STATISTICAL ANALYSIS PLAN - MODULE I

STATISTICAL METHODOLOGY

PROTOCOL P2-86893-001

A Multicenter, Prospective, Randomized, Double-Masked, Phase 2 Study Evaluating the Safety, Tolerability, and Efficacy of Topical AG-86893 in Patients with Pterygium

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SIGNATURES

The undersigned have approved this Statistical Analysis Plan for use in this study.

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1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) – Module I is to describe the related procedures and statistical methodologies used to process study data, analyze study data, and report results for Protocol P2-86893-001 sponsored by Allgenesis Biotherapeutics Australia Pty Ltd (the Sponsor; local Sponsor Trial Runners Australia Pty Ltd).

This SAP should be read in conjunction with the latest version of the designated study protocol and its case report forms (CRF), and the related SAP Module II – Tables, Graphs, Figures, and Listing.

1.1 Changes from Protocol

Please refer to Section 10.4 PROTOCOL AMENDMENT HISTORY of protocol V3.0 for all amended contents. The following content are those may affect statistical analysis plan. The SAP and TFL shells have been amended accordingly:

Section	Contents (*italic are added contents*)
Study Objective	• *Evaluate the dose response of AG-86893 on pterygium vascularity, volume and vessel length (exploratory)*
Study Visit	There will be 6 *possible* clinic visits, including a 14-day screening period (from Day -14 to -2), followed by a ~~n in-clinic~~ treatment/observation period (Day 1, Day 7 *[may be conducted as a phone follow-up]*, and Day 28), and 2 post-treatment follow-up visits for safety monitoring (Day 56 and Day 84).
Plasma Drug Monitoring	Plasma drug monitoring will be collected on Day 1 and Day 28 pre-dose and post-dose at 0.5 and 1 ~~,2 and 4~~ hours after the morning dose; on Day 56, a single sample will be collected
Study Eye	If both eyes are affected and meet the inclusion criteria, the eye with the higher overall hyperemia score will be used as the study eye. *If both eyes are eligible and have the same hyperemia score, the right eye will be selected as the default study eye*

2 STUDY OBJECTIVES

The study safety objective is to evaluate the safety, tolerability of AG-86893 in participants with pterygium.

The study efficacy objectives are to evaluate the dose response of AG-86893 on:

1) conjunctival hyperemia
2) localized pterygium conjunctival hyperemia
3) pterygium vascularity, volume and vessel length.

The pharmacokinetic objective is to determine plasma concentrations of AG-86893, if data available.

3 STUDY DESIGN

This is a Phase 2 prospective, multi-center, randomized, double-masked, vehicle controlled, parallel-group, dose-response study. Approximately **70** study participants in up to **12** investigational sites throughout **Australia** will be randomized in **1:1:1** ratio into AG-86893 vehicle, 0.1% AG-86893, or 0.3% AG-86893 group. Both eyes will be screened for study eligibility, but only **one** eye (selected for the highest grade of hyperemia) will be enrolled and dosed in the study.

Study participants must be diagnosed with pterygium hyperemia and meet the study Inclusion/Exclusion Criteria (see study protocol Sections 5.1 and 5.2).

3.1 Study Measurements

3.1.1 Primary Efficacy Measure

The primary efficacy measurement is the **overall conjunctival hyperemia score as graded by the central reading center.** Conjunctival hyperemia will be measured in 4 quadrants of the ocular surface and graded using a 5-point scale:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Very severe

The overall conjunctival hyperemia is the average of the score of each quadrant. Digital slit-lamp photos will be captured and submitted to the central reading center for assessment.

3.1.2 Secondary Efficacy Measure

The secondary efficacy measurement is the **localized pterygium conjunctival hyperemia.** It is the score of the quadrant with the pterygium as assessed by the central reading center using digital slit-lamp photos.

3.1.3 Exploratory Efficacy Measure

Exploratory measurements include the following:

- **Pterygium vascularity:** The vascularity of the body of the pterygium will be quantified by pixel analysis as assessed by the central reading center using the above digital slit-lamp photos.
- **Pterygium vessel length:** Using the above digital slit-lamp photos, the length of the vessels within the pterygium will be assessed by the central reading center.

- **Pterygium volume** (at selected study sites for baseline, wk4, wk8 only): Pterygium volume on the AS-OCT images will be assessed by the central reading center.

3.1.4 Safety and Other Measures

a) Vital Sign and Laboratory Findings

Vital signs as listed below will be performed at all visits.

