Protocol No./Title: A Phase 2b Randomized, Double-masked, Active-controlled, Dose-response Study of the Safety and Efficacy of H-1337 in Subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension

NCT No.: 05913232

Document Date: 30 January 2024

D. Western Therapeutics Institute, Inc.

Statistical Analysis Plan

Protocol Number: H1337-C202
Investigational Drug Product: H-1337
IND Number: 131440

A Phase 2b Randomized, Double-masked, Active-controlled, Dose-response Study of the Safety and Efficacy of H-1337 in Subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension

Author(s):	Esmeralda Meunier, M.Sc.
Document Status:	Final
Version Dates:	Version 1.0: 19SEP23 Version 2.0: 30JAN24

Statistical Analysis Plan

REVIEWERS APPROVAL SIGNATURES

Protocol: H1337-CS202

A Phase 2b Randomized, Double-masked, Active-controlled, Dose-response Study of the Safety and Efficacy of H-1337 in Subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension

Date: 30JAN2024

The persons listed below are authorized to sign the Statistical Analysis Plan for this study.

Yuichi Hidaka Date: Jan. 31/2024

Mr. Yuichi Hidaka
D. Western Therapeutics Institute, Inc.

Date: 01 FEB 2024

Esmeralda Meunier, M.Sc.
Biostatistician
Z-estima Ltd.

Contents

Summary of Changes

Version 1.0	Initial Version
Version 2.0	Updates to reflect Protocol Version 3.0 and comments received from U.S. FDA on 4 January 2024. The Intent-to-Treat population is redefined as per FDA's comments. The main analyses are conducted on the Intent-to-Treat population instead of the Per-Protocol population. The repeated measures model of the main analysis contains additional information as per FDA's feedback. The random effect is updated to subject instead of center. Details on diurnal intraocular pressure calculations are added.

Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Distance Visual Acuity
b.i.d.	twice a day
CI	Confidence Interval
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimetre of mercury
OD	right eye
OHT	Ocular Hypertension
OS	left eye
OU	both eyes
POAG	Primary Open Angle Glaucoma
PP	Per-Protocol
PT	Preferred Term
q.a.m.	every morning
q.p.m.	every afternoon/evening
RGC	retinal ganglion cells
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHODRUG	World Health Organization Drug Dictionary

1 Introduction

This document presents the statistical analysis plan (SAP) for D. Western Therapeutics Institute, Inc. Protocol H1337-CS202: A Phase 2b Randomized, Double-masked, Active-controlled, Dose-response Study of the Safety and Efficacy of H-1337 in Subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OHT). This SAP describes the endpoints, datasets and analyses planned for the efficacy and safety of this study. The variables and methods described in this plan supersede those described in the protocol. If revisions are needed after finalizing, then this document will be amended. All SAP amendments will be finalized prior to locking the database. All deviations from the analyses described in the final SAP will be noted in the clinical study report.

This analysis plan is based on protocol version 3.0, dated 19JAN2024.

1.1 Study Background

Glaucoma is a slowly progressive optic neuropathy characterized by a loss of retinal ganglion cells (RGC) and optic nerve axons resulting in vision loss. As elevated intraocular pressure (IOP) is a major risk for loss of visual field and optic nerve, reduction of IOP by medical, laser and/or surgical means is the current standard of care for patients with glaucoma. While there are many therapies available, each has its own benefits and risks. Some patients, even with proper diagnosis and treatment, still continue to have progressive glaucomatous loss of visual function and/or optic nerve.

H-1337 is a selective multi-kinase inhibitor, and the proposed mechanism of action of the compound is hypothesized to involve inhibition of kinases that play a role in controlling intracellular cytoskeletal dynamics and contractility. While the regulation of IOP by the conventional (trabecular) outflow pathway is complicated, extracellular matrix expression and trabecular meshwork cytoskeletal shape and contractility appear to be important to control outflow resistance.

In a previous controlled study, H-1337 Ophthalmic Solution showed clinically and statistically significant ocular hypotensive activity and was well tolerated, with a relatively low incidence of hyperemia. The present study aims to extend the previous findings with additional concentrations and doses, as well as including an active control (timolol ophthalmic solution).

