a Novartis company

Short Title

Simbrinza BID Adjunctive to PGA

Long Title

Additive Effect of Twice Daily Brinzolamide 1% /Brimonidine 0.2% Fixed Dose Combination as an Adjunctive Therapy to a Prostaglandin Analogue

TDOC-0050474 Version 1.0 replaces TDOC-0018786 Version 1.0 (11-Mar-2015)

Protocol Number:	GLH694-P001 / NCT02419508
Study Phase:	4
Sponsor Name and Address:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099
Investigational Product:	SIMBRINZA™ Brinzolamide 1%/Brimonidine 0.2% tartrate ophthalmic suspension
US IND# / EudraCT	2015-000736-15
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: GLH694-P001**
Investigational Product:	SIMBRINZA ™	**Study Phase:**
	Brinzolamide 1%/ Brimonidine 0.2% tartrate ophthalmic suspension	☐ 1 ☐ 2 ☐ 3 ☒ 4 ☐ N/A

Active Ingredient: Brinzolamide 1%/Brimonidine 0.2%

Protocol Title: Additive Effect of Twice Daily Brinzolamide 1% /Brimonidine 0.2% Fixed Dose Combination as an Adjunctive Therapy to a Prostaglandin Analogue

Investigator(s)/ No. of Sites: Multicenter, approximately 33 sites

No. of Subjects Approximately 280 subjects enrolled, 180 subjects randomized, 162 subjects evaluable

Duration of Treatment: Approximately 42 days

Study Population: Adult subjects with open-angle glaucoma or ocular hypertension who require multiple pharmaceutical therapy for control of IOP or with inadequately controlled IOP while on a PGA monotherapy.

Objective(s): To demonstrate the additive IOP lowering effect of Brinzolamide 1%/Brimonidine 0.2% (dosed BID) when added to a PGA in patients with open-angle glaucoma or ocular hypertension.

Methodology: Multicenter, randomized, double-masked, parallel-group study

Treatments:

Investigational Product:	SIMBRINZA® Brinzolamide/Brimonidine tartrate ophthalmic suspension 1%/0.2%
Route of Administration:	Topical ocular drops
Duration of Treatment:	Approximately 42 days
Dosage:	1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00)
Prostaglandin analogues:	TRAVATAN PQ (Travoprost

Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099	
		ophthalmic solution preserved with Polyquad) 0.004%
		XALATAN (Latanoprost) 0.005%
		LUMIGAN (Bimatoprost) 0.01%
	Route of Administration:	Topical ocular drops
	Duration of Treatment:	Run-in period followed by treatment for approximately 42 days
	Dosage:	1 drop instilled once per day in affected eye(s) in the evening
	Control Article:	Brinz/Brim Vehicle
	Route of Administration:	Topical ocular drops
	Duration of Treatment:	Approximately 42 days
	Dosage:	1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00)

Subject Selection:

Inclusion Criteria:

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

2. After signing the Informed Consent Form, subjects previously on combination therapy must simultaneously initiate study-specific PGA therapy and must be washed out of all other adjunctive medications (miotics and oral/topical carbonic anhydrase inhibitors, 5 days; alpha and alpha/beta agonists, 14 days; beta-antagonists, 28 days) prior to Eligibility Visit 1.

   Subjects who were previously on one of the study-specific branded PGA monotherapy for at least 28 days prior to the Screening Visit should also be considered potential study candidates (see MOP section 5.1.1.1 for possible screening/washout scenarios).

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

Protocol Number: GLH694-P001

3. Qualifying Mean IOP measmements (after washout) at both the Eligibility 1 and 2 Visits in at least 1 eye (the same eye[s]) must be 19 and < 32 mmHg at 09:00.

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.

Exclusion Criteria:

1. Women of childbearing potential, 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 cmTently 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 biith control methods to prevent pregnancy throughout the study (further definition can be found in Section 12.7).

Effective contraceptive measures include:

- Total abstinence (when this is in line with the prefen ed and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation 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

Spon sor: Alcon Research, Ltd.
6201 South Freeway
Fmt Worth, Texas
76134-2099

Protocol Number: GLH694-P001

been confnmed 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 pa1tn er for that subject
- Use of oral, injected or implanted hmm onal methods of contraception or other form s of hmmonal contraception that have comparable efficacy (failure rate <l%), for example hmmone vaginal ring or transdermal hmmone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

2. Any fo1m of glaucoma other than open-angle glaucoma or ocular hype1tension.

3. Central cornea thickness (CCT) greater than 620 µm as measured by pachymetly in either eye (see MOP for fmther details).

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

5. Cup/disc ratio greater than 0.80 (horizontal or ve1tical measurement) in either eye.

6. Severe centr·al visual field loss in either eye or field loss threatening fixation in either eye.

   Severe centr·al visual fi eld loss is de fined as a se nsiti vity of less than or equal to 10 dB in at least 2 of the 4 visual field test points closest to the point of fixation.

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

Protocol Number: GLH694-P001

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

8. Ocular trauma in either eye within the past 6 months prior to the Screening visit.

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

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

11. Best-corrective 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. Other ocular pathology (including severe dry eye) in either eye that may, in the opinion of the Investigator, preclude the safe administration of a topical ocular alpha-adrenergic agonist and/or topical ocular carbonic anhydrase inhibitor and/or topical ocular PGA.

13. Intraocular surgery in either eye within the past 6 months prior to the Screening visit.

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

15. 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. History of active, severe, unstable or uncontrolled cardiovascular (eg, coronary insufficiency,

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

Protocol Number: GLH694-P001

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

22. 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 (ie, β-adrenergic blocking agents). The dosing regimen of these medications should not change during the study.

23. Hypersensitivity to alpha-adrenergic agonist drugs, topical or oral carbonic anhydrase inhibitors, prostaglandins, sulfonamide derivatives, or to any component of the study medications in the opinion of the Investigator.

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

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

Protocol Number: GLH694-P001

25. Subjects who cannot safely discontinue all glucocmticoids administered by any route prior to the Eligibility 1 visit and continue to not use during the study.

    Steroid washout duration:

    a. Chronic therapy - 4 weeks
    b. Intennittent therapy-2 weeks

26. Subjects who, in the opinion of the Investigator, cannot discontinue all !OP-lowering ocular medication(s) except the study provided PGA therapy per the appropriate washout schedule prior to the Eligibility 1 visit.