- Temperature ((Celsius)
- Respiratory Rate
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Heart Rate
- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m^2)

Blood and urine samples will be collected for lab tests at Screening, Day 28, Day 84 or Early Discontinuation, and Unscheduled visits for the following tests:

- Urinalysis
- Hematology
- Serum chemistry

b) Physical Characteristics

c) Pregnancy Testing (for child-bearing participants)

d) Electrocardiogram (ECG) Findings

ECG will be performed at Screening, Day 1, Day 28, Day 84 or Early Discontinuation, and Unscheduled visits. Findings will be recorded as Abnormal or Normal.

e) Best-corrected Visual Acuity (BCVA)

BCVA using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity protocol will be assessed for both eyes at **all** scheduled visits. The number of letters read correctly will be recorded for both eyes.

f) Intraocular Pressure (IOP)

IOP (mmHg) will be measured using Goldmann applanation tonometer for both eyes at **all** scheduled visits.

g) Tear Film Break-up Time (TFBUT)

TFBUT (seconds) will be performed for the study eye first, then the other eye at Day 1, Day 28, Day 56, Day 84 (only if abnormal findings on Day 56) and Early Discontinuation visits.

h) Lissamine Green Conjunctival Staining

Conjunctival staining will be performed for the study eye first, then the other eye at Day 1, Day 28, Day 56, Day 84 (only if abnormal findings on Day 56) and Early Discontinuation visits using the following grading:

0 = None
1 = Mild
2 = Moderate
3 = Severe.

i) Biomicroscopy

Slit-lamp biomicroscopy examination for both eyes will be performed at **all** visits for following measurements:

- Eyelids (Abnormal, Normal. If Abnormal, specify)
- Conjunctiva (0 = None, 0.5 = Trace, 1 = Mild, 2 = Moderate, and 3 = Severe)
- Cornea (0 = None, 0.5 = Trace, 1 = Mild, 2 = Moderate, and 3 = Severe)
- Iris (0 = None, 0.5 = Trace, 1 = Mild, 2 = Moderate, and 3 = Severe)
- Lens Status (Clear, Opacity, Pseudophakic, Aphakic)
  If Opacity:
  - Nuclear Cataract Grade (: <1, 1, 1.5, 2, 2.5, 3, >3)
  - Posterior Subcapsular Cataract Grade (: <1, 1, 1.5, 2, 2.5, 3, >3)
  - Cortical Cataract Grade (: <1, 1, 1.5, 2, 2.5, 3, >3)

j) Ophthalmoscopy Findings

Dilated fundus examination will be performed for both eyes at Screening, Day 1, Day 28, Day 84 or Early Discontinuation, Unscheduled visits for the following assessments:

- Vitreous (Abnormal (CS), Abnormal (NCS), Normal. If Abnormal, specify)
- Macula (Abnormal (CS), Abnormal (NCS), Normal. If Abnormal, specify)
- Optic Nerve (Abnormal (CS), Abnormal (NCS), Normal. If Abnormal, specify)
- Peripheral Retina (Abnormal (CS), Abnormal (NCS), Normal. If Abnormal, specify)

3.1.5 Pharmacokinetic Measure (if applicable)

A subset of 6 participants from each treatment group will participate in a PK study to collect blood samples on the morning of Day 1 and Day 28 at pre-dose, at 0.5, 1 hour post-dose. On Day 56, a single blood sample will be collected. Plasma drug concentrations will be measured using a validated liquid

chromatography, tandem mass spectrometry assay, with a target lower limit of quantitation of 0.020 ng/mL.

3.1.6 Patient Questionnaire

At Day 1 (prior to dosing), Day 28 (prior to dosing), Day 56, Day 84, Early Discontinuation or Unscheduled visits, the participant will complete a questionnaire querying about the severity and frequency of following symptoms of the **study eye**:

- Blurred Vision
- Burning/Stinging
- Grittiness
- Itchiness
- Pain
- Redness
- Tearing

Frequency of Symptoms:

0 = Never
1 = Rarely
2 = Occasionally
3 = Sometimes
4 = Often
5 = Always
9 = Not Assessed

Severity of Symptoms:

0 = None
1 = Mild
2 = Moderate
3 = Severe
9 = Not Assessed

3.2 Study Visits and Schedule of Events

Participants will participate in the study for approximately **14** weeks (Screening period up to **2** weeks, treatment period for **4** weeks, and post-treatment follow-up period for **8** weeks). There will be a total of **6** clinic visits: screening (from **Day -14 to -2**), up to **3** in-clinic treatment/observation at **Day 1, Day 7** (optional), and **Day 28**, and **2** post-treatment follow-up visits for safety monitoring at **Day 56 and Day 84**. Activities and medical procedures to be performed at each study visit are summarized in the study protocol Section 1.3.