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the ocular hypotensive efficacy of 3 dose regimens of H-1337 compared to timolol maleate 0.5% in subjects with POAG or OHT treated for up to 28 days.

2.2 Secondary Objective

The secondary objective of this study is to evaluate the local ocular and systemic safety of 3 dose regimens of H-1337.

2.3 Exploratory Objective

The exploratory objective of this study is to evaluate the efficacy of diurnal IOP measurements of 3 dose regimens of H-1337 compared to timolol 0.5%.

2.4 Primary Efficacy Endpoint

The primary efficacy measure is the mean change in IOP from Baseline IOP (mmHg) in the study eye for each group on Day 28 at each matched time point as compared to Timolol.

2.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints of the study are as follows:

- The observed IOP, change from Baseline, and % change from Baseline in IOP in the study eye at each matched time point at each visit.
- The observed mean diurnal IOP, change from Baseline and % change from Baseline in the study eye in mean diurnal IOP at each visit,
- The proportion of subjects with IOP ≤ 18 mmHg in their study eye at each time point at each visit, and with the mean diurnal IOP ≤ 18 mmHg in the study eye for each visit.

2.6 Safety Endpoints

The safety endpoints of the study are as follows:

- Incidence of Ocular and systemic Adverse Events (AE),
- The observed blood pressure and pulse, and change from Baseline at each visit,
- The observed best-corrected visual acuity (BCVA) and change from Baseline at each visit.

3 Study Design and Procedures

3.1 Overall Study Design

This is a parallel group, double-masked, active-controlled study to evaluate the ocular hypotensive efficacy of 3 dose regimens of H-1337 compared to timolol maleate 0.5% in subjects with POAG or OHT treated for up to 28 days.

Each subject's participation will consist of two phases: a Screening Phase (Screening and Baseline Visits) where subjects will suspend dosing of any current ocular hypotensive therapy, and a Dosing Phase, starting on Day 1.

Following the washout period (if required), the subject will return for applicable inclusion/exclusion evaluations at the Baseline Visit (Day 1). A subject meeting all inclusion/exclusion criteria at Pre-T_0 will be randomized to the Investigational Product (IP). Both eyes will be dosed and evaluated for safety throughout the trial.

Dosing will be initiated at Day 1. Subjects will be dosed for up to 28 days during which time they will be monitored for safety, tolerability, and efficacy.

Subjects will be randomized to 4 arms:

- Group 1: H-1337 0.6% Ophthalmic Solution b.i.d.
- Group 2: H-1337 1.0% Ophthalmic Solution b.i.d.
- Group 3: H-1337 1.0% Ophthalmic Solution q.a.m. and H-1337 placebo q.p.m.
- Group 4: Timolol 0.5% Ophthalmic Solution b.i.d

The trial will evaluate the safety and efficacy of 3 dose regimens of H-1337 and timolol maleate (0.5%, b.i.d.) OU for 28 days.

Efficacy evaluation will be made based upon the study eye.

3.2 Schedule of Visits and Assessments

The schedule of visits is defined as follow:

- Screening Visit
- Day 0
- Day 1
- Day 7
- Day 14
- Day 28

A schedule of study assessments and procedures is available in Appendix 1.

3.3 Sample Size Justification

The sample size is driven by interest in the IOP lowering effect of H-1337. The study is designed to test whether one or more concentrations of H-1337 are non-inferior to the timolol control in the reduction of IOP. As benefit is represented by a negative number, non-inferiority is achieved when the upper limit of the confidence interval of the difference in treatment (H-1337 minus Timolol) is strictly lower than the non-inferiority margin.

A sample size of 45 subjects per group will allow for at least 90% power to establish non-inferiority of H-1337 over Timolol based on a non-inferiority limit of 2 mmHg, a standard deviation of 3.0 mmHg and a 1-sided t-test (alpha=0.05).

Assuming that 10% of the subjects will not be eligible in the Intent-to-Treat (ITT) population, a total of 50 subjects per group is required.

3.4 Analysis Populations

3.4.1 Safety Analysis Population

The Safety population is comprised of all randomized subjects who receive at least one dose of IP. If subjects received the wrong IP at any time during the study, the IP actually received for the majority of the study will be used as the treatment group for that subject.

