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: 19 January 2024

Clinical Study Protocol

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

Protocol Number:	H1337-CS202
Investigational Drug Product:	H-1337
IND Number:	107,895
Development Phase:	Phase 2b
Medical Monitor:	Robert D Williams, MD Telephone: (360) 298-5325

Sponsor Contact: D. Western Therapeutics, Inc.
7th Floor, CK21 Hirokoujifushimi Building
Nagoya shi
Aichi, Japan 460-0003
Attention: Shigenobu NAKAZORA shinakazora@dwti.co.jp
Telephone: 81-52-218-8785

Date of Protocol:	19 Jan 2024
Version:	3.0
Amendment History:	Version 1.0 7 December 2022
	Version 2.0 7May 2023

Confidentiality Statement

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number: H1337-CS202

Protocol 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

No party involved in the conduct of this study will modify this protocol without obtaining D. Western Therapeutics Inc.'s written agreement. Any modification will require appropriate written confirmation and any protocol amendment must follow written policies as stated in this protocol.

This trial will be conducted in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, and local ethical and legal requirements.

D. Western Therapeutics, Inc. Approval:

Signature: Date:

Yuichi Hidaka Jan. 29 / 2024

Name: Yuichi Hidaka
President and CEO
D. Western Therapeutics, Inc.

INVESTIGATOR PROTOCOL SIGNATURE PAGE

Protocol Number: H1337-CS202

Protocol 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

By signing below, the investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by D. Western Therapeutics, Inc., prior to seeking approval from the Institutional Review Board/Ethics Committee.

The investigator also agrees to conduct the study in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, and local ethical and legal requirements.

Investigator's Signature: _____

Printed Name: _____

Name of Institution: _____

Date: _____

Protocol Version 3.0
19JAN2024
Approximately 110 subjects enrolled.

Version 2.0 dated 7 May 2023 was changed as follows:

- Corrections, clarifications and minor changes to inclusion/exclusion criteria to reflect investigator input during conduct of study to date
- Changing +12 hours diurnal IOP measurement to optional due to logistical challenges in office practice and subject recruitment
- Statistical section to reflect comments received from U.S. FDA on 4 January 2024, as well as changes to diurnal IOP measure analyses.

These modifications do not change subject exposure or safety.

Protocol Version 2.0
7MAY2023
No subjects enrolled.

Version 1.0 dated 7 December 2022 was changed to clarify study procedures and subject qualifications.

This does not change subject exposure or safety.

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Protocol Synopsis

Protocol Number:	H1337-CS202
Study 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
Study Objectives:	Primary Objective: 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. Secondary Objectives: Evaluate the local ocular and systemic safety of 3 dose regimens of H-1337. Exploratory Objectives: • Evaluate the efficacy of diurnal IOP measurements of 3 dose regimens of H-1337 compared to timolol 0.5%
Study Population:	Subjects with bilateral POAG or OHT
Number of Subjects:	Approximately 200
Investigational Products:	H-1337 0.6% Ophthalmic Solution b.i.d. H-1337 1.0% Ophthalmic Solution b.i.d. H-1337 1.0% Ophthalmic Solution q.a.m. H-1337 placebo q.p.m. Timolol 0.5% Ophthalmic Solution b.i.d.
Route and Duration of Administration:	Topical eye drop; 28 days treatment
Study Design:	The trial will evaluate the safety and efficacy of 3 dose regimens of H-1337 (0.6% b.i.d., 1.0% b.i.d. and 1.0% q.a.m., and timolol maleate (0.5%, b.i.d.) OU for 28 days. Efficacy assessments will be made based upon the study eye. The study eye is the eye that meets all entry criteria including the intraocular pressure (IOP) inclusion criteria. If both eyes qualify the study eye is the eye with the higher 8 am IOP on Baseline (Day 1). If both eyes have the same 8 am IOP on Baseline (Day 1), the study eye is the right eye.
Primary Efficacy Measure:	Change from baseline in IOP in 3 dose regimens of H-1337 compared to timolol 0.5%., b.i.d. at 28 days in subjects with POAG or ocular hypertension.