27. Mean IOP 2'.: 32mmHg at any time point, in either eye, during the Screening/Eligibility Phase.

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

Assessments:

Primary Efficacy:

- Mean change from baseline (on PGA) in diurnal IOP (mean of 09:00 and 11:00 time points) at Week 6

Secondary Efficacy:

- Mean diurnal IOP at Week 6
- Mean percentage change from baseline in diurnal IOP at Week6
- Mean change from baseline in IOP at 11:00 at Week 6
- Mean percentage change from baseline at 11:00 at Week 6
- Mean change from baseline in IOP at 09:00 at Week 6
- Mean percentage change from baseline at 09:00 at Week 6

[redacted]

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

Protocol Number: GLH694-P001

[redacted]

Safety:

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

Statistical Methods:

One eye from each subject will be chosen as the study eye and only the study eye will be used for analysis. If only 1 of a subject'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. Randomization will be stratified according to region and type of PGA (Lumigan, Xalatan, Travatan).

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 1 of the 2 scheduled on-treatment visits. The Safety set will consist of all who received a dose of

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

Protocol Number: GLH694-P001

study medication.

Primaiy Efficacy:

The prima1y efficacy analysis will be an assessment of differences between treatments in mean change from baseline in diurnal IOP at Week 6 (subject IOP averaged over the 09:00 and 11:00 time points). The null and alternative hypotheses for the ptimaiy analysis ai·e:

Ho: $\mu_{BrinzBrim+PGA} = \mu_{Vehicle+PGA}$

H1: $\mu_{BrinzBrim+PGA} \neq \mu_{vehicle+PGA}$

where $\mu_{srinzBrim+PGA}$ refers to mean diurnal IOP change from baseline for subjects randomized to receive brinzolamide / brimonidine plus PGA, and $\mu_{v\ ehicie+PGA}$ refers to mean diurnal IOP change from baseline for subjects randomized to receive Vehicle plus PGA. The treatment difference in mean diurnal IOP change from baseline will be tested based on the least squares means derived from a repeated measures mixed model. This model will include fixed effects of treatment, visit, type of PGA, region, and the interaction of treatmentand visit; the baseline diurnal IOP as a covai·iate, and the random effect of subject within the subject's treatment, region, and type of PGA.

Secondaiy efficacy:

Analyses of treatment differences of seconda1y endpoints will use the same methods as those for the prima1y endpoint. Hypothesis tests will use the same null and alternative hypotheses as above, with μ representing the mean for the variable being tested.

A closed step-down testing procedure will be used for hypothesis testing of prima1y and seconda1y endpoints; therefore, no multiplicity adjustment is needed. The testing order (all based on IOP at Week 6) will be

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

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

Protocol Number: GLH694-P001

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

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

[redacted]

Sample Size Justification:

With 81 evaluable subjects per treatment group in the primary efficacy analysis, there is at leas t 90% power to detect a difference in mean change from base line in dimn al IOP at Week 6 IOP of 2.0 mmHg between the treatment groups. This calculation is based on the assumption of a common standard deviation for mean change from baseline in diurnal IOP as small as 3.5 mmHg and as large as 3.9 mmHg and the use of a two-sample two-sided t-test performed at the a=0.05 level of significance.

Assmning a drop-out rate of 10%, approximately 90 subjects per treatment group will be randomized to ensure the required number of evaluable subjects in the final efficacy analysis.

1.1 Amendments

Amendment 2

1. Remove 16:00 IOP collection time point at all visits.

Rationale: The 12-hr trough and 2-hr peak effects of Simbrinza are seen at 9:00 and 11:00, respectively, and are the critical measurement time points for the study. The 16:00 time point provides further daytime data but is proving to be a major barrier to recruitment. Removing the late day 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 (9:00 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.

2. Reduce E1 & E2, 09:00 am, IOP inclusion criteria (#3) from ≥ 21 and < 32 mmHg to ≥ 19 and < 32 mmHg.

Rationale: 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.

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

Itemized Changes:

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

I. Reduction of E1 and E2 (09:00) IOP inclusion criteria from ≥ 21 and < 32 mmHg to ≥ ***19*** and < 32 mmHg:

- Synopsis, Inclusion Criteria, #3 –

  the Eligibility 1 and 2 Visits in at least 1 eye (the same eye[s]) must be ≥ ***19*** ~~21~~ and < 32 mmHg at 09:00.

- Synopsis, [redacted]

  [redacted]

- Subject Population, 8 –

  in at least 1 eye (study eye) ≥ ***19*** ~~21~~ and < 32 mmHg at 2 consecutive visits (Eligibility 1 and Eligibility 2)

- Duration of Exposure, 9.2.2 –

  and present with uncontrolled IOP (≥ ***19*** ~~21~~ mmHg) at Screening may skip the 28 day run-in

- Table 10-1, Study Plan by Treatment Group –

  Mean IOP for both Eligibility Visits must be: ≥ ***19*** ~~21~~ mmHg and < 32 mmHg

- Table 10-3, Activity for Eligibility 1 and Eligibility 2 Visits –

  Mean IOP must be ≥ ***19*** ~~*21*~~ *and < 32 mmHg*

- Demographics and Baseline Characteristics, 11.3 and Baseline Characteristics, 11.3.2-

  In addition, baseline IOP (***19*** ~~21~~-26 mmHg, 27-32 mmHg)

- Subgroup Analysis Methods, 11.4.1.2.1 –

  sex, race, baseline IOP (***19*** ~~21~~-26 mmHg, 27-32 mmHg),

- [redacted]

  [redacted]

II. Remove 16:00 IOP collection time point at all visits.

- Synopsis, Primary efficacy –

Mean change from baseline (on PGA) in diurnal IOP (mean of 09:00, ***and*** 11:00 ~~and 16:00~~ time points) at Week 6

- Removal of 16:00 visits and assessments previously completed at 16:00 will be completed at 11:00 time point in the following tables:

  1. Overview of Study Plan, 2 –
  2. Table 10-3, Activity for Eligibility 1 and Eligibility 2 Visits –
  3. Table 10-4, Activities for Week 2 and Week 6 (Exit) Visits –

- Eligibility 1 and Eligibility 2 Visits, 10.2.2 –

  ELIGIBILITY 1 AND ELIGIBILITY 2 VISITS: [09:00 (+/-30 MIN) ***AND*** 11:00 (+/- 30 MIN), ~~AND 16:00 (+/- 30 MIN)~~ EXAMINATIONS]

- Week 2 and Week 6 Visits, 10.2.3 –

  WEEK 2 AND WEEK 6 (EXIT) VISITS: [09:00 (+/- 30 MIN) ***AND*** 11:00 (+/- 30 MIN), ~~AND 16:00 (+/- 30 MIN)~~ EXAMINATIONS]

III. Summary statistical changes in absence of 16:00 IOP time point

The following sections contain text as described below:

1. Synopsis, Secondary Efficacy –
2. Secondary Efficacy, 11.4.2 –
3. Multiplicity, 11.6 –

Changed from:

- ~~Mean change from baseline in IOP for each time point (09:00, 11:00, 16:00) at Week 6~~

- ~~Mean percentage change from baseline in IOP for each time point (09:00, 11:00, 16:00) at Week 6~~

Changed to:

- ***Mean change from baseline in IOP at 11:00 at Week 6***
- ***Mean percentage change from baseline at 11:00 at Week 6***
- ***Mean change from baseline in IOP at 09:00 at Week 6***
- ***Mean percentage change from baseline at 09:00 at Week 6***

IV. Additional changes

- Clarified of exclusion 27, Synopsis -

  Mean IOP 2': 32 mmHg at any time point, ***in either eye,*** dming the Screening/Eligibility Phase.