3.4.2 Intent-to-Treat Population

The ITT population is defined as all randomized. Subjects will be analyzed according to the treatment assigned at randomization, irrespective of dosing adherence or any deviations in the IP received.

3.4.3 Per-Protocol Population

The Per-Protocol (PP) population is defined as subjects from the ITT population who satisfy pre-randomization inclusion/exclusion criteria, receive at least dose of IP and complete at least one on-therapy study visit. Individual subject visits and data points that do not satisfy protocol criteria may be excluded from PP analyses. Evaluability will be determined prior to unmasking of treatment assignments.

4 Statistical Methodology

4.1 Definitions and Conventions

Listings present the subjects individual data, while summary tables present the summary statistics of subjects data.

Summary statistics will be presented for continuous variables, by way of n, mean, standard deviation (SD), median, minimum and maximum. For categorical variables including binary variables, frequency counts and percentages will be presented. Percentages will be calculated using the total number of subjects per treatment groups or the total number of subjects with an assessment per treatment groups, depending on the nature of the analysis.

In addition, 95% 2-sided confidence intervals (CIs) will be presented, where relevant. In case of percentages, the CI will be computed using the Clopper-Pearson method. The CI will be computed for continuous variables using a t-test analysis.

Summary statistics will be displayed by treatment groups, which will be labelled as follow:

- Group 1: H-1337 0.6%
- Group 2: H-1337 1.0% b.i.d
- Group 3: H-1337 1.0% q.a.m
- Group 4: Timolol 0.5%

Baseline Value is defined as the last non-missing value prior to the first IP administration for vital signs, BCVA, biomicroscopy and dilated ophthalmoscopy (Day 1 Pre-T_0 for vital signs, BCVA and biomicroscopy; Screening for dilated ophthalmoscopy). For IOP and conjunctival hyperemia grading, time-matched baseline values are defined at Pre-T_0 on Day 1 (Visit 3), T_0+2 hours, T_0+4 hours, T_0+8 hours and T_0+12 hours on Day 0 (Visit 2). For mean diurnal IOP, baseline is defined at Day 0.

Change from Baseline is defined as the difference in value of the assessment between the considered visit and the baseline value. In the case of IOP and conjunctival hyperemia grading, change from Baseline is the difference in value of the assessment between the considered visit at a particular timepoint and the corresponding baseline value.

Study eye is defined as the eye that meets all entry criteria including the IOP criteria after washout. Should both eyes meet the criteria then the study eye will be the eye with the higher 8 am IOP at Baseline (Day 1). If both eyes have the same 8 am IOP at Baseline (Day 1), the study eye will be the right eye.

SAS® version 9.4 or above will be used to perform the analyses.

4.2 Handing of Missing Data

To reduce the incidence of missing data, sites and subjects will be trained in methods to encourage continued participation to maximize the completion rate and overall quality of the trial. With regard to the primary efficacy variable, IOP, there are steps taken in the procedure for collecting these data to minimize the likelihood of spurious data.

Missing data will not be imputed.

4.3 Adjustment for Multiplicity

To account for the multiple comparisons of the primary endpoints, adjustment for multiplicity will be fulfilled by using a hierarchical testing, based on a fixed-sequence procedure defined in Table 1.

First, the primary endpoint is tested for non-inferiority at all 5 time points at Day 28 and all 4 on-treatment time points at Day 1 for the first pre-defined Group comparison listed in Table 1. If the upper limit of the 2-sided 95% CI of the difference between H-1337 and Timolol is strictly lower than the value 1.5, then non-inferiority is concluded. If non-inferiority is concluded at the 9 timepoints, then testing of the second listed Group Comparison in Table 1 can take place at the 2-sided alpha level of 0.05. Otherwise, non-inferiority cannot be concluded and no further formal testing takes place.

The same sequential approach is then applied to the remaining endpoints listed in Table 1. Endpoints are tested in the order defined in Table 1.