Secondary Efficacy Measure:	• Mean IOP in 3 dose regimens of H-1337 compared to timolol 0.5%., b.i.d. at 28 days in subjects with POAG or ocular hypertension. • Mean diurnal IOP in 3 dose regimens of H-1337 compared to timolol 0.5%., b.i.d. at 28 days in subjects with POAG or ocular hypertension. • Proportion of subjects with IOP $\leq$ 18 mmHg at each time point at each visit, and with the mean diurnal IOP $\leq$ 18 mmHg for each visit.
Safety Endpoints:	Ocular and systemic Adverse Events (AE)
Study Assessments:	The following assessments and procedures will be performed: • Medical and ocular history • Prior and current concomitant medications and procedures • Adverse events • Heart rate and blood pressure • Best-corrected visual acuity (ETDRS) OU • Biomicroscopy OU • Conjunctival Hyperemia Grading OU • Intraocular pressure (Goldmann tonometry) OU • Gonioscopy OU • Pachymetry OU • Visual field testing (automated, threshold) OU • Ophthalmoscopy (dilated) OU
Statistical Considerations:	This trial has $\geq$ 90% power to detect a clinically significant difference of 2.0 mm Hg, assuming SD of 3.0 mm Hg (ALY337-201), and α=0.05 (1-sided). A hierarchical analysis will be performed starting with 1.0% H-1337 b.i.d. Thus, no adjustment for multiplicity will be performed.
Pharmacokinetic Endpoints	None

Inclusion Criteria:	To be eligible for trial participation subjects must meet all the following criteria: 1. 18 years of age or older. 2. Diagnosis of bilateral primary open angle glaucoma or ocular hypertension. 3. One qualifying IOP criteria after washout: • Baseline (Day 1) at T_0 (T_0 = 8 am ± 30 min [IOP time]) IOP ≥ 23 mmHg in the study eye. 4. IOP criteria after washout ≤ 32 mmHg OU at all qualifying time points/visits. 5. Best-corrected visual acuity (BCVA) in both eyes of 20/200 or better on Snellen, equivalent to + 1.0 log Mar at Visit 1 Screening. 6. Able and willing to sign informed consent, follow study instructions and complete all study visits. 7. As applicable, must be willing to discontinue the use of all ocular hypotensive medication(s) in both eyes prior to receiving the study medication and for the entire course of the study. 8. Able to self-administer or have a caretaker administer investigational product eye drops.

Exclusion criteria	To be eligible for trial participation subjects must not meet any of the following criteria: <u>Ocular:</u> Exclude subjects with: 1. Closed or very narrow angles (Grade 0-1) (*see Section 5, gonioscopy*) or those the investigator judges as occludable and/or with evidence of peripheral anterior synechiae (PAS) ≥ 180 degrees by gonioscopy within 6 months prior to Screening Visit in either eye. (Patent laser iridotomy with Grade 1-2 angles is acceptable in either eye, providing the PAS criteria are still met). 2. Previous glaucoma intraocular surgery in either eye (including cyclodestructive procedures). Prior laser trabeculoplasty (ALT or SLT) in either eye is allowed if performed more than 6 months prior to Screening Visit. 3. Any non-glaucoma intraocular surgery within 3 months prior to Screening Visit in either eye. 4. Intraocular laser surgery such as laser capsulotomy, laser iridotomy, and/or retinal laser within 1 month prior to Screening Visit in either eye. 5. Significant media opacity in either eye that would impede adequate posterior segment examination. 6. Contraindications to pupil dilation in either eye. 7. Other forms of glaucoma such as primary congenital, juvenile onset, chronic angle closure, and secondary glaucoma of any type including corticosteroid-induced, inflammation-induced, or exfoliation glaucoma in either eye. Pigment dispersion syndrome/glaucoma is permitted in either or both eyes. 8. Clinically significant corneal dystrophy, epithelial or endothelial disease, corneal irregularities or scarring that, in the investigator's judgment, would impede an accurate measurement of IOP or visualization of intraocular anatomy in the study eye. 9. Prior netarsudil use in either eye which resulted in clinically significant adverse events leading to discontinuation of treatment including: conjunctival hyperemia, subconjunctival hemorrhage, cornea verticillata, or reticular bullous epithelial edema. 10. History of refractive surgery in either eye (i.e., radial keratotomy, PRK, LASIK). 11. History of corneal cross-linking procedure in either eye. 12. Unwillingness to be contact lens free during study participation. 13. Any history of uveitis, keratitis, or scleritis in either eye. Note: SPK associated with ocular surface disease is