3.3 Sample Size Considerations

An empirical sample size estimation was used as this is an exploratory study. Approximately 20 evaluable study participants are planned for each treatment group. Therefore, a total of approximately 70 participants will be enrolled at up to 12 sites in order to achieve a planned 60 evaluable participants after accounting for potential drop-outs.

3.4 Randomization and Masking

Eligible participants will be assigned in 1:1:1 ratio into 1 of the 3 treatment groups. A central randomization scheme will be prepared by an unmasked Trial Runners representative and dispensed via an Interactive Web Response System (IWRS). Randomization schedule will be optimized as much as possible to achieve a balanced distribution of treatment assignment by investigational site, baseline hyperemia severity (grade of 2 vs. > 2), and PK participation.

Randomization assignment will occur by site personnel via IWRS once a participant's eligibility is determined by the investigator and confirmed by the central reading center. The IWRS will provide a unique Subject ID to be used in all study documents as the study identifier.

Study drug will be labeled with medication kit numbers, and the IWRS will provide each site with the specific medication kit number(s) for each randomized participant at the time of randomization. Sites will dispense study drug according to the IWRS instructions. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

Treatment assignment will be masked to the study participants, the investigators, all study-site personnel (with the exception of the unmasked drug administrator), study monitoring personnel, as well as Central Reading Center personnel during the entirety of the study. Day 28 efficacy and safety results based on the 1st database lock will be presented with unmasked treatment group, but no disclosure of treatment assignment at individual participant level.

3.5 Study Drug Administration and Compliance

There are three study groups:

- 0.1% AG-86893
- 0.3% AG-86893
- AG-86893 vehicle

All 3 study interventions will be delivered to the study eye as a single eye drop (~40 µL) TID using the provided white, opaque, low-density polyethylene (LDPE) eye dropper bottle.

A single study eye drop will be administered to each participant on Day 1 visit by an independent, unmasked drug administrator who is not involved in participant's treatment and assessment. Study participants will then self-dose a single eye drop of the assigned eye drop to the study eye three times each day approximately 8 hours apart (e.g., morning, afternoon, and evening) until the Day 28 visit.

Two bottles of the assigned study eye drop will be provided to each participant at Day 1. Participants will be instructed to bring both bottles with them for the Day 7 (if in-clinic) and Day 28 visits, or to any unscheduled visits. Both bottles will be collected at Day 28 to be returned to the Sponsor or its designee for destruction.

Treatment compliance will be assessed based on Patient Diary on daily dosing. Good compliance is defined as the following: used the study eye drops at least **70%** of the time during treatment according to diary entries, AND at least **4 of the 6** scheduled applications in the **2 days** prior to the visit.

3.6 Concomitant Therapy

Ocular medications, other than artificial tears and ocular decongestants, are prohibited. Ocular decongestants must be washed out for a minimum of 7 days prior to baseline and use is prohibited 2 days before any study visit. Topical drops for examination procedures, such as anesthetics, dilating agents, fluorescein and lissamine green, are permitted.

Systemic medications that may interfere or confound the evaluation of conjunctival hyperemia are prohibited and should be washed out at least **7 days** prior to baseline. Washout should not commence until after written informed consent has been obtained. Refer to the Manual of Procedures (MOP) for examples of prohibited medications.

Medication considered necessary for the participant's welfare may be given at the discretion of the investigator and must be recorded in the eCRFs. Participants should be instructed to maintain a stable dose of chronic medications during the study whenever possible. All concurrent medications (prescription, over-the-counter and supplements), adjunct therapies, and concurrent procedures will be recorded on the appropriate eCRF page.

3.7 Adverse Events

Any unfavorable and unintended medically significant changes in vital sign (including an abnormal laboratory finding), symptom, or disease after the time of signing the consent form, whether or not related to the study eye drops, will also be recorded as an adverse event (AE). An AE that results in any of the following outcomes is considered a serious adverse event (SAE):

- Death
- Life-threatening AE

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Worsening of the pterygium is not an AE, unless the lesion growth is greater than expected.

The following information will be collected and tabulated for all AEs:

- Verbatim description
- Date of Onset
- Date of Resolution, or Stabilization, or Ongoing
- Severity (Mild, Moderate, Severe)
- Relationship to Study Intervention (Not related, Unlikely related, Possibly related, Related)
- Action taken against study intervention (None, Study eye drop interrupted, or withdrawn)
- Outcome (Recovered/Resolved, recovered/Resolved w/Sequelae, Recovering/Resolving, Not Recovered/Not Resolved, Fatal, Unknown)
- Whether the AE led to study discontinuation
- Whether or not a concomitant medication or procedure was required
- Classified as a serious adverse event (SAE) or not
- SAE Code (Death, Life-threatening, Inpatient, or prolonged hospitalization, Persistent or significant disability/incapacity, Congenital anomaly or birth defect, Other medically important event)

The collection of AEs and SAEs will commence from the time the Informed Consent Form is signed and continue until the last day of study participation (Day 84). Events will be followed for outcome information until resolution or stabilization during the study or continue until **7 days** (for non-serious AEs) or **30 days** (for SAEs) after the last day of study participation (Day 84).