For the first 3 rows in Table 1, non-inferiority at the 1.5 threshold at all 9 timepoints must be shown to allow to proceed to the next row. For the last 3 rows in Table 1, non-inferiority at the 1.0 threshold at 5 or more timepoints must be shown to allow to proceed to the next row.

Table 1 Pre-defined Sequence for Hierarchical Testing

Order	Group Comparison	Non-Inferiority Criteria
1	H-1337 1.0% Ophthalmic Solution b.i.d. vs Timolol 0.5% Ophthalmic Solution b.i.d	1.5 threshold at all 9 time points
2	H-1337 0.6% Ophthalmic Solution b.i.d vs Timolol 0.5% Ophthalmic Solution b.i.d	1.5 threshold at all 9 time points
3	H-1337 1.0% Ophthalmic Solution q.a.m. vs Timolol 0.5% Ophthalmic Solution b.i.d	1.5 threshold at all 9 time points
4	H-1337 1.0% Ophthalmic Solution b.i.d. vs Timolol 0.5% Ophthalmic Solution b.i.d	1.0 threshold at 5 or more time points
5	H-1337 0.6% Ophthalmic Solution b.i.d vs Timolol 0.5% Ophthalmic Solution b.i.d	1.0 threshold at 5 or more time points
6	H-1337 1.0% Ophthalmic Solution q.a.m. vs Timolol 0.5% Ophthalmic Solution b.i.d	1.0 threshold at 5 or more time points

4.4 Disposition

The number and percentage of subjects enrolled (signed informed consent), randomized, and the number of subjects who receive at least one dose of IP will be summarized by treatment groups and overall. The following additional summaries will be presented:

- The number and percentage of subjects included in the Safety Analysis population, the ITT population and the PP population;
- The number and percentage of subjects who complete the study;
- The number and percentage of subjects who withdraw from the study and the reason for withdrawal;
- The number and percentage of subjects with a protocol violation and with a major protocol violation;
- The number and percentage of subjects who attend a study visit, for each study visit.

Percentages will be calculated on the number of subjects who are randomized.

4.5 Washout Period

A listing including information on whether a subject enters the washout period or not, the type of used ocular hypotensive therapy and the length of the washout period will be created for each subject in the Safety Analysis Population.

4.6 Demographics and Baseline Characteristics

Gender, age, ethnicity, race and iris colour will be summarized by treatment groups and overall.

Age will be calculated as the number of years, as an integer value, from date of birth to the date of the informed consent signature. In other words, age is the truncated integer of the difference between date of birth and the date of the informed consent signature.

Baseline IOP, BCVA and central corneal thickness (measured by pachymetry) will be summarised by treatment group (and overall) and eye (study eye and fellow eye). Central corneal thickness will be calculated as the mean of the 3 collected measurements.

Gonioscopy

The number and percentage of subjects with a confirmed normal anatomy will be summarized by treatment group (and overall) and eye. In addition, the number and percentage of subjects within each category of the Shaffer grade will be summarized by treatment group (and overall) and eye (study eye and fellow eye).

Visual Fields

The number and percentage of subjects with a normal, abnormal not clinically significant and abnormal clinically significant visual fields assessment will be summarized by treatment group (and overall) and eye (study eye and fellow eye). This will be calculated on the subgroup of eyes with a visual fields assessment meeting the protocol definition of reliability.

Summaries will be presented for the Safety, ITT and PP populations.

4.7 Medical and Ocular History

Medical and ocular history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26 or higher.

The number and percentage of subjects under each medical history term, coded by system organ class (SOC) and preferred term (PT), will be summarized by treatment for the safety population. Ocular history will also be presented on both the study eye and the fellow eye. All percentages will be based on the number of subjects or eyes in the safety population within each treatment group. If a subject has a medical/ocular history term more than once, the subject will be counted only once under any given SOC or PT.

4.8 Prior and Concomitant Medications

All medications will be coded using the World Health Organization drug dictionary (WHODRUG) version January, 2023 or higher.

Incidence of prior and concomitant medication will be presented by treatment, Anatomical Therapeutic Chemical (ATC) Level 4 and PT for the safety population. Ocular medication will be presented on both the study eye and the fellow eye combined.

Prior medications are those that start and stop before exposure to treatment. Concomitant medications are all medications taken during the study period, including those started before but ongoing at the time of the first IP dose.