	permitted. 14. Any history of penetrating ocular trauma in either eye. 15. History within 3 months prior to Screening Visit of clinically significant moderate or severe chronic or active blepharitis, ocular dermatitis, or recent ocular conjunctivitis and/or ocular inflammation in either eye. Mild blepharitis, hyperemia (due to prostaglandin use) and/or blepharitis, and/or mild or inactive seasonal allergic conjunctivitis and non-infectious dermatitis are acceptable. 16. Corneal thickness < 480 or > 620 µm in the study eye. Pachymetry measurement within 6 months prior to Screening Visit is acceptable. 17. Advanced or severe glaucoma with progressive visual field loss, NFL thinning documented by OCT, and/or optic nerve changes in either eye that, in the investigator's best judgment, prevent safe withdrawal from treatment for the time periods required in this protocol. Note: 1) Subjects may be switched to different IOP lowering therapy with a shorter washout period as long as the appropriate washout is met prior to Visit 2. 2) Visual fields must be reliable, defined as those with a) fixation losses less than or equal to 33%, b) false positives less than or equal to 33% and c) false negatives less than or equal to 33%. 18. In the investigator's best judgment, progressive retinal (including, but not limited to worsening dry AMD, presence of active wet AMD, or unstable diabetic retinopathy) or optic nerve disease in either eye from any cause other than glaucoma. Mild BDR is permitted. 19. Any prior intravitreal corticosteroid injection in either eye. 20. Sub-tenon's, sub-conjunctival or periocular corticosteroid injections within the 6 months prior to Screening Visit in either eye. 21. Any use of ocular topical corticosteroids in either eye within 7 days, or chronic (as determined by the investigator) topical steroids within 28 days, prior to Baseline Day 1 and ensuing trial participation. 22. Known hypersensitivity to any component of the H-1337 formulation, including BAK, timolol maleate, or to topical anesthetics or diagnostic drops to be used during the study. 23. Any ocular condition that, in the investigator's judgment, could prevent the subject from safe participation the study. 24. Planned ocular surgery or intraocular injection procedure in either eye during study participation. <u>General/Systemic:</u> Exclude subjects with:

	25. Participation in a clinical study with use of any investigational drug or treatment within 30 days prior to Baseline (Day 1). 26. Prior use of H-1337 27. Clinically significant systemic, psychiatric or psychological disease (for example, renal, hepatic, uncontrolled diabetes, uncontrolled blood pressure, autoimmune disorders, psychiatric disorders, endocrine disorders, or any other disorders) or dependency which, in the investigator's judgment, would be unsafe and interfere with interpretation of the study results or the subject's ability to comply with the study requirements. 28. Contraindication to beta-blocker usage including: reactive airway disease, uncontrolled heart failure, or second as well as third degree cardiac block, myasthenia gravis. 29. Anticipated changes or initiation of medications which might affect IOP and/or systemic blood pressure within 7 days prior to Baseline/Day 1 (e.g., including, but not limited to: oral anti-hypertensives such as sympathomimetic agents, beta-adrenergic blocking agents, alpha agonists, alpha adrenergic blocking agents, calcium channel blockers, angiotensin converting enzyme inhibitors; [diuretics are allowed]), and 2 months prior to Baseline/Day 1 for corticosteroids (i.e., oral, nasal, topical [dermal, mucosal], and/or inhaled corticosteroids). If there are no further anticipated changes in medications that could affect IOP and/or systemic blood pressure, then once the subject is stable on their new dose of medication for the required time period, the subject may complete the Baseline Visit, assuming that all other screening requirements are met. Medications used on an adjustable or sliding scale based on testing results are allowed. Note: Vaccines are permitted. 30. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at the Screening Visit and at Baseline (Day 1) prior to randomization in the study and must not intend to become pregnant during the study. 31. History of drug or alcohol abuse within the last 5 years. 32. Unwillingness to refrain from consumption of alcohol or cannabinoids, including tetrahydrocannabinol (THC) and cannabidiol (CBD), in any form by any delivery route, on

	the day prior to each study visit after Visit 1 Screening. 33. Related to site study staff and/or site employees.

Table 1. Time and Events 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.

List of Abbreviations

AE	Adverse Event
ALT	Argon Laser Trabeculoplasty
AMD	Age-related Macular Degeneration
AUC	Area Under the Curve
BAK	Benzalkonium Chloride
BCVA	Best Corrected Visual Acuity
BID	Twice Daily
BP	Blood Pressure
CAI	Carbonic Anhydrase Inhibitor
°C	Degrees Celsius
CFR	Code of Federal Regulations
CME	Cystoid Macular Edema
CRF	Case Report Form
ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice(s)
GLP	Good Laboratory Practice(s)
Hg	Mercury
HR	Heart Rate
hr	Hour
IB	Investigator's Brochure
IC	Informed Consent Document
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LASIK	Laser-Assisted In Situ Keratomileusis
LDPE	Low Density Polyethylene
logMAR	Logarithm of the minimum angle of resolution
Mins	Minutes

