse Events

A nonserious AE is defined as any untoward change in a subject's medical health that does not meet serious criteria noted below (eg, is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, is not disabling, etc.).

All adverse events must be reported regardless of whether or not they are related to the study treatment.

Non-serious AEs must be reported in the EDC system within 10 calendar days of the Investigator's or site's knowledge of the event.

Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse experience that meets any of the following criteria:

- Results in death.
- Is life-threatening.

  NOTE: *Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.*

- Requires hospitalization or prolongation of existing hospitalization.

  NOTE: *In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs.*

  If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

  NOTE: *The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.*

- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life- threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed

in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in a subject's hospitalization, or the development of drug dependency or drug abuse.

All available information on a serious adverse event(s) and any other associated AE, if applicable, must be forwarded to the study Sponsor immediately (ie, within 24 hours of the Investigator's or site's knowledge of the event) as follows:

In studies utilizing EDC (electronic data capture), all available information for the SAE and any associated AE(s) must be entered immediately into the EDC system.

***NOTE**: Should the Electronic Data Capture (EDC) system become non-operational, the site must complete the appropriate paper Serious Adverse Event Form. The completed form is communicated to the study Sponsor either by fax at* [redacted] *or by email at* [redacted] *within 24 hours of the Investigator's or site's awareness, however, the reported information must be entered into the EDC system once it becomes operational.*

Additional information for any applicable event is to be reported as soon as it becomes available. Any complaints from the subject on a past event previous to initiation of the study but that is resolved at the time of the first visit must be reported to Alcon following the usual pharmacovigilance circuit.

In addition to the reporting of serious adverse events to the study sponsor, the SAE must be reported to the IRB / IEC according to their requirements.

Sponsor representatives and their contact information are provided in the Manual of Procedures (MOP) that accompanies this protocol.

If the SAE was due to a hospitalization of the subject, a copy of the discharge summary is to be forwarded to the study Sponsor as soon as it becomes available. In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant laboratory tests also may be requested. Further, depending upon the nature of the SAE, the Sponsor may request copies of applicable parts of the subject's medical records.

An assessment of seriousness will also be performed for all adverse events by a study Sponsor physician utilizing the same criteria. If an adverse event reported for an Investigator's subject is upgraded to a serious adverse event by a study Sponsor physician, the Investigator will receive a notification by the study Sponsor.

12.4 Intensity and Causality Assessments

For every AE, the Investigator must assess the seriousness, intensity (severity) and causality (relationship to study treatment). Specifically, events should be classified as mild, moderate, or severe. The assessment of causality will be based upon the categories of related and not related. These classifications should be based on the following definitions:

Intensity (Severity):

Mild	An event is mild if the subject is aware of, but can easily tolerate the sign or symptom.
Moderate	An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

Causality:

Related	Adverse events classified as related may be either definitely related or possibly related where a direct cause and effect relationship between the study treatment and the event has not been demonstrated but there is a reasonable possibility that the event was caused by the study treatment.
Not Related	Adverse events classified as not related may either be definitely unrelated or simply unlikely to be related (ie, there are other more likely causes for the adverse event).

For a serious adverse event reported by an Investigator as not related that upon review of the available data by the study sponsor physician is assessed (upgraded) to be related, the Investigator will receive a notification.

12.5 Unmasking of the Study Treatment

Masked information on the identity of the assigned test article will be provided for each subject. If the treatment code needs to be broken in the interest of subject safety, the Investigator is encouraged to contact an appropriate study sponsor representative prior to unmasking if there is sufficient time. Dependent upon the individual circumstances (ie, medical emergency), the code may be broken prior to contact with the Sponsor. The study Sponsor must be informed in all cases in which the code was broken and of the

circumstances involved.

Additionally, the Sponsor may be required to unmask the subject if the AE meets criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to fulfill expedited regulatory reporting requirements.

12.6 Follow-Up of Subjects with Adverse Events

The Investigator is responsible for adequate and safe medical care of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. Any additional data from these follow-up procedures must be documented and available to the Sponsor who will determine when the data need to be documented on the case report forms.

12.7 Pregnancy in the Clinical Trial

Women who are pregnant or breast-feeding are excluded from participation in the study. Women of childbearing potential or women considered post-menopausal are not excluded from the study as long as adequate birth control methods are being utilized. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant, following menarche and until becoming post-menopausal unless permanently sterile. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

All women of childbearing potential are required to use adequate birth control methods which are summarized in the protocol’s exclusion criteria.

Prior to clinical trial enrollment, female subjects of childbearing potential must be advised of the importance of avoiding pregnancy during the trial and the potential risks associated with an unintentional pregnancy. During the trial, female subjects are to be instructed to contact the Investigator immediately if they suspect they might be pregnant. Alcon must be contacted immediately, treatment discontinued, and the subject exited from the study.

In addition, complications of pregnancy may be reportable and will be decided on a case

by case basis. A Sponsor prepared form will be utilized to capture all pregnancy related information until the outcome of the pregnancy.