A subject with more than one occurrence of the same medication in a particular ATC class will be counted only once in the total of those reporting medications in that particular ATC class.

4.9 Concomitant Procedures

Procedures will be coded using the MedDRA Version 26 or higher.

The number and percentage of subjects under each procedure term, coded by SOC and PT, will be summarized by treatment for the safety population. Percentages will be based on the number of subjects in the safety population within each treatment group. If a subject has a procedure term more than once, the subject will be counted only once under any given SOC or PT.

4.10 Treatment Exposure

The number and percentage of subjects by number of missed doses will be summarized by eye and treatment. In addition, the number of missed doses will be summarized by eye and treatment using summary statistics for continuous variables.

Duration of drug exposure is defined as the number of days a subject receives an IP dose. The number and percentage of subjects in each category will be summarized by eye and treatment. The categories are: <7 days, 7 to <14 days, 14 to <21 days, 21 to <28 days, ≥28 days.

4.11 Efficacy Analyses

All efficacy analyses will be performed using both the ITT and PP populations. Missing values will not be imputed.

4.11.1 Primary Efficacy Analyses

Change from Baseline in IOP (mmHg) at Day 28 and Day 1 (on-treatment time points) in the study eye is the primary efficacy endpoint. It will be summarized by timepoint and treatment group in the ITT population primarily and in the PP population secondarily. The endpoints will be analysed using an analysis of covariance (ANCOVA) model including baseline value and treatment groups as independent variables. The least square (LS) means, standard error (SE) and 2-sided 95% CI will be reported for each treatment group at each post-randomization visit.

In addition, the differences between treatments (H-1337 vs Timolol) will be calculated for each H-1337 treatment group. A time-matched longitudinal model adjusting for baseline and including a random effect for subject will be used to calculate the LS mean, SE, and 2-sided 95% CI for the between-treatments differences. The model will also be tested for treatment by visit and treatment by time points interactions. If no interactions are detected, the main effect model will be used. The variance-covariance matrix-structure used in the model will be the unstructured (TYPE=UN). If convergence is not achieved, a compound-symmetry structure will be used (TYPE=CS).

The testing procedure for non-inferiority will be performed as described in Section 4.3.

Missing values will not be imputed.

All summaries generated for IOP will be using the mean/median value recorded in the case report form.

4.11.2 Secondary Efficacy Analyses

The secondary efficacy endpoints are all related to IOP in the study eye.

Change from Baseline in IOP at Day 7 and Day 14 in the study eye will be summarised by visit, timepoint and treatment group. The endpoints will be analyzed using an ANCOVA model including baseline value and treatment groups as independent variables. The LS means, SE and 2-sided 95% CI will be reported for each treatment group at each post-randomization visit.

In addition, the differences between treatments (H-1337 vs Timolol) will be calculated and summarised by visit, timepoint and treatment group (for each of the H-1337 groups). The ANCOVA model will be used to calculate the LS mean, SE, and, 2-sided 95% CI for the between-treatments differences.

Similar analyses will be performed for the following endpoints:

- IOP,
- percentage change from Baseline in IOP,
- mean diurnal IOP (12-hour diurnal),
- change from Baseline in mean diurnal IOP (12-hour diurnal),
- percentage change from Baseline in mean diurnal IOP (12-hour diurnal),
- mean diurnal IOP (8-hour diurnal),
- change from Baseline in mean diurnal IOP (8-hour diurnal),
- percentage change from Baseline in mean diurnal IOP (8-hour diurnal).

Where multiple IOP assessments are made on the same day, mean diurnal IOP (12-hour diurnal) is defined as the average of all multiple assessments (Pre T_0 is excluded from the calculation). Mean diurnal IOP (8-hour diurnal) is defined as the average of all assessments up to 04:00pm (Pre T_0 is excluded from the calculation). The visit at which a subject is missing more than (>) 2 assessments for the calculation of mean diurnal IOP will be excluded from the analysis in the PP population.

