Phase IV Comparison of Combigan BID vs Simbrinza TID in Subjects Currently Treated with Latanoprost for Open-Angle Glaucoma or Ocular Hypertension

Protocol Title:	Phase IV Comparison of Combigan BID vs Simbrinza TID in Subjects Currently Treated with Latanoprost for Open-Angle Glaucoma or Ocular Hypertension
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Contact Information

Title of Study: Phase IV Comparison of Combigan BID vs Simbrinza TID in Subjects Currently Treated with Latanoprost for Open-Angle Glaucoma or Ocular Hypertension

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Project Personnel and Conflicts of Interest

All study investigators and study coordinators who have study-related contact with subjects or identifiable data from subjects are listed below.

Role	Name
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Sub-I	Michael W. Evans, M.D.
Sub-I	J. Zachary Forsey, M.D.
Study Coordinator	April Kettering, CRA
Study Coordinator	Chelsea Allred, COA

No investigator or study staff member and/or their immediate family members has any conflict of interest in the design, conduct, or results of this study.

Brief Summary

Purpose

To compare Combigan BID vs Simbrinza TID in approximately 40 subjects currently being treated with Latanoprost for Open-Angle Glaucoma or Ocular Hypertension. Both of these drugs are currently FDA approved as combination therapy for patients with Open-Angle Glaucoma or Ocular Hypertension. The purpose of this clinical trial would be to assess which treatment, if either, is superior in lowering intraocular pressure (IOP). A secondary objective is to assess the tolerability of each drug.

Participants

Approximately 40 subjects adults, male or female, age 18 and older, of any ethnicity or race with the diagnosis of Open-Angle Glaucoma or Ocular Hypertension currently being treated with latanoprost for at least six weeks prior to screening.

Procedures (methods):

After acquisition of properly obtained informed consent, subjects will under the go the following assessments: Review of medical and ophthalmic history, demographics, review of concomitant medications, review of ocular symptoms, vital signs (*BP, Resp, Pulse*), Best Corrected Visual Acuity (BCVA), Intraocular Pressure (IOP) measurement, Biomicroscopy, Ophthalmoscopy, Gonioscopy, Central Corneal Thickness measurement (Pachymetry), urine pregnancy test (*if of child-bearing potential*), and Visual Field.

Purpose and Rationale

Prostaglandins, such as latanoprost, are the most common initial therapy for POAG and OHT. Patients being treated for POAG and OHT with latanoprost often require adjunctive therapy to achieve target pressures. Patients are often switched to a combination therapy for a number of reasons including improved efficacy, tolerability, and/or compliance. Little head-to-head data exists comparing the current marketed combination products Combigan and Simbrinza. This study will serve as a data reference comparing safety, efficacy, and tolerability of Combigan and Simbrinza.

Subjects

Adults, male or female, age 18 and older, of any ethnicity or race with the diagnosis of Open-Angle Glaucoma or Ocular Hypertension currently being treated with latanoprost for at least six weeks prior to screening. Subjects will be identified from Investigator's current patient population.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Open-angle glaucoma or ocular HTN
- Currently treated with Latanoprost for min of 6 weeks
- IOP must be ≥ 10 mmHg and ≤ 34 mmHg at screening visit while on Latanoprost
- Male or Female 18 yrs and older
- BCVA 20/100 or better OU
- Pachymetry >470 and < 640
- Women of childbearing potential must have a negative urine pregnancy test at the screening/baseline visit
- Patient willing and capable of providing informed consent

Exclusion Criteria:

- C/D >0.8
- Visual field loss, which in the opinion of the investigator is functionally significant
- Current use of ocular steroids
- Concurrent significant active ocular disease History: (within 3 months prior to Screening) of ocular laser, intraocular, filtering or refractive surgery or planned ocular surgery of any kind during study participation
- Change, within prior 30 days or anticipated change, in any systemic medication that is known to affect IOP
- Uncontrolled systemic disease
- Significant ocular hyperemia at baseline
- Prior glaucoma procedure within 3 months
- Females who are pregnant, nursing, or planning a pregnancy or who are of childbearing potential and not using a reliable method of contraception
- Known allergy or sensitivity to any study medication
- Asthma or any other known medical condition that the investigator feels would put patient at increased risk from any of the study medications
- Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to Screening

Full Description of the Study Design, Methods and Procedures

This research study will compare two currently FDA approved and marketed combination treatments for open-angle glaucoma and/or ocular hypertension. The main objective of the study is to assess which drug is superior in lowering the intraocular pressure of the subjects. The secondary objective is to compare the tolerability of each drug in regards to the following known side effects: Oral effects (bad taste, dry mouth) and Ocular comfort effects (itching, burning, stinging, burning on instillation, blurred vision).

Subjects will be discontinued from their current Latanoprost regimen and randomized 1:1 to either Combigan 0.2/0.5% BID or Simbrinza 1/0.2% TID. Duration of treatment for each arm will be 90 days. Subjects will discontinue Latanoprost at Visit 1 and begin either Combigan 0.2/0.5% BID or Simbrinza 1/0.2% TID on the evening of Visit 1 (approximately 8pm). Both are ophthalmic drops and will be placed in the eye by the subject according to the appropriate dosing scheduled (Combigan BID, Simbrinza TID).