- Remove Medical Monitor, Synopsis, Exclusion -

  Changed from: The Medical Moai.tor may declare any subject ineligible for a valid medical reason.

  Changed to: The Medical ***Director*** may declare any subject ineligible for avalid medical reason.

- Removal of identifying specific participating regions, Synopsis and Sections 11.4 & 11.4.3 -

  ~~Center Location(s)/ Europe, Australia, Latin America, and Canada~~

  If both eyes are equal then the right eye will be selected for analysis. Randomization will be stratified according to region (EU (EHrope, AHst rn.lia), LACA. t (Latia Ameriea, Csa ada)) and type of PGA therapy.

  Age categ01y: <50, 50-65, >65; Sex; Race; regioa (EU (EHrnpe, AHstrnlia), L l\.CM t (L atifl Araeriea, C aliada))

- Subject Confidentiality and Methods used to Minimize Bias, 9.4 -

  The Investigator must ensure that the subject's anonymity is maintained throughout the comse of the study. In part ic ul ar, the Investigator must keep **aa eRn>Um eat *a subject*** log with confidential identifying infonnation that con esponds to the subject number, *subject name and medical ID number* s aad initials of each study part icipant. At the end of the clinical study, the Sponsor will collect a copy of the el.'lfollraea t *subje ct* log w itho u t any identifying subject inf01mation. All documents submitted to the Sponsor will identify the subjects exclusively by number aaa demog rap bi e in fo rm at ioR. No other personally identifying inform at io n sho uld be transmitted to the Sponsor.

- Screen Visit (Day -28), 10.2.1, item no. 18 -

  Schedule the subject to return in 28 days (, +*1* day) for the Eligibility 1 Visit.

- WEEK 2 AND WEEK 6 (EXIT) VISITS, 10.2.3 -

  Note: *The Week 6 Visit should be conducted 42 days (4---J-- ±3 d ays) following the Eligibility 2 Vi.sit.*

- Sampl e Size Justification, Synopsis and Section 11.10 -

  This calculation is based on the assumption of a common standard deviation for mean *change from baseline in diurnal* IOP as small as 3.5 mmHg and as large as 3.9 mmHg and the use of a two-sample two-sided t-test performed at the a =0.0 5 leve l of signifi cance.

- Efficacy Analyses, 11.4 -

  Unless otherw ise spe c ified , all stati stie aJ aBalyses *significant testing* will be *at the* 5% *level* (two-sided) at the 5% level.

- Adverse Section is updated;
  - *Procedures for Recording and Reporting AEs and SAEs, 12.3 -*
    Any pre-existing medical conditions or signs/symptomspresent in a subject prior to the start of the study (ie,before informed consent is signed) should be recorded in the baseline history section of the CRF.Any medical occurrences having an onset after informed consent but prior to the start of study treatment (ie, initiation of treatment with test article) should also be recorded in the baseline history section within the CRF.

  - *Serious Adverse Events, 12.3-*

1J0ns0r Centaet	**Gasiness aK NamlJe F**	**Ema il**
[redacted]	[redacted]	[redacted]

Amendment 1

TDOC-0050474 Version 1.0 replaces TDOC-0018786 Version 1.0 (11-Mar-2015)

Due to changes in document management system, tables have been re-numbered.

Purpose of Amendment: The primary purpose of this amendment is to implement required changes received from regulatory authorities.

Rationale: Clarification of women of childbearing potential, effective contraception methods, storage of PGAs, and safety reporting timeframe.

Current Study Status: No subjects have been enrolled at the time of this amendment.

Case Report Form Revision Required:	☐ Yes	☒ No
Informed Consent Modifications Required:	☒ Yes	☐ No
Applicable Investigators:	☒ All	☐ Selected (list below)

Itemized Changes:

1. **Title Page**

   Added: TDOC-0050474 Version 1.0 replaces TDOC-0018786 Version 1.0 (11-Mar-2015)

2. **Section 1: Synopsis – Treatments**

   Changed from: Investigational Product

   Changed to: Prostaglandin Analogues

3. **Section 1: Synopsis – Exclusion Criterion #1**

   Modified from:
   Women of childbearing potential (who are not postmenopausal for at least 1 year or surgically sterile) are excluded from participation if they are currently pregnant, have a positive result on the urine pregnancy test at Screening, or intend to become pregnant during the study period; are breast-feeding; are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study (see MOP for further details).

Modified to:

Women of childbearing potential, 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 (further definition can be found in Section 12.7)

Effective contraceptive measures include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation 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 transdermal hormone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

4. Section 3: Abbreviations

Added:

IMP – Investigational Medicinal Product

IP – Investigational Product

PSD – Pattern Standard Deviation

SBP – Systolic Blood Pressure

VF – Visual Field

5. **Section 5.1: Study Rationale and Background**

   Added the following statement to the end of this section:
   A summary of the known and potential risks and benefits associated with SIMBRINZA and Prostaglandin Analogues can be found in the Summary of Product Characteristics (SmPC) or Product Information equivalent.

6. **Section 9.1: Identity of Study Treatments**

   Added: or 8 mL

7. **Section 9.1: Identity of Study Treatments**

   Modified 2nd paragraph from:
   TRAVATAN, XALATAN, and LUMIGAN are unmasked medications provided by the Sponsor. TRAVATAN should be securely stored according to the label. Once the bottle is opened, it should be discarded after 4 weeks from first opening. XALATAN should be protected from light. Unopened XALATAN must be stored under refrigeration at 2-8ºC (36-46ºF) and opened XALATAN may be stored in temperatures up to 25ºC (77ºF) and is viable for 6 weeks. LUMIGAN should be securely stored according to the label. Once the bottle is opened, it should be discarded after 4 weeks from first opening.

   Modified 2nd paragraph to:
   PGAs will be unmasked (open labeled) product. TRAVATAN, XALATAN, and LUMIGAN are unmasked medications provided by the Sponsor. Storage of PGAs should be in accordance with the country product labeling.

8. **Section 12.1: General Information**

   Added: The determination of clinical relevance is based upon the medical judgment of the Investigator

9. **Section 12.2: Monitoring for Adverse Events**

   Modified last statement of 1st paragraph from:
   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 following exposure to the study treatment.

Modified last statement of 1st paragraph to:
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.