4 STUDY PARAMETERS

4.1 Participant Disposition

Participants who completed the Day 84 visit will be considered as having reached Study Completion, otherwise, they will be classified in the Study Discontinuation group.
Reason(s) for discontinuation will be recorded and could include the following:

- Withdrawal of consent
- Administrative decision by the investigator or Sponsor
- Significant protocol deviation
- Participant noncompliance, or other significant protocol deviation

- Safety concern by the investigator or Sponsor
- Lost to follow-up

Time in the study will be computed as following:

Time in Study (Study duration) = Last Date in study – Date of First Dose + 1

4.2 Study Treatment Group

For safety and PK analysis, participants will be grouped based on the treatment actually received.

For efficacy analysis, it will be based on the treatment assigned per randomization, even it differs from the treatment actually received.

4.3 Primary Efficacy Endpoints

The primary efficacy measure is the overall conjunctival hyperemia score graded by the masked reading center and defined as the average of the scores of each quadrant. The primary efficacy endpoint is the change from baseline in overall conjunctival hyperemia score at Day 28.

The primary efficacy analysis will be based on the modified intent-to-treat (mITT) population.

4.4 Secondary Efficacy Endpoints

Secondary endpoints include:

- Change from baseline in conjunctival hyperemia score in the study quadrant at Day 28

4.5 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- Change from baseline in pterygium vascularity at Days 28 and 56
- Change from baseline in pterygium volume (in selected sites only) at Days 28 and 56
- Change from baseline in pterygium vessel length at Days 28 and 56

4.6 Pharmacokinetic Endpoints (if available)

Data on plasma drug concentrations, if available, will be collected for those participating in the sub-study. Pharmacokinetic endpoints include:

- Individual and mean concentration and standard deviation for Day 1, Day 28, and Day 56
- Partial Area Under the Curve ($AUC_{0\text{-}1h}$) on Day 1 and Day 28

4.7 Safety Endpoints

The Medical Dictionary for Regulatory Activities nomenclature (MedDRA V21.0 at time of SAP publication, or the current version when superseded) will be used to code AEs.

Treatment-emergent AEs are any AEs with an onset date equal to or after the date of the first dose and **within 3 days** after the last dose of the study eye drop. A pre-existing event that worsens after the first dose date is considered a treatment emergent event. Treatment-related AEs are any AEs with a relationship of unlikely related, possibly related or related to study medication, or AEs with a missing relationship.

Safety endpoints include:

- Adverse events
- Concomitant medications
- Concurrent procedures
- Vital signs
- Laboratory tests (urinalysis, hematology, and serum chemistry parameters)
- Electrocardiogram
- Best-corrected visual acuity
- Intraocular pressure using a Goldmann applanation tonometer
- Biomicroscopy
- Tear film break-up time
- Lissamine green conjunctival staining
- Ophthalmoscopy

4.7.1 Events of Special Interest

The following events of special interest will be monitored and may trigger an IDMC meeting, as well as may trigger study treatment interruption.

Abnormal liver function test results:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and (total bilirubin >2x ULN or International Normalized Ratio [INR] >1.5)
- ALT or AST >3x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- Any other safety signals observed during routine data review that warrant convening of the IDMC, in the opinion of the Medical Monitor

Special ocular events:

- Ocular inflammation, including iritis and uveitis
- ≥2 grade increase in corneal edema, corneal staining or edema
- ≥2 grade increase in any cataract
- IOP change of ±7 mmHg from baseline
- Loss of 15 letters or more BCVA

For each type of AE reported, the number and percent of participants will be tabulated based on the preferred term. The tables will be generated by relationship to treatment as well as by system organ class and severity, for treatment-emergent AEs, as well as pre-treatment AEs (occurring prior to first dose) and post-treatment AEs (occurring 3 days after the last dose).

5 ANALYSIS POPULATIONS

Five analysis populations will be defined and used in the statistical analyses: (1) intent-to-treat population, (2) safety population, (3) modified intent-to-treat (mITT) population, (4) per-protocol (PP) population, and (5) if available, PK sub-study population for PK analysis.

5.1 Intent-to-treat population

The intent-to-treat population will include all participants who signed an informed consent for study participation and has received a randomization assignment.

5.2 Safety Population

The safety population will include all randomized participants who receive at least one (1) dose of study eye drop. Results will be presented based on the treatment actually received. All safety analyses will be conducted using the safety population.