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor. If electronic records are maintained, the method of verification must be determined in advance of starting the study. At a minimum, source documents should include the following information for each subject:

Subject identification (name, sex, race)
Documentation of subject eligibility
Date of informed consent
Dates of visits
Documentation that protocol specific procedures were performed
Results of study parameters, as required by the protocol
Trial medication accountability records
Documentation of AEs and other safety parameters (if applicable)
Records regarding medical histories and the use of concomitant therapies prior to and during the study
Date of trial completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

CRFs will be provided to the sites (electronic); only designated individuals may complete the CRFs. The CRFs will be submitted at regular intervals based upon the clinical trial visit schedule. It is expected that all data reported will have corresponding entries in the source documents and that the Principal Investigator will review the reported data and certify that the CRFs are accurate and complete. No subject identifiers should be recorded on the CRFs beyond subject number, and demographic information.

13.2 Data Review and Clarifications

The CRF data will be reviewed against the subject's source data by the study monitors to ensure completeness and accuracy. After monitoring has occurred at the clinical sites and the

CRFs have been submitted, additional data clarifications and/or additions may be needed. Data clarifications and/or additions are documented and are part of each subject's CRFs.

13.3 Regulatory Documentation and Records Retention

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the Sponsor and the Investigator's files will be reviewed as part of the ongoing study monitoring. Financial information is not subject to regulatory inspection and should be kept separately.

Additionally, the Investigator must keep study records and source documents until the Sponsor provides written approval for their destruction. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, the Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the **latest** marketing approval).

14 References

Aung T, Laganovska G, Paredes TJH, Branch J, Tsorbatzoglou A, Goldberg, I. Twice-Daily Brinzolamide/Brimonidine Fixed Combination versus Brinzolamide or Brimonidine in Open-Angle Glaucoma or Ocular Hypertension. Ophthalmology 2014;121(12):2348-55.

Gandolfi SA, Lim J, Sanseau AC, Restrepo JCP, Hamacher T. Randomized Trial of Brinzolamide/Brimonidine versus Brinzolamide Plus Brimonidine for Open-Angle Glaucoma or Ocular Hypertension. Adv Ther 2014; 31(2):1213-27.

Higginbotham EJ, Hansen J, Davis EJ, Walt JG, Guckian A. Glaucoma medication persistence with a fixed combination versus multiple bottles. Curr Med Res Opin. 2009;25(10):2543-7.

Kable JW, Murrin LC, Bylund DB. In vivo gene modification elucidates subtype-specific functions of alpha(2)-adrenergic receptors. J Pharmacol Exp Ther. 2000;293(1):1-7.

Kamibayashi T, Maze M. Clinical uses of α2-adrenergic agonists. Anesthesiology. 2000;93:1345-9.

Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701–13.

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):724-30.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983. 70(3):659-63.

Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001;108:1943–53.

Nasser QJ, Stewart WC. Glaucoma treatment and diagnostic trends. Rev Ophthalmol. 2006;13:87-93.

Nguyen QH, McMenemy MG, Realini T, Whitson J, Goode SM. Phase 3 Randomized 3-Month Trial with an Ongoing 3-Month Safety Extension of Fixed-Combination Brinzolamide 1%/Brimonidine 0.2%. Journal of Ocular Pharmacology and Therapeutics. 2013;29(3):290-7.

Summer A, Tielsch JM. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. Arch Ophthalmology 1991;109:1090-95.

Schwartz GF, Pate VD, Burk C, Bennett T. Patient persistency with topical glaucoma therapy is higher with fixed dose brimonidine/timolol than with two-bottle combinations. Association of Research in Vision and Ophthalmology; 2010:185. (Abstract).

Stewart WC, Stewart JA, Nelson LA, Kruft B. Physician attitudes regarding prostaglandin treatment for glaucoma in the United States and Europe. Eur J Ophthalmol. 2008;18(2):199 204.

Stewart WC, Jenkins JN, Stewart JA. Survey assesses prostaglandin use. Rev Ophthalmol. 2005;12:Article 844.

Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet. 2004;363(9422):1711-20.

Whitson JT, Realini T, Nguyen QH, McMenemy MG, Goode SM. 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. Clinical Ophthalmology 2013; 7:1053-60.

Wilson MR, Coleman AL, Yu F, Bing EG, Sasaki IF, Berlin K, et al. Functional status and well-being in patients with glaucoma as measured by the Medical Outcomes Study Short Form-36 questionnaire. Ophthalmology. 1998;105(11):2112-6.

Wu Sy, Hennis A, Nemesure B, at al. Impact of glaucoma, lens opacities, and cataract surgery on visual functioning and related quality of Life the Barbados Eye Studies. Invest Ophthalmol Vis Sci 2008; 49:1333-8.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
04/06/2017 16:51:31	[redacted]	[redacted]
04/07/2017 09:16:51	[redacted]	[redacted]
04/07/2017 21:02:02	[redacted]	[redacted]
04/10/2017 13:21:09	[redacted]	[redacted]