10. Section 12.3: Procedures for Recording and Reporting AEs and SAEs

Modified from: (ie, within one working day of the Investigator's or site's knowledge of the event)

Modified to: (ie, within 24 hours of the Investigator's or site's knowledge of the event)

11. Section 12.6: Follow-Up of Subjects with Adverse Events

Removed the last sentence:
All AEs (serious and non-serious) received 1 month after subject's last visit will be considered and processed as spontaneous events (following the usual pharmacovigilance circuit).

12. Section 12.6: Follow-Up of Subjects with Adverse Events

Modified 1st paragraph to read as follows:
Women who are pregnant or breast-feeding are excluded from participation in the study. Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized or women considered post-menopausal. 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 (e.g. 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 and should be used during the study.

2 OVERVIEW OF STUDY PLAN

Activity	Screen	Eligibility 1[a]		Eligibility 2 (3-8 days from Eligibility Visit 1)		Week 2 (14 ± 3 days from Eligibility 2)		Week 6 (Exit) Visit (42 ± 3 days from Eligibility 2)		UNSC Visit	Early Exit[b]
		09:00	*11:00*	*09:00*	*11:00*	*09:00*	*11:00*	*09:00*	*11:00*		
Informed Consent[c]	X										
Demographics	X										
Med Hx & Con. Meds	X										
Change in Med Hx/Con Meds		X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X	X	X	X						
Urine Pregnancy Test[d]	X[f]								X[f]		X[f]
Best-Corrected VA	X	X		X		X		X		X	X
Automated Perimetry	X[e]								X[f]		X[f]
Slit-Lamp Exam	X	X		X		X		X		X	X
IOP (Goldmann)	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy	X										
Pachymetry	X										
Dilated Fundus Exam	X								X	X	X
Blood Pressure & Pulse Rate	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Meds	X				X						
Instill Study Meds in Office						X		X			
Adverse Event	X	X	X	X	X	X	X	X	X	X	X
Collect Study Meds				X				X		X	X
Exit Subject & Complete Exit Form									X		X

a E1 should be conducted from 1 to 29 days after Screening, according to the run-in/washout schedule
b Perform assessments on subjects who discontinue study participation prior to Week 6 visit.
c Must be signed/dated before study procedures are performed.
d Required on all female subjects of childbearing potential.
e At Screening (preferably) or in between Screening and E2
f May be conducted anytime during the visit.

3 ABBREVIATIONS

AC	Anterior chamber
ADR	Adverse drug reaction
AE	Adverse event
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
Con Meds	Concomitant medications
CRF	Case report form
dB	Decibel
E1	Eligibility 1
E2	Eligibility 2
CRF	Case report form
EDC	Electronic data capture
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
HIPAA	Health insurance portability and accountability act
Hx	History
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
IWRS	Inter-active web response system
LOCF	Last observation carried forward
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
NSAID	Non-steroidal anti-inflammatory drug
OAG	Open-angle glaucoma
OC	Observed case
OD	Right eye
OHT	Ocular hypertension
OS	Left eye
OU	Both eyes
PGA	Prostaglandin analogue
PI	Principal investigator
PPS	Per protocol set
PQ	Polyquad
PSD	Pattern Standard Deviation
QA	Quality assurance
QD	Once a day
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	SAS statistical software, SAS Institute Inc., Cary, NC
SBP	Systolic Blood Pressure
TID	Three times a day
US	United States
VF	Visual Field

4 TABLE OF CONTENTS

List of Tables

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 patients 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 subjects 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 5 almost 40% of patients needed 2 or more medications to achieve their target IOP (Kass et al 2002), and in the Collaborative Initial Glaucoma Treatment Study (CIGTS) after year 2 more than 75% of patients needed 2 or more medications to reach their target IOP (Lichter et al 2001).

It is well known that the complexity of treatment (doses per day, number of bottles) can affect patient adherence to medications. To this end, combination therapies with drugs of differing but complementary mechanisms of action may simplify treatment for patients and offer other potential benefits such as eliminating a required waiting time between the two instillations in order to avoid drug washout or they may also decrease exposure to preservatives such as

benzalkonium chloride, which is known to have adverse effects on the ocular surface and to increase treatment side effects (Baudouin 2010).

In addition to the potential clinical benefits, the cost of fixed combination therapy may be less than the combined cost of the component medications in many countries (Rylander 2008). Studies have shown that the direct costs (visits, surgeries, medications, etc) and indirect costs (visual impairment, social rehabilitation, etc) of glaucoma increase with elevated IOP, disease progression, late stages of the disease, and poor adherence and persistence (Oostenbrink 2001, Lee 2006). By increasing the subject's compliance and IOP control, fixed combination therapy could also potentially decrease the direct and indirect costs of glaucoma.

SIMBRINZA is a fixed dose combination IOP-lowering topical therapy comprised of Brinzolamide (1% or 10mg/mL) and Brimonidine tartrate suspension (0.2% or 2 mg/mL). 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 for reducing/decreasing elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction. 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 for the same indication.

A summary of the known and potential risks and benefits associated with SIMBRINZA and Prostaglandin Analogues can be found in the Summary of Product Characteristics (SmPC) or Product Information equivalent.

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 concern for the use of SIMBRINZA. The development of fatigue/drowsiness may impair a person's ability to

operate a motor vehicle or machinery. Patients 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 patients 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 patients 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 patients 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 patients, or in conditions where the cornea is compromised. [redacted]

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.

Prostaglandin Analogues

The most frequent adverse event associated with the use of topical ocular PGAs is hyperemia. Hyperemia generally occurs at the onset of use and generally subsides or resolves over time without the addition of concomitant therapy or resolves with discontinued use of the PGA. Other common adverse events associated with this class of medicinal product include periocular skin hyperpigmentation or discolouration, iris hyperpigmentation, and changes in eyelash length, thickness, pigmentation, and/or number of lashes. These changes generally occur after several months to years of dosing and usually do not require the addition of concomitant therapy. In addition, these adverse events usually resolve with the discontinued use of the medication (with the exception of iris hyperpigmentation, which is most likely permanent).

Less common or rare adverse events with a possible association to the use of a topical ocular PGAs include cystoid macular edema, anterior chamber inflammation (ie, anterior uveitis, iritis, and iridocyclitis), and herpes simplex keratitis. The occurrence of cystoid macular edema in patients dosing with a PGA has been reported at a low incidence. It appears that this event is more likely to occur in patients with predisposing risk factors (aphakia, pseudophakia with a ruptured posterior capsule during surgery, history of uveitis, or retinal inflammatory or vascular disease). Caution is advised with the use of a topical ocular PGA in patients with predisposing risk factors. Anterior chamber inflammation and herpes simplex keratitis have been reported at a low incidence in patients dosing with a topical ocular PGA. These events have been reported in both patients with risk factors for the development of these conditions and in patients with no known risk factors. Prescribing physicians should be aware of the possible development of these conditions (Alm 2008, Cracknell 2009).