mL	Milliliter
Mm	Millimeter
mOsm	Milliosmoles
OD	Right Eye
OS	Left Eye
OHT	Ocular Hypertension
OTC	Over The Counter
OU	Both Eyes
PK	Pharmacokinetic
POAG	Primary Open Angle Glaucoma
PP	Per Protocol
PRK	Photorefractive Keratectomy
QD	Once-daily
RGC	Retinal Ganglion Cells
ROCKi	Rho Kinase Inhibitor
SAE	Serious Adverse Event
SLT	Selective Laser Trabeculoplasty
SPK	Superficial Punctate Keratitis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TM	Trabecular Meshwork
US	United States
VF	Visual Fields
µm	Micrometer

1. 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. Glaucoma is generally asymptomatic until advanced irreversible disease has occurred. Data from population-based surveys indicate that one in 40 adults older than 40 years has glaucoma with loss of visual function, which equates to 60 million people worldwide being affected and 8·4 million being bilaterally legally blind. Even in developed countries, half of glaucoma cases are undiagnosed (Quigley 2011, Glaucoma Research Foundation. https://glaucoma.org/glaucoma-facts-and-stats/).

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 intraocular pressure 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. Further evaluations might explore the dose-response and therapeutic potential compared to a positive control, as well as the effect of H-1337 on aqueous humor dynamics (Hartman et al, 2022).

The present study aims to extend the previous findings with additional concentrations and doses, as well as including a positive control (timolol ophthalmic solution).

1.1 Investigational Agent

H-1337 is a selective multi-kinase inhibitor. The Sponsor hypothesizes that inhibition of kinases that control intracellular cytoskeletal dynamics at the level of the trabecular meshwork and other cells that regulate flow is a mechanism that will improve outflow. As open-angle glaucoma is a disease of decreased trabecular outflow, the Sponsor believes that H-1337 beneficially enhances aqueous outflow by modulating the contractile state of trabecular meshwork ™ cells to decrease resistance to fluid transport.

The H-1337 investigational drug product is a preserved, isotonic, sterile ophthalmic solution at two concentrations (w/v) (0.6% and 1.0%), buffered at pH 6.5 (range 6.3 – 6.7), as is the placebo. Sodium chloride is used to adjust the osmolarity to 280 - 320 mOsm/kg. The primary drug product packaging is a white, sterile low-density polyethylene (LDPE) multi-dose 5 mL bottle with LDPE nozzle/dropper insert and high-density polyethylene (HDPE) ophthalmic cap.

The bottle is packaged into an aluminum foil overwrap to protect from water vapor transmission. The placebo control (vehicle) will consist of the components of the ophthalmic formulation without H-1337.

Timolol ophthalmic solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate. The pH of the solution is approximately 7.0, and the osmolarity is 274-328 mOsm/kg. Each mL of timolol ophthalmic solution 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients: monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and purified water. Benzalkonium chloride 0.01% is added as preservative.

1.2 Preclinical and Human Data

For complete information on the preclinical studies performed, please see the Investigator's Brochure.

H1337, in the first human trial (ALY337-201) was generally well tolerated. Instillation site pain, instillation site erythema, and vision blurred were reported, usually mild in severity without an apparent dose-response.; instillation site erythema, blurred vision, and muscle strain were reported in 3 subjects at moderated intensity.

1.3 Risk/Benefits

Based on the results of ALY337-201, the first human trial, the risk/benefit ratio for this trial appears acceptable. Refer to the Investigator's Brochure for complete information on prior studies performed with H1337.

1.4 Dose Rationale

Ocular PK data in rabbits and monkeys confirmed that H-1337 exhibits dose-related effects and can reduce IOP for upwards of 8-12 hours. The clinical doses, treatment period (28 days), and dosing regimen (BID) are expected to have an acceptable safety profile and have been selected based on preclinical toxicology data. The total daily administered dose of H-1337 in human subjects will be approximately 1.72 mg/day (or 0.03 mg/kg/day based on a 60-kg individual) when administered twice daily in both eyes at the maximal concentration of 1.0%.
In a previous clinical study, 3 concentrations of H-1337 Ophthalmic Solution (0.06%, 0.02% and 0.6%) dosed twice-daily (b.i.d.) provided similar ocular hypotensive outcomes. In the present study, a high concentration of 1.0% is planned to be used both once (q.d.) and twice (b.i.d.)-daily. The dose is supported by preclinical safety studies. The highest dose from the previous study (0.6%, b.i.d.), as well as a positive marketed control, timolol ophthalmic solution 0.5%, b.i.d., will be included for comparison.