The number and percentage of subjects with IOP ≤18 mmHg will be summarized by visit, timepoint and treatment group. The 2-sided 95% CI will be calculated using the Clopper-Pearson method. In addition, the difference in proportions between treatments (H-1337 vs Timolol) will be calculated and summarised by visit, timepoint and treatment group (for each of the H-1337 groups). The 2-sided 95% CI for the difference in proportions will be computed using the Wald method.

A similar analysis will be performed for the following 2 endpoints:

- number and percentage of subjects with mean diurnal IOP (12-hour diurnal) ≤18 mmHg, and
- number and percentage of subjects with mean diurnal IOP (8-hour diurnal) ≤18 mmHg.

4.11.3 Additional Efficacy Analyses

Intraocular Pressure

All analyses performed for IOP in the study eye will be repeated for the fellow eye.

4.12 Safety Analyses

All safety analyses will be performed in the Safety population. Missing data will not be imputed.

4.12.1 Adverse Events

Treatment-emergent adverse events (TEAE) are defined as AEs starting on or after the first dose of IP. A pre-existing event that worsens in severity after receiving the first dose of IP is treated as a new TEAE with date of onset set to the date of the increased severity. Summary tables will include TEAEs only. TEAEs will be summarized by treatment and overall. Non-treatment emergent AEs will be listed only.

An ocular event is an event where the site of the event is reported as both eyes (OU), right eye (OD) or left eye (OS).

Proportion of subjects reporting an event will be calculated based on the number of subjects in the corresponding treatment group. The 95% CI will be calculated using the Clopper-Pearson method.

The number and percentage of subjects reporting any event, any non-ocular event, and any ocular event will be summarized.

An overall summary table of TEAE will be provided by treatment group and location (non-ocular and ocular) for the following categories:

- Number and percentage of subjects with a TEAE
- Number and percentage of subjects with a treatment-related TEAE
- Number and percentage of subjects with a TEAE leading to IP discontinuation
- Number and percentage of subjects with a TEAE leading to study discontinuation
- Number and percentage of subjects with a serious TEAE
- Number and percentage of subjects with a treatment-related serious TEAE
- Number and percentage of subjects with a TEAE leading to death

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26 or higher. The following summaries will be provided:

- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- Serious TEAEs by SOC and PT
- TEAEs leading to IP discontinuation by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAE leading to death by SOC and PT
- TEAEs by SOC, PT, and maximum severity
- Treatment-related TEAEs by SOC and PT

In the above summaries, when multiple events of the same SOC or PT are reported, subjects are counted only once under each SOC and PT. If a subject has the same AE on multiple occasions, the highest severity (severe, moderate, mild) recorded for the event will be presented. Missing severity will be considered as severe. Events reported as definitely, probably or possible related to IP and events with a missing relationship will be considered as related to IP. The above summaries will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

In addition, listings for SAEs, deaths, and AEs leading to IP discontinuation will be provided.

4.12.2 Vital Signs

Heart rate and blood pressure (systolic and diastolic), and change from baseline, will be summarized by treatment group, visit and timepoint.

4.12.3 Best-corrected Visual Acuity

Best-corrected visual acuity (BCVA) and change from Baseline in BCVA will be summarized in the logMAR scale by eye (study eye and fellow eye), visit and treatment group.

In addition, categorical summaries of change from Baseline in BCVA will be generated. The number and percentage of subjects with >2 lines loss, >1-2 lines loss, 0-1 line loss, >0 to 1 line gain, >1 to 2 lines gain and >2 lines gain will be summarized by eye (study eye and fellow eye), visit and treatment group.

4.12.4 Slit Lamp Biomicroscopy

The number and percentage of subjects within each category of slit lamp examinations will be summarized by treatment group, visit, timepoint and eye (study eye and fellow eye).

4.12.5 Conjunctival Hyperemia Grading

The number and percentage of subjects within each grading category will be summarized by treatment group, visit, timepoint and eye. In addition, shift from baseline will be summarized by treatment group, visit, timepoint and eye (study eye and fellow eye).

4.12.6 Dilated Ophthalmoscopy

The number and percentage of subjects within each assessment category will be summarized by treatment group, visit and eye (study eye and fellow eye).

4.13 Subgroup Analysis

No subgroup analyses will be performed.