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 SIJ\ifBRIN ZA fi xed co m bin at ion 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 1s contraindicated,

which all contribute to a positive benefit:risk profile for subjects.

P1·ostaglandin Analogues

Prostag landin analogs are effective in lowering IOP and have often replaced p bl oc ker s as first-line therapy in lowering intraocular pressure. In some patients however, target IOPs will not be reached and an adjunctive therapy will be required.

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

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. 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 180 subjects to be randomized at approximately 35 sites. Competitive enrollment is acceptable with no more than 27 subjects at any one site. To participate in the study, subjects must have been on branded PGA [Travatan (travoprost), Xalatan (latanoprost), or Lumigan (bimatoprost)] monotherapy for at least 4 weeks (28 days) and have a mean IOP measurement at 09:00 in at least 1 eye (study eye) ≥ 19 and < 32 mmHg at 2 consecutive visits (Eligibility 1 and Eligibility 2). The expected duration of subject participation in the study is approximately 11 weeks (5 visits). The complete inclusion and exclusion criteria are presented in Section 1.

9 TREATMENTS ADMINISTERED

At the Screening Visit, the PI will assign subjects into one of 3 prostaglandin analogue therapy groups [Travatan (travoprost), Xalatan (latanoprost), or Lumigan (bimatoprost)]. Assuming the subject qualifies, each subject will remain on PGA (selected at Screening Visit) throughout the duration of the study.

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

9.1 Identity of Study Treatments

Investigational Group:	SIMBRINZA+ PGA
Control Group:	Vehicle + PGA

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 or 8 mL with SIMBRINZA or Vehicle. Masked Investigational Products (SIMBRINZA or Vehicle) should be securely stored in accordance with the label.

PGAs will be unmasked (open labeled) product. TRAVATAN, XALATAN, and LUJ\.1IGAN are unmasked medications provided by the Sponsor. Storage of PGAs should be in accordance with the countJ.y pro du ct labe lin g.

A te m perat ur e log w ill be m aintai n e d 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

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

One drop of PGA is to be applied topically to the eye daily in the evening.

The study medications should be dosed in both eyes unless there is a potential safety issue to the subject in the opinion of the Investigator.

Subjects should be reminded to:

- Shake the masked IP prior to instillation,
- If evening instillation of both !OP-lowering medications occurs at the same time, instill the PGA first, wait 15 minutes, then instill the masked IP, and
- Attempt to consistently instill both PGA and masked IP at approximately the same time each evening.

- Return all used and unused bottles at each visit.

9.2.2 Duration of Exposure

All subjects in the study will receive PGAs for the duration of the study, including run-in/washout, eligibility, and masked treatment periods.

Exception - subjects who were previously prescribed one of the study-specific branded PGAs as monotherapy (ie, TRAVATAN PQ 0.004%, XALATAN 0.005%, or LUMIGAN 0.01%) and present with uncontrolled IOP (19 mmHg) at Screening may skip the 28 day run-in period if documentation exists in the subject's medical chart co nfirm ing use of the study specific PGA monotherapy for at least 4 weeks (28 days) immediately prior to screening.

Masked SIMBRINZA or Vehicle will be received at the E2 Visit following randomization for the 42 day treatment phase.

9.2.3 Methods Used to Determine Dosage

The dosage and BID dosing regimen for SIMBRINZA is based on the dosage and dosing regimen of the marketed product. The dosage and QD dosing regimen for TRAVATAN 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01% are based on the dosage and dosing regimen of these marketed PGA analogues.

9.3 Accountability Procedures

Upon receipt of unmasked TRAVATAN 0.004%, and XALATAN 0.005%, and LUMIGAN 0.01% and masked IP from the Sponsor, the Investigator or designee will conduct an inventmyof all products. Designated study staff will provide the study dtugs to the subjects in accordance with their EDC assigned subject numbers and the randomization schedule. During the study, the Investigator must maintain records of study treatment dispensation and collectionof PGAs and 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, PGA therapy is open labeled and will be dosed during the run-in/washout phase (Screening Visit through E2) and for the duration of the masked treatment period of approximately 42 days. 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 or PGA. Kits containing PGA will also be labeled to identify the PGA, protocol and kit numbers.

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 open-angle glaucoma and/or ocular hypertension who are insufficiently controlled on monotherapy or are already on multiple 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 and a Run-in/Washout phase 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 at Week 2 and Week 6 (Exit Visit) as shown in Table 10-1.

Table 10–1 Study Plan by Treatment Groups

Treatment Group	**Study Phase**	
	Phase I (Screening/Eligibility Phase)	**Phase II (Masked Treatment Phase)**
	Screening and Eligibility Visits	Week 2 and Week 6 (Exit) Visits
SIMBRINZA + PGA (TRAVATAN PQ 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01%)	Begin dosing with PGA at bedtime on the evening of the screening visit & Washout of all other IOP-lowering medications if on multiple therapies <u>Mean IOP for both Eligibility Visits must be:</u> **≥ *19* mmHg and < 32 mmHg** in at least 1 eye at **09:00 time point** (<u>while on *PGA monotherapy)*</u> *The same eye(s) must qualify at <u>both</u> 09:00 time points.* *The mean IOP in either eye must not be greater than or equal to 32 mmHg at any time point.*	SIMBRINZA BID (09:00 & 21:00) and PGA QD (at bedtime)
Vehicle + PGA (TRAVATAN PQ 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01%)		Vehicle BID (09:00 & 21:00) and PGA QD (at bedtime)

Following the screening procedures and the initial evaluation of inclusion and exclusion criteria, subjects not on a study specific branded PGA for at least 28 days prior to Screening, will start the appropriate run-in period to ensure documented use of the PGA for a minimum of 28 days. Simultaneously, subjects on multiple IOP-lowering medications will start the appropriate washout period based on the type of ocular hypotensive medication as described in Table 10-2.

Table 10-2 Ocular Hypotensive MedicationWashoutSchedule

Type of Ocular Hypotensive Medication*	Washout Pe1i od* Screening to Eligibility 1 Visit
Miotics and Oral/Topical Carbonic Anhydrase Inhibitors (CAI)	5 days ± 1 day
Alpha and alpha/beta agonists	14 days ± 1 day
Beta-antagonists and Prostaglandin Analogues (with the exception of study-specific PGA)	28 days ± 1 day
Combination Dmgs (use longest wash-out period of individual components)	Up to 28 days ± 1 day

10.2 Visits and Examinations

All procedures and the coITes pondent sc or ing must be perform ed as detailed in the Manual of Procedures (MOP).

10.2.1 SCREENING VISIT (DAY -28)

The intent of the Washout phase is to determine intraocular pressure at the Eligibility 1 and Eligibility 2 Visits while only on PGA analogue monotherapy (PGA baseline).