The following data will be collected by the Investigator and designated study team members:
Relevant (as determined by the Investigator)

- Medical History
- Ophthalmic History
- Demographics
- Concomitant Medications
- Ocular Symptoms
- Vital Signs (BP, Resp, Pulse)
- Best Corrected Visual Acuity (BCVA)
- Intraocular Pressure (IOP)
- Biomicroscopy (Slit Lamp Exam)
- Ophthalmoscopy
- Gonioscopy
- Central Corneal Thickness (Pachymetry)
- Urine Pregnancy Test (if child-bearing potential)
- Visual Field

All ophthalmic exams are routine Open-Angle Glaucoma/Ocular Hypertension assessments. Participation in the study may require earlier and will require more frequent performance of assessments.

A detailed description of each visit is listed below:

Visit 1 (Day 0): ICF, Med/Oph Hx, Con-Meds, Ocular Symptoms Assessment, Vitals (*BP, RES, HR*), BCVA, IOP (*8am, 10am, and 4 pm*), Biomicroscopy, Ophthalmoscopy (*non-dilated if a dilated exam has been performed within 6 months. Dilated if no dilated exam within 6 months*), Gonioscopy (*if not performed within 12 months*), Visual Field (*if not performed within 12 months*), Central Corneal Thickness (*if not performed within 12 months*), Urine Pregnancy test (*women of childbearing potential only*), IP dispensing

Visit 2 (Day 7 +/- 2 days): PHONE CALL ONLY- Med/Oph Hx , Con-Meds, Adverse Events, Ocular Symptoms Assessment

Visit 3 (Day 30 +/- 3 days): Med/Oph Hx, Con-Meds, Ocular Symptoms Assessment, BCVA, IOP (*8am, 10am, and 4pm*), Biomicroscopy, IP dispensing, Adverse Event

Visit 4 (Day 90 +/- 3days): Med/Oph, Hx Con-Meds, Ocular Symptoms Assessment, Vitals (*BP, RES, HR*), BCVA, IOP (*8am, 10am, and 4pm*), Biomicroscopy, Ophthalmoscopy (*non-dilated if a dilated exam has been performed within 6 months. Dilated if no dilated exam within 6 months*), Central Corneal Thickness (*if not performed within 12 months*), Gonioscopy, Adverse Event

Unscheduled: Con-Meds, Ocular Symptoms Assessment, Vitals (*BP, RES, HR*), BCVA, IOP (*8am, 10am, and 4pm*), Biomicroscopy, Ophthalmoscopy (*non-dilated if a dilated exam has been performed within 6 months. Dilated if no dilated exam within 6 months*), Central Corneal Thickness (*if not performed within 12 months*), Adverse Event

The patient and one study coordinator will be unmasked. The investigator will be masked. The investigator and a masked coordinator will complete all ophthalmic exams to avoid bias. Open label drug will be dispensed in a site provided non-see-through pouch to avoid risk of unmasking. Randomization will be conducted by assigning arm to individual subject numbers prior to beginning of enrollment. This master list will be held by unmasked personnel and kept in a secure location. As subjects enroll, they will be assigned a number in sequential order.

Adverse Experiences

Adverse Events

Adverse events occurring during the study will be recorded on an adverse event case report form. If adverse events occur, the first concern will be the safety of the study participants.

Definitions

Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the subject has been administered study drug.

Adverse events will be assessed, documented, and recorded in the CRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each subject a general, non-directed question such as “How have you been feeling

since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate case report form.

Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a subject requires hospitalization is not reportable as a serious adverse event.

Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

Relationship to Study Drug

A determination will be made by the investigator of the relationship (if any) between an adverse event and the study drug, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug.

Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate case report form.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health

authorities. Any adverse event that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) must be immediately reported to Allergan but no later than 15 calendar days after learning of a serious adverse event. Serious adverse events must be recorded on the Serious Adverse Event Form provided by Allergan. All subjects with a serious adverse event must be followed up and the outcomes reported. In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the Serious Adverse Event form.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.

3. Provide Allergan with a complete, written description of the adverse event(s) on the Serious Adverse Event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

Benefits to Subjects and/or Society

This study may or may not benefit the individual subjects. A potential benefit to subjects may be better control of the subject's IOP. The potential benefit to society is the knowledge of possible superiority of one drug over the other to reduce IOP. This is especially of interest as Combigan requires BID dosing while Simbrinza require TID dosing. The other potential benefit to society is the knowledge of comparative tolerability and ocular discomfort associated with each drug.

Full Description or Risks and Measures to Minimize Risks

See package inserts for each drug for full list of risks.

Most common side effects:

Combigan: 5 to 15% experience allergic conjunctivitis, conjunctival folliculitis, conjunctival hyperemia, eye pruritis, ocular burning and stinging

Simbrinza: 3 to 5% experience blurred vision, eye irritation, dysgeusia, dry mouth, eye allergy

Data Monitoring and Analysis

For safety purposes the Principal Investigator will review the study data on each subject enrolled.

For statistical analysis, summary tables will be provided for baseline variables (demographics, dispensing, medical history). IOP is the primary endpoint- Summarized by treatment for each visit. All safety endpoints will be presented descriptively.

Collect or Receive Identifiers

Names, telephone numbers, social security numbers and any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older will be collected or received.

Identifiers in Research Data

The collected or received identifiers listed above will not be linked or maintained with the research data.

Confidentiality of the Data

Paper records will be kept in a secure location accessible to only research personnel.

Whenever feasible, identifying information will be removed from study related documents.

Data Sharing

The collected or received identifiers will not be shared with anyone outside the immediate research team.

Appendix

Patient Questionnaire

~~Patient Diary~~