4.14 Interim Analysis

No interim analysis is planned.

5 Summary of Changes from the Protocol

The sample size section of the protocol refers to a non-inferiority limit of 2, while the thresholds of 1.5 and 1 will be used in the analysis of the primary endpoint.

In the protocol, the primary endpoint refers to Day 28 only. In the SAP, the primary endpoint is concluded as non-inferior based on the 5 time points at Day 28 and the 4 on-treatment time points at Day 1.

6 List of Programming Summary & Analysis Tables

The list and layout of the summary tables and listings will be described in a separate document.

7 Appendices

7.1 Appendix 1 – Time and Event Schedule

Assessments/Procedures[1]	**Screening (-49 to 1 days)**	**Day 0 (-4 to -1)**	**Day 1 Baseline/Randomization**	**Day 7** (± 1 day)	**Day 14** (± 1 day)	**Day 28** (± 2 days) **Last Dosing Day**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Informed Consent	X					
Medical and Ocular History	X	X	X			
Concomitant Medications/Procedures	X	X	X	X	X	X
Adverse Event Assessments	X	X	X	X	X	X
Randomization			X			
IP Administration in Office (AM dose)[2]			X (T_0)	X (T_0)	X (T_0)	X (T_0)
Assess IP Compliance				X	X	X
Heart Rate/Blood Pressure (± 30 min)		X Pre-T_0 T_0 + 1 hr T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]	X Pre-T_0 T_0 + 1 hr T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]		X Pre-T_0	X Pre-T_0 T_0 + 1 hr T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]
Urine Pregnancy Test(if applicable)	X	X				X
Best-corrected Visual Acuity (ETDRS)	X	X	X Pre-T_0	X Pre-T_0	X Pre-T_0)	X Pre-T_0)
Biomicroscopy	X	X	X Pre-T_0 T_0 + 2 hrs T_0 + 4 hrs	X Pre-T_0	X Pre-T_0	X Pre-T_0, T_0 + 2 hrs, To + 4 hrs
Conjunctival Hyperemia Grading (direct visual observation using photographic reference scale)		X Pre-T_0 T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]	X Pre-T_0 T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]		X Pre-T_0	X Pre-T_0 T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]

[1] When possible, one examiner should conduct all ocular assessments for a subject during a single visit. If possible, the same examiner should conduct all ocular assessments for a subject throughout the duration of the study. Ocular parameters should be assessed OU.
[2] T_0 corresponds to actual AM dosing of the investigational product. For Baseline, T_0 is immediately after Pre-T_0, expected to be 8 am ± 30 mins.
[3] T_0 +12 hrs is optional for new subjects participating under Protocol V3.0.

Assessments/Procedures[1]	**Screening (-49 to 1 days)**	**Day 0 (-4 to -1)**	**Day 1 Baseline/Randomization**	**Day 7** (± 1 day)	**Day 14** (± 1 day)	**Day 28** (± 2 days) **Last Dosing Day**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Intraocular Pressure[4] (Goldmann Tonometry)	X	X Pre-T_0 T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]	X Pre-T_0 T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]	X Pre-T_0	X Pre-T_0	X Pre-T_0 T_0 + 2 hrs T_0 + 4 hrs T_0 + 8 hrs T_0 + 12 hrs[3]
Gonioscopy[5]	X					
Pachymetry[6]	X					
Visual Fields (automated, threshold)[7]	X					
Ophthalmoscopy (dilated)	X					X

[4] Timing of IOP measurements for each subject should be consistent throughout the study. Calculate timepoints in relation to T_0: timepoints +2 and +4 hrs after T_0 must be separated from the prior timepoint by at least 1½ hrs and timepoints +8 and +12 hrs must be separated from the prior timepoint by at least 3 ½ hours. Every effort should be made to conduct Visit 6 Day 28 Pre-T_0 and In-Office IP Administration (AM dose) at the identical time as done on Visit 3 Day 1.

[5] Gonioscopy within 6 months of Screening acceptable.

[6] Pachymetry performed at screening will be used for inclusion/exclusion criteria only. Pachymetry within 6 months of Screening acceptable.

[7] Reliable visual fields within 6 months of Screening acceptable.