If in the opinion of the Investigator, the subject can stop all !OP-lowering medications and simultaneously start TRAVATAN 0.004 % , or XALATAN 0.005 %, or LUMIGAN 0.01% monotherapy for the specified washout, it would be preferable.

However, it may be in the interest of the subject to continue concomitant therapy with a CAI (eg, PGA therapy and AZOPT) and stop AZOPT therapy at least 5 days prior to El visit while continuing daily PGA analogue therapy.

Additionally, there may be other subjects who were previously prescribed TRAVATAN 0.004%, or XALATAN 0.005 %, or LUMIGAN 0.01% monotherapy and return to the site with uncontrolled IOP as defined in the eligibility criteria. These subjects do not need an additional 28 day run-in period with PGA. If all other Inclusion/Exclusion criteria are met, the Eligibility 1 Visit 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.	Indicate Investigator-designated PGA that subject will be assigned.
5.	Screen the subject for protocol inclusion/exclusion criteria as per Section 1.
6.	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.
7.	Perform a urine pregnancy test if the subject is a woman of childbearing potential.
8.	Perform pulse and blood pressure measurements.
9.	Assess best-corrected visual acuity (BCVA), OU.
10	Conduct automated perimetry, OU.
11	Perform a slit-lamp examination (biomicroscopy), OU.
12	Perform Goldmann applanation tonometry, OU.
13	Conduct gonioscopy, OU.
14	Perform pachymetry, OU.
15	Perform a dilated fundus examination, OU.
16	Washout concomitant ocular hypotensive medication(s) Instruct subjects who qualify for the study and are on additional ocular hypotensive medication(s) other than a study branded PGA to discontinue the prescribed IOP-lowering medication(s). Subjects must be able to discontinue use of concomitant IOP-lowering medication(s) based on the appropriate schedule (see Table 10.1.-2), but remain on TRAVATAN 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01% monotherapy throughout the duration of the study. The washout period of longest duration should be used when the subject is taking multiple ocular hypotensive medications for more than 1 class.

17	Dispense TRAVATAN 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01% at the Screening Visit. Instruct each subject to instill the medication daily at bedtime, OU. Instill the first dose of the study specific branded PGA on the evening of the Screening Visit and continue instillation for the duration of the run-in/washout phase (up to 29 days). **Exception:** The Run-in/Washout Phase duration may be reduced for those subjects who demonstrate uncontrolled IOP and were on TRAVATAN 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01% monotherapy for at least 28 days prior to the Screening Visit.
18	Schedule the subject to return in 28 days (+1 day) for the Eligibility 1 Visit. (See exception above for those uncontrolled subjects previously prescribed TRAVATAN 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01% monotherapy) 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.

10.2.2 ELIGIBILITY 1 AND ELIGIBILITY 2 VISITS: [09:00 (+/-30 MIN) AND 11:00 (+/- 30 MIN) EXAMINATIONS]

Table 10-3 Activities for Eligibility 1 and Eligibility 2 Visits

Activity	Eligibility1 (El) Visit		Eligibility 2 (E2) Visit	
	09:00	**11:00**	09:00	**11:00**
Docmnent that the subject has daily administered PGA therayp for 28 days.	X			
Document date and time of last instillation. RESCHEDULEthe visit if the subjectdid not dose the previous evening.	X		X	
Update Medical Hist0y1 /Concomitant Medications	X	X	X	X
Obtain Blood Pressme and Pulse Rate	X	X	X	X
Perfonn BCVA, OU	X		X	
Perf01m slit lamp exam (Aqueous cells, aqueous flare, lens, status ofl ens), OU	X		X	
Measme IOP (Goldmann), OU *Mean JOP must be;;::*19 *and< 32mmHgin atleast one (same) eye(s) at 09:00.* *Mean IOP must be less than 32 mmHg in either eye at* ***all*** *time points.* *The mean JOP is defined as the average of two or more JO P read ings in the sam e eye .*	X	X	X	X
Schedule the subject to return for the Eligibility 2 Visit (E2) in 3-8 days following El Visit prior to 09:00		X		
Verify i11cl u s ionlex c lu s ion criteria. ***Only subjects meetinR all requirements can be randomized***				
Randomize the subject upon confirmation of eligibility.				X
Dispense to the subject the conesponding masked study medications and PGA kits, document in the dispensing logs.				X
Instrnct the subject to sta1tdosing the same evening. For subjects wearing contact lenses, instrnct them to remove the lenses before the instillation of the study medication & wait approximately 15 minutes after dose before insettin g the lenses again. PGA analogue - Daily dosing at bedtime. Masked IP - BID dosing at 09:00 and 21:00 (± 30 minutes)				X
Schedule the successfully randomized subject to retmn for the Week 2 Visit in 14 ±3 days following E2 Visit prior to 09:00 (± 30 minutes).				X

NOTE:

- The Eli gibility 1 Visit should be cond ucted 1-29 days following the Screening Visit based on the n m-in/washout period.
- The Eligibility 2 Visit should be conducted 3-8 days following the Eligibility 1 Visit.
- The PGA and Masked IP should be dosed in both eyes unless there is a potential safety issue 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 PGA therapy and 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 instrnctions 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-insel1ing lenses.

b) MUST 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) Instill 1 drop of PGA in each affected eye daily at bedtime for approximately 6 weeks.

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

1. Instill PGA first
11. Wait approximately 15 minutes before instilling masked IP
111. 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 (± 30 minutes) for the Week 2 Visit.

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

- *instill the dose of PGA at bedtime and masked study medication at 21:00 (± 30 minutes) the night 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 the morning of the study visit.*** *The morning dose will be instilled in the office after the 09:00 IOP measurement.*
- ***DO NOT*** *discard any unused or empty bottles,*
- *bring all PGA and 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 WEEK 2 AND WEEK 6 (EXIT) VISITS: [09:00 (+/- 30 MIN) AND 11:00 (+/- 30 MIN) EXAMINATIONS]

NOTE:

The Week 2 Visit should be conducted 14 days (± 3 days) following the Eligibility 2 Visit.

The Week 6 Visit should be conducted42 days (± 3 days) following the Eligibility 2 Visit.

Table 10–4 Activities for Week 2 and Week 6 (Exit) Visits

Activity	Week 2 Visit		Week 6 (Exit) Visit	
	09:00	**11:00**	**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	X
Perform a urine pregnancy test if subject is female of child bearing age				[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	
Perform Goldmann applanation tonometry, OU. Record time of IOP measurements	X	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	X	
Approximately 15 minutes after the IOP measurements, instill the masked IP in the office. Record the time of instillation by the site.	X		X	
Perform 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	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

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. 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 following sections).

10.4 Discontinued Subjects

Discontinued subjects are those who withdraw or are withdrawn from the study after the Screening Visit. 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 obse1vations on an Adverse Event (AE) Fo1m.