5.3 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all randomized participants who receive at least one dose of study eye drop and had conjunctival hyperemia evaluated at both the Day 1 and Day 28 visits. This is the efficacy population. Results will be presented by the treatment assigned during randomization.

The primary efficacy analyses will be conducted using the mITT population.

5.4 Per Protocol Population

The per-protocol (PP) population will consist of all participants in the mITT population who do not have major protocol deviations considered to affect the primary efficacy variable, have been at least 70% compliant with the study treatment according to participant dosing diary AND have been administered IP according to protocol at least 4 of the 6 doses immediately prior to that study visit.

The rules for determining exclusion from the per-protocol population will be made and implemented prior to database lock.

Sensitivity analyses of the primary efficacy analyses will be conducted using the PP population.

5.5 Pharmacokinetic Sub-Study Population (If available)

The Pharmacokinetic (PK) sub-study population, if available, will consist of participants who participate in the PK sub-study and have all blood samples available for PK analysis. Results will be presented by the treatment actually received.

6 STATISTICAL METHODS

All data processing, summarization, and analyses will be performed using SAS® Version 9.4 or higher.

Unless otherwise specified, for continuous variables, descriptive statistics will include the number of participants/eyes (n), mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized using frequency and percentages.

Unless, otherwise stated, missing data will be handled as is, except when the aforementioned dates are required for calculations, the partial dates will have either '01' or 'Jan' imputed with an exception for dates related to AEs where the date closest to the last event (screening, first dose, last dose, etc.) should be used rather than arbitrary '01' of that month.

All efficacy data will be summarized by treatment group and time point using appropriate descriptive statistics. Summaries will be presented for both the mITT and PP populations. Due to the small number of participants that are expected to be enrolled at each center, all summaries and analyses will be performed using data pooled across centers.

Baseline results will be those recorded prior to dosing. In cases where more than one pre-dose observation has been recorded, the **last recording** will be identified as the baseline result.

Study days will be numbered relative to the date of the first dosing. The start of study (Day 1) will be defined as the date on which a participant takes the first dose of any study medication, as recorded on the CRF. Relative to study start, days will be numbered ...-2, -1, 1, 2, ... with Day - 1 being the day prior to the start of study medication (Pre-Dose).

Recorded data will be assigned to evaluation/assessment windows. If more than one clinical evaluation is made within a window for a particular visit, the record with the date closest to the targeted window will be used except for AEs where the **worst assessment** will be used.

Visit windows and analytical windows are defined as follow:

Visit	Targeted Window	Analytical Window
Pre-dose (Screening)	Day -14 to Day -1	Day -18 to Day -1
Visit 1 (First dosing date)	Day 1	Day 1
Visit 2 (optional)	Day 7 (± 3 day)	Day 2 to Day 16
Visit 3 (End of treatment visit)	Day 28 (± 3 days)	Day 17 to 3 days after the last dose and up to Day 42
Visit 4	Day 56 (± 5 days)	Day 43 to Day 70
Visit 5 (End of study visit)	Day 84 (± 5 days)	Day 71 to End of Study

6.1 Participant Disposition

The number and percentage of participants will be summarized by the assigned treatment group and overall for the following:

- Participants screened, randomized, discontinued, completed treatment, completed study
- Participants in the safety population
- Participants in the mITT population
- Participants in the PP population
- Participants in the PK sub-study, if applicable
- Time in treatment, in study
- Participants at each visit
- Participants at each investigational site
- Participants discontinued and reason(s)
- Participants excluded from efficacy analysis and reason(s)

Individual participant disposition data will be listed.

6.2 Treatments

6.2.1 Extent of Study Drug Exposure

Exposure to treatment and treatment compliance will be summarized by the assigned treatment group.

Exposure (i.e., treatment time, days) will be determined as following:

Time in Study Treatment (Treatment duration) = Date of Last Dose – Date of First Dose + 1

Treatment compliance will be determined as study eye drops being used at least 70% of the time since last visit according to patient diary entries, AND at least 4 of the 6 scheduled applications in the 2 days prior to the visit.

Exploratory analyses will be conducted to understand the relationship between exposure and response.

6.2.2 Concomitant Medications

Concomitant medications taken during the study will be coded per the World Health Organization (WHO) Drug dictionary (WHODrug Sept 2017 version at the time of SAP publication, or the current version when superseded). When two medications are coded to the same preferred term, both will be counted.

Medications with partial dates that do not allow determination of whether prior or concomitant will be considered concomitant.

Participant listing of prior and concomitant medication will be presented.