Any subject who exits early from the study must undergo all procedures outlined at Week 6. Additionally, the Exit F01m mu st be compl eted an d one of the following reasons for discontinuation must be identified:

- Discontinued Study due to Screen Failure
- 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 Drng
- Discontinued Study due to Physician Decision
- Discontinued Study due to Pregnancy
- Discontinued Study due to Progressive Disease
- Discontinued Study due to Protocol Violation
- Discontinued Study due to Study Te1minated by Sponsor
- Discontinued Study due to Technical Problems
- Discontinued Study due to Withdrawal by Subject
- Discontinued Study due to Other Reasons

Finally, to ensure the safety of all subjects who discontinue early, Investigators should assess each subject and, if necessa1y, advise them of any therapies and/or medical procedures that might be needed to maintain their health.

10.5 Clinical Study Termination

If the clinical study is prematurely te1minated or suspended, the Sponsor will infmm the Investigator and the regulat01y autho riti es of the te1mi nation/ suspension and the reason(s) for the te1mi nation/suspension. The Investigator should promptly notify the IEC/IRB of the te1mi nation or suspension and of the reasons. The Sponsor rese1ves the right to close the investigational site or te1minate the study in its entirety at any time, for reasonable cause. Reasons for the closure of an investigational site or te1mination 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 patients/subjects by the Investigator

The Investigator also may tenninate 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 confinnation of and instructions for study tennination.

11 ANALYSIS PLAN

11.1 Subject Evaluability

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

All subjects who consented to participate in the study will be evaluated in the pre-treatment safety analysis set. All subjects who are randomized and receive a dose of investigational product will be evaluable for the t1eatment-emergent safety analysis set. All subjects who receive study medication and who complete at least 1 scheduled on-therapy study visit will be evaluated in the full analysis set. All subjects who receive the study medication to which they were randomly assigned, satisfy pre-randomization inclusion/exclusion criteria, and who complete at least 1 scheduled on-therapy study visit will be evaluated in the per protocol analysis set. In addition, individual subject visits and data points that do not satisfy protocol criteria may be excluded from the per protocol analysis set. The final subject evaluability will be deten nined prior to breaking the code for masked treatment assignment and locking the database.

11.2 Analysis Data Sets

11.2.1 Full Analysis Sets

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

All 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 Per Protocol Set

The per protocol set (PPS) will be evaluated only for the primary efficacy endpoint to confirm results from the FAS.

All subjects who receive the study medication to which they were randomly assigned, satisfy pre-randomization inclusion/exclusion criteria, and who complete at least 1 scheduled on-therapy study visit will be evaluated in the per protocol analysis set. In addition, individual subject visits and data points that do not satisfy protocol criteria may be excluded from the per protocol analysis set.

11.2.3 Safety Set

There will be two safety analysis sets – pre-treatment safety analysis set and treatment-emergent safety analysis set. The pre-treatment safety analysis set will include all subjects who consented to participate in the study. The pre-treatment safety analysis set will be the set used to summarize the occurrence of adverse experiences prior to exposure of investigational product. The treatment-emergent safety analysis set will be used for each of the safety parameters and adverse events occurring after exposure to investigational product.

11.3 Demographic and Baseline Characteristics

Subject characteristics summaries include tables and listings such as demographics (age, gender, race, ethnicity, iris color, and region) and baseline characteristics (baseline IOP by time point, baseline diurnal IOP, baseline IOP category (19-26 mmHg, 27-32 mmHg), prostaglandin analogue (PGA) run-in monotherapy, corneal thickness, and diagnosis) for all analysis sets (safety, FAS, and PPS). 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, ethnicity, iris color and region will be summarized as categorical variables.

11.3.2 Baseline Characteristics

Baseline IOP by time point, diurnal baseline IOP, and corneal thickness will be summarized as continuous variables. In addition, baseline IOP (19-26 mmHg, 27-32 mmHg), PGA run-in

mono therapy (Lumigan, Xalatan, Travatan), and corneal thickness categ01y (0.55 mm, >0.55 to 0.60 mm and >0.60 mm) will be summarizedas categolical variables.

11.4 Efficacy Analyses

Unless othe1wise specified, all significant testing will be at the 5% 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-treatment visits. The Safety set will consist of all who received a dose of study medication.

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 sh1dy 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. Randomization will be stratified according to region and type of PGA therapy.

Note that baseline conesponds to a visit where subjects are cmTently taking a PGA monotherapy

11.4.1 Primary Efficacy

The prima1y 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 hype1iension who are cmTently on prostaglandinanalogue monotherapy.

The prima1y endpoint is:

- Mean change from baseline in diurnal IOP at Week 6

The prima1y efficacy analysis will be an assessment of differences between treatments in mean change from baseline in diurnal IOP at Week 6 (patient IOP 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: $\mu_{BrinzBrim+PGA} = \mu_{Vehicle+PGA}$

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

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

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

11.4.1.2 Analysis Methods

The treatment difference in mean diurnal IOP change from baseline will be examined with a pair-wise test at each scheduled on-therapy visit with Week 6 as the primary endpoint. The treatment difference in mean diurnal IOP change from baseline at Week 6 will be tested based on the least squares means derived from a repeated measures mixed model. This model will include fixed effects of treatment, visit, type of PGA, region, and the interaction of treatment and visit; the baseline diurnal IOP as a covariate; and the random effect of subject within the subject's treatment, region, and type of PGA.

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

Primary inference will be based on the FAS. The primary analysis will be repeated on the PPS to investigate sensitivity of including subjects who do not completely conform to protocol requirements.

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 sites, age category (< 65, ≥ 65 and furthermore as < 50, 50-64, ≥ 65), sex, race, baseline IOP (19-26 mmHg, 27-32 mmHg), PGA run-in monotherapy (Lumigan, Xalatan, Travatan), corneal thickness category (≤0.55 mm, > 0.55 to 0.60 mm and > 0.60 mm) will be summarized descriptively (N, mean, standard deviation) for the primary end point.

11.4.2 Secondary Efficacy

The secondary endpoints are

- Mean dimn al IOP at Week 6
- Mean percentage change from baseline in dimnal IOP at Week 6
- Mean change from baseline in IOP at 11:00 at Week 6
- Mean percentage change from baseline in IOP at 11:00 at Week 6
- Mean change from baseline in IOP at 09:00 at Week 6.
- Mean percentage change from baseline in IOP at 09:00 at Week 6.

11.4.2 .1 Stati stical Hypotheses

The null and alternative hypotheses for each of the secondary analyses are:

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

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

where µBrinzBrim+PGArefe rs to the mean of eac h seco nda1y endpo in t forsubjectsrandomizedto receive brinzolamide / brimonidine plus PGA, and µvehicie+PGA refe rs to the m ea n o f the same endpoint in the con esponding group of subjects randomized to receive Vehicle plus PGA.