6.2.3 Treatment Discontinuation and Rescue Medications

As there is no pharmacologic treatment for pterygium, no rescue medication is proposed in this study. Therefore, no switch treatment will be considered. The participant will be exited from the study after discontinuation from the study treatment. Investigators may direct participants to the use of eye drops (e.g., artificial tears, decongestant drops, etc.) as appropriate, to alleviate any symptoms related to the participant's condition.

Efficacy assessment collected from the treatment discontinuation exit will be mapped to the next scheduled visit and considered as observed data. (i.e., the mapping will be performed prior to any data imputation if any).

Safety assessment for the treatment discontinuation exit will not be mapped. Instead, it will be treated as the last assessment during treatment period.

6.3 Demographic and Baseline/Screening Characteristics

All demographic and baseline data will be summarized per the assigned treatment and overall using the safety population. The following variables will be presented:

- Age (years)
- Age group (18 - 35, 36 - 50, 51 – 65, ≥ 66 yrs)
- Gender (Female, Male)
- Child Bearing Potentials (for females only – No, Yes. If No, Reason - Bilateral oophorectomy; Bilateral tubal ligation; Hysterectomy; Post-menopausal)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

- Race (American Indian or Alaska Native; Asian; Australian Aboriginal or Torres Strait Islander; Black; Native Hawaiian or Other Pacific Islander; White. If Other, list of specified.)
- Iris Color (Black; Blue; Brown; Green; Grey; Hazel; Other. If Other, list of specified.)

6.4 Protocol Deviations

Individuals participant listing of protocol deviation will be provided.

6.5 Efficacy Evaluation

All efficacy analyses will be based on the mITT population.

The primary statistical approach for assessment of difference among the treatment groups in change from baseline to Day 28 in conjunctival hyperemia score will be based on a mixed effect model. Significant baseline characteristics and their interaction might be included as covariant. Mean changes for each treatment group and the differences in mean changes will be estimated with the Least-Square means generated by the mixed model. Multiplicity adjustment will be conducted with Bonferroni approach.

6.5.1 Primary Efficacy Variables

The primary endpoint is the change from baseline in overall conjunctival hyperemia score at Day 28, so, scores from Days 1 and 28 will be analyzed. The null hypothesis is that there is no difference between AG-86893 and AG-86893 vehicle in the change from baseline to Day 28 in the overall conjunctival hyperemia score. The alternative hypothesis is that the active group is different from vehicle in the change from baseline to Day 28 in the overall conjunctival hyperemia score. It was expected that the active group is at least 50% better than that of vehicle in the change of overall conjunctival hyperemia score.

To reserve the familywise error rate, the main treatment effect will be first assessed at the global level at $\alpha = 0.05$. If this is significant, then pairwise comparisons will be conducted using the Bonferroni adjustment for multiplicity between 1) 0.1% AG-86893 and AG-86893 vehicle; 2) 0.3% AG-86893 and AG-86893 vehicle; and 3) 0.1% AG-86893 and 0.3% AG-86893 for dose selection.

6.5.2 Secondary and Exploratory Variables and Sub-Study Variables

Secondary, exploratory and exploratory sub-study numerical endpoints will be explored using the same approach as outlined for the primary efficacy analysis and might include the following:

- Change from baseline in conjunctival hyperemia score at the study quadrant at Days 28
- Change from baseline in pterygium vascularity at Days 28 and 56

- Change from baseline in pterygium vessel length at Days 28 and 56
- Change from baseline in Pterygium volume at Days 28 and 56
- IOP
- BCVA in letters read correctly
- Biomicroscopy parameters for conjunctiva, cornea, and iris. Lens status scale
- TFBUT
- Lissamine green conjunctival staining score
- Fundus
- Participant questionnaire

6.5.3 Sensitivity Analysis

In order to assess the robustness of the primary efficacy results derived from the mITT population, a sensitivity analysis will be conducted using the PP population with the above-mentioned mixed effect model for the primary efficacy endpoint.

6.6 Safety Analyses

The safety and tolerability of AG-86893 will be determined by incidence and severity of treatment emergent AEs, abnormal changes in vital signs, clinical and laboratory results, BCVA, IOP, eye examinations, biomicroscopy and ophthalmoscopy examinations.

All safety analysis will be based on the Safety population.

6.6.1 Adverse Events

All AEs reported during the study period will be recorded and coded using MedDRA terminology (MedDRA V21.0 at time of SAP publication, or the current version when superseded). An AE will be considered as treatment-emergent adverse event (TEAE) if it has an onset during the treatment period. A pre-existing event that worsens after the first dose date and within 3 days after the last dose date is considered a treatment emergent event.