Thus, success reflects a greater mean estimate for the adjunctive therapy (brinzolamide / brimonidine plus PGA) relative to Vehicle plus PGA in each secondaiy endpoint comparison.

11.4.2.2 Analysis Methods

Analyses of treatment differences of secondaiy endpoints will use the same methods as those for the prima1yendpoint. Hypothesis tests will use the same null and alternative hypotheses as above, with µ representing the mean for the variable being tested.

Descriptive statistics will also be repo1ted for each of the seconda1yendpoints.

[redacted]

[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 closed step-down testing procedure will be used for hypothesis testing of primary and secondary endpoints; therefore no multiplicity adjustment is needed. 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 mean diurnal IOP
- Difference between treatments in mean percentage diurnal IOP change from baseline
- Difference between treatments in IOP change from baseline at 11:00
- Difference between treatments in percentage IOP change from baseline at 11:00
- Difference between treatments in IOP change from baseline at 09:00
- Difference between treatments in IOP change from baseline for each time point at 9:00

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

11.7 Safety Analysis

The safety endpoints in this study are automated perimetty, fundus parameters, best-con ected 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, frequency and percents for adverse events, and mean changes from baseline as appropriate.

11.8 Health Economics

Not applicable.

11.9 Interim Analyses

Not applicable.

11.10 Sample Size Justification

With 81 evaluable subjects per treatment group in the primaiy efficacy analysis, there is at least 90% power to detect a 2.0 mmHg difference in mean cha nge from baseline in diurnal IOP at Week 6 betweenthe treatment groups. This calculation is based on the assumption of a common standard deviation for mean change from baseline in diurnal IOP as small as 3.5 mmHg and as large as 3.9 mmHg and the use of a two-sample two-sided t-test performed at the $a=0.05$ level of significance.

Assuming a drop-out rate of 10%, approximately 90 subjects per treatment group will be randomized to ensure the required number of evaluable subjects in the final efficacy analysis.

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

Any pre-existing medical conditions or signs/symptoms present in a subject prior to the start of the study (ie, before informed consent is signed) should be recorded in the baseline history section of the CRF. Any medical occurrences having an onset after informed consent but prior to the start of study treatment (ie, initiation of treatment with test article) should also be recorded in the baseline history section within the CRF.

Subsequent to signing an informed consent form, all untoward medical occunences that occm dming the course of the study must be documented on an Adverse Event Fo1m (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 assessmentof 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 cunent hospitalization, is not disabling, etc.). All adverse events must be repmted regardless of whether or not they are related to the study treatment.

For nonselious adverse events, an AEF containing all available info1mation will be collected on a routine basis according to instructions provided by the study sponsor.

Serious Adverse Events

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

- 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 complicati on 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 disrnption of a person's ability to conduct n01mal 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/bilth defect.

- Is an import ant medical event. An impmt ant medical event is an event that may not result in death, be life- threatening, or requil·e 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 drng dependency or drng abuse.

All available information on a serious adverse event(s) and any other associated AE, if applicable, must be forwa1·ded to th e stud y Spon sor imm ediatel y (ie, w ithin 24 ho urs of the Investigator's or site's knowledge of the event) as follows:

- In studies utilizing EDC (electronic data capture), all available info1mation 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 faxed to the study Sponsor at within 24 hours of the Investigator's or sites awareness; however, the reported information must be entered into the EDC system once it becomes operational (Table 12-1).*

- Additional information for any applicable event is to be rep01ted 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 repo1ted to Alcon following the usual pha1macovig1ance circuit.

In addition to the reporting of serious adverse events to the study sponsor, the SAE must be 1·eport ed to the IRB / **IE C according to their requirements.**

Sponsor representatives and their contact inf01mation are provided in the Manual of Procedures that accompanies this protocol.

If the SAE was due to a hospitalization of the subject, a copy of the discharge summa1y is to be fo1warded 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 laborato1y tests also may be requested. Fmther, depending upon the nature of the SAE, the Sponsor may request copies of applicable p01tions of the subject's medical records.

An assessment of seriousness will also be performed for all adverseevents by a study Sponsor physician utilizing the same criteria. If an adverse event repo1t ed 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.

Safe ty Events of Special Interest

In addition, the following cases will be collected and forwarded to the study Sponsor within 24 hours:

- Pregnancy exposmes to the medicinal product.
- Overdose, abuse and misuse cases.
- Lack of efficacy cases (based upon Investigator's clinical judgment).
- Medication enors.

Theseevents may be reported on the AE form in the EDC system.

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).

An assessment of causality will also be performed by a study sponsor physician utilizing the same definitions. 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 are not excluded from the study as long as adequate birth control methods are being utilized or women considered post-menopausal. 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 (e.g. 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 and should be used during the study.

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 patients 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 patient exited from the study.

Although not necessarily adverse, for the purposes of this trial, pregnancies will be reported on the adverse event form. 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/ethnicity)
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 (paper or 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).

13.4 Quality Assurance and Quality Control

The Sponsor will be responsible for implementing and maintaining quality assurance and quality control systems to ensure the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements. The Sponsor will secure agreement from all involved parties to ensure direct access to all trial related sites, source data and documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the Sponsor with the Investigator/Institution and any other parties involved in the clinical trial will be provided in writing as part of the protocol or as a separate agreement.

14 References

Alm A, Grierson I, Shields MB. Side effects associated with prostaglandin analog therapy. Surv Ophthalmol 2008;53:S93-105.

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.

Baudouin C, Labbe A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad, and the ugly. Prog Retin Eye Res. 2010;29(4):312-34.

Cracknell KPB, Grierson I. Prostaglandin analogues in the anterior eye: Their pressure lowering action and side effects. Exp Eye Res 2009;88:786-91.

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.

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

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.

Oostenbrink JB, Rutten-van Molken MP, Sluyter-Opdenoordt TS. Resource use and costs of patients with glaucoma or ocular hypertension: a one-year study based on retrospective chart review in the Netherlands. J Glaucoma. 2001;10(3):184-91.

Rolando M, Brezzo G, Giordano P, Campagna P, Burlando S, Calabria G. The effect of different benzalkonium chloride concentrations on human normal ocular surface: a controlled prospective impression cytology study. In: Van Bijsterweld OP, Lemp MA, Spinelli D, eds. The Lacrimal System. Amsterdam: Kagler & Ghedini; 1991. p. 89–91.

Rylander NR, Vold SD. Cost analysis of glaucoma medications. Am J Ophthalmol. 2008;145(1):106-13.

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:
03/27/2017 17:55:04	[redacted]	[redacted]
03/28/2017 17:19:42	[redacted]	[redacted]
03/28/2017 18:04:27	[redacted]	[redacted]
03/30/2017 20:50:17	[redacted]	[redacted]