The incidence of all TEAEs will be summarized using system organ class and preferred term by treatment group and overall. Adverse events will also be presented by relationship and severity. Further, serious adverse events and those events leading to discontinuation will also be presented.

Participants may have more than one AE per system organ class and preferred term. At each level of participant summarization, a participant will be counted once if they reported 1 or more events and will be reported with the highest severity. In cases where severity or relationship is missing, the most conservative approach will be taken (i.e. highest severity and assumed to be related).

The following overall summary will be presented by treatment and overall:

- Total number and percent of participants with
    - All AEs
    - Mild AEs
    - Moderate AEs
    - Severe AEs
    - Not related AE
    - Related AE
    - AE leading to death
    - AE leading to treatment discontinuation

- Total number and percent of participants with SAE
    - Mild SAE
    - Moderate SAE
    - Severe SAE
    - Not related SAE
    - Related SAE
    - SAE leading to Death
    - SAE leading to treatment discontinuation

The following summary tables of AEs will be presented by treatment and overall:

- Total number and percent of participants with AEs
    - By system organ and preferred term
    - By frequency for SAEs

- Total number and percent of participants treatment-related AEs
    - By preferred term and severity

The number and percent of participants with significant vital sign and laboratory findings during study will be summarized by group and overall.

The number and percent of participants with the following special interest events will be summarized by group and overall.

- Abnormal liver function (as defined in section 4.7.1)
- Ocular events

Participant level listing will be provided with related information that include AE onset/resolution date, study days, duration, preferred terms, relationship to study eye drop, action taken, outcome, and sorted by treatment, subject ID and onset date.

6.6.2 Vital Sign, Laboratory and Ocular Findings

The following assessments will be summarized by group and overall for each study visit.

- Tear film break-up time
- Lissamine green conjunctival staining
- Intraocular pressure
- Best-corrected visual acuity
- Electrocardiogram

The number and percent of participants with abnormal findings at each visit for the following assessments will be summarized by group and overall.

- Slit-lamp biomicroscopy examination
- Dilated fundus examination

6.7 Pharmacokinetic Analyses (if data available)

Pharmacokinetic analysis, if applicable, will be based on the PK sub-population using a model-independent approach.

Drug plasma concentration data will be summarized for each dose by descriptive statistics using SAS®. AUC_{0-1h} will be estimated using linear trapezoidal method.

Individual and mean concentration at each time point, C_{max}, T_{max}, and AUC_{0-1h}, where applicable, will be presented by treatment group for Day 1 and Day 28. On Day 56 individual and mean ± SD will be presented.

Individual and mean concentration-time curves will be presented for Day 1, and Day 28 to illustrate the dynamic change of plasma concentration from hour 0 to 1.

6.8 Patient Questionnaire

Severity and frequency scores of each symptoms of the study eye will be summarized by group for each visit.

7 CONVENTIONS AND ALGORITHMS

7.1 Decimal Points

All summary tables involving percentages will round the percentages off to 1 decimal place.

All summary tables involving descriptive statistics of continuous variables will round the mean and median to 1 decimal place more than the variable's standard form and round the standard deviation to 2 decimal places more than the variable's standard form. The standard form of a percent change variable is 0 decimal places.

7.2 Study Days

Study days will be computed for each visit and AE event.

Study Days = Date of Visit/Event - Date of First Dose + 1

Or, if the visit/event occurs prior to the Day 1

Study Days = Date of Visit/Event - Date of First Dose

Date of First Dose is the Day 1 Visit date.

Last Date in study is the Day 84 Visit or the last visit where the participant was seen by the investigator. If lost-to-follow-up, the last date of contact is the Last Date in study.

If a participant had contact with the site after the final visit (e.g. for AE follow up), the last visit date will be the Last Date in study, not the contact date.

Time in Study (Study duration) = Last Date in study – Date of First Dose + 1

Time in Study Treatment (Treatment duration) = Date of Last Dose – Date of First Dose + 1

7.3 Multiple Occurrence of Events

When summarizing AEs, potentially clinically important laboratory findings, potentially clinically important vital signs, and participants with multiple occurrences of an event will be counted only once in the summary. When AEs are summarized by severity, if the participant has multiple occurrences of the same AE, the most severe will be used for the summary.

When summarizing concomitant medications by drug class and by preferred term, if two medications are coded to the same preferred term, both will be counted for a participant.

7.4 Summary Tables/Listings

Summary tables, participant listings, graphs and any supportive SAS output will include a "footer" of explanatory notes that will indicate, when applicable:

- date of data extraction

- date and time of output generation
- SAS program name that generates the output

Null summary tables will be presented with a note stating that "No Participants Met Criteria."

Individual participant listings will be provided as support for summary tables and serve as a data source substitute when a summary table is deemed either inappropriate or unnecessary. All participant listings will be sorted by participant number. When applicable, the participant listings will include the visit date, and days relative to the start of first treatment.

7.5 **Pharmacokinetic** Data (if available)

All Day 1 pre-dose concentration values below the limit of quantification (BLOQ) will be treated as zero. Due to the small sample size in this sub-study and the anticipated low plasma concentration, for the purpose of mathematical operation, instead of treating post-dose concentration BLOQ values as zero for statistical analyses, these values will be set as "missing". However, for the display of the order statistics (minimum, first quartile [Q1], median, third quartile [Q3], maximum), if at least 1 reading is BLOQ for the time point, then the minimum value will be displayed as "BLOQ". If more than 50% of the readings are BLOQ for the time point, then the minimum and median values will be displayed as "BLOQ". If all values are BLOQ for the time point, then all statistics will be displaced as "BLOQ".

BLOQ values will be presented as "BLOQ" in the concentration data listing.

8 INTERIM ANALYSES

No interim analysis for efficacy is planned for this study.

Two database locks are scheduled for this study. The first database lock will occur after all participants completed the Day 28 visit for the primary efficacy analysis (including grading by the central reading center), localized pterygium conjunctival hyperemia, PK analysis (if applicable), and summary of safety data gathered up-to-date. The final lock will occur at study completion (Day 84) for longer term assessment of safety, tolerability, treatment effect, and plasma concentrations monitoring of AG-86893 (if applicable). Eligibility for analysis will be determined prior to each database lock.

9 QUALITY CONTROL AND VALIDATION

Derived datasets will be independently reprogrammed by a second programmer. The separate datasets produced by the two programmers must match 100%.

Tables will be independently reprogrammed by a second programmer for numeric results. Statisticians will be involved in the process of validating tables that include inferential statistical results.

Figures will be checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

Please refer to the following Trial Runners Standard Operating Procedures for details on related activities/procedures.

CN-SOP-6001 Preparation & Communications of Key Results
CN-SOP-6002 SAP Development and Maintenance
CN-SOP-6003 Analysis Datasets Development
CN-SOP-6301 Running of Statistical Programs
CN-SOP-8001 SAS Programming Standards
CN-SOP-8002 SAS Requirements Specifications
CN-SOP-8003 Program Design-Implementation
CN-SOP-8004 Program Verification and Validation
CN-SOP-8005 Running of SAS Programs

10 REFERENCES

1. Stein, C., Offen, W. (2005). Analysis of Clinical Trials Using SAS: A Practical Guide. SAS Press: Cary, NC.
2. Hochberg, Y., Tamhane, A.C. (1987). Multiple Comparison Procedures. Wiley, New York.
3. Hommel, G. (1988). A stagewise rejective multiple test procedure based on a modified Bonferroni test. Biometrika. 75, 383 test. Biometrika. 75, 383-386.

(more references in study protocol Section 11)

APPENDIX 1 GLOSSARY OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AS-OCT	anterior-segment optical coherence tomography
BCVA	best-corrected visual acuity
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CONSORT	consolidated Standards of Reporting Trials
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDTA	ethylenediaminetetraacetic acid
FGF-2	fibroblast growth factor-2
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information
HPMC	hypromellose; hydroxypropyl methylcellulose
HREC	Human Research Ethics Committee
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	International Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDPE	low-density polyethylene
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMPs	matrix metalloproteinases

MOP	Manual of Procedures
NOAEL	no-observed-adverse-effect-level
PDGFR	platelet-derived growth factor
PDGFRβ	platelet-derived growth factor receptor β
PK	pharmacokinetic(s)
PP	per-protocol
RBC	red blood cell
RLD	reference listed drug
QC	quality control
QID	4 times daily
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
T_{max}	time to reach maximum plasma concentration
TID	3 times daily
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
YAG	yttrium aluminium garnet

APPENDIX 2 SAMPLE SAS CODE FRAGMENT

For estimation of main treatment effect:

SAS pseudo code for main treatment effect and LS mean estimation:

```
proc mixed data=xxx;
  where mitt='Y';  *select the designated analysis population here (e.g.,
itt, pp);
  class TREAT;  *include other categorical covariants;
  model CHANGE_OVERALL = TREAT/ddfm=statterth; *if any, include covariants
and interaction terms;
  lsmeans TREAT/pdiff cl adjdfe=row adjust=bon;
  (ods output statements)
run;
```

SAS pseudo code for estimation of proportions and 95% CI, and the difference in proportions:

```
proc freq data=xxx;
  tables  VAR1 * VAR2/ alpha = 0.05 riskdiff (CL = MN);
  * Miettinen and Nurminen inverted score test;
(ods statements)
run;
```