1.5 Trial Conduct

This study will be conducted in accordance with current US FDA regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, and local ethical and legal requirements.

1.6 Population

Study population will include subjects of either sex and of any race/ethnicity over 18 years of age with a diagnosis of bilateral primary open-angle glaucoma or ocular hypertension.

2. STUDY OBJECTIVES

Primary Objective:

- 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.

Secondary Objectives:

- Evaluate the local ocular and systemic safety of 3 dose regimens of H-1337.

Exploratory Objectives:

- •Evaluate the efficacy of diurnal IOP measurements of 3 dose regimens of H-1337 compared to timolol 0.5%.

3. STUDY DESIGN

3.1 Study Design

The trial will evaluate the safety and efficacy of 3 dose regimens of H-1337 (0.6% b.i.d., 1.0% b.i.d. and 1.0% q.a.m., and timolol maleate (0.5%, b.i.d.) OU for 28 days (± 2-day allowable window for Day 28).

Approximately 200 subjects will be randomized and dosed for 28 days. The parallel group, double-masked, active-controlled study will include the following dosing cohorts:

- H-1337 0.6% Ophthalmic Solution b.i.d. (n=50)
- H-1337 1.0% Ophthalmic Solution b.i.d. (n=50)
- H-1337 1.0% Ophthalmic Solution q.a.m. and H-1337 placebo q.p.m. (n=50)
- Timolol 0.5% Ophthalmic Solution b.i.d (n=50)

3.2 Randomization

H-1337 and its control (timolol) will be packaged in similar bottles which are concealed in identical packaging. An interactive web response system (IWRS) will be used for randomization.

3.3 Maintenance of Randomization Codes

The study will be double-masked to reduce potential bias in clinical assessments. Upon approval of D. Western Therapeutics, Inc., and prior to initiation of the study, an unmasked statistician will generate and maintain the randomization codes which are consistent with the study design.

Other study statisticians will be masked to the identity of the treatments until all data have been entered into the database and locked.
In the case of an emergency only, if it is necessary for the investigator (or a treating physician) to know the treatment a subject is receiving, site personnel can complete the subject treatment breaking code procedure in IWRS. The mask should be broken only for safety purposes and only if knowing the drug allocation will have a direct impact on the subject's immediate medical management. If at all possible, the Medical Monitor should be contacted prior to emergency unmasking:

Robert D Williams, MD
iopdoc1@gmail.com
Telephone: (360) 298-5325

If this is not possible and unmasking occurs without prior Medical Monitor approval, the Medical Monitor must be notified within 24 hrs. The circumstances leading to unmasking of each subject are to be promptly communicated via telephone and/or in writing to the sponsor (or sponsor's designee) and the IRB. Every effort should be made to keep the subject in the trial after the randomization code is broken until the completion of all visits.

3.4 Trial Treatment

Subjects will receive one of four dosing arms: H-1337 (0.6% b.i.d., 1.0% b.i.d. and 1.0% q.a.m. with H-1337 placebo q.p.m.), and timolol maleate (0.5%, b.i.d.) OU for 28 days . IP will be administered bilaterally throughout the trial.

The IWRS will assign a kit number to subjects who qualify for randomization. Each IP kit will contain 3 inner cartons. The first carton containing 2 pouches (each pouch containing 1 a.m. and 1 p.m. bottle) will be dispensed on Day 1 (Baseline). The second carton will be dispensed to the subject on Day 14. The third carton will serve as a back-up should the subject require a replacement carton.

3.5 Duration

Each subject's participation will consist of two phases: a Screening Phase (Screening and Baseline Visit 2 and Visit 3 Pre-T_0) where subjects will suspend dosing of any current ocular hypotensive therapy, and a Dosing Phase, starting on Day 1 after Pre-T_0. If a subject is not using ocular hypotensive therapy at Screening Visit 1, there is no applicable washout period and the Baseline Visit should occur within 1 to 42 days after Screening Visit 1.

A subject could participate in the study for a total of up to approximately 11 weeks. Subjects who meet the applicable inclusion/exclusion criteria at the Screening Visit will discontinue use of any current ocular hypotensive therapy during the washout period. (Note: At Investigator's discretion for subject's safety, initiation of a different IOP lowering therapy with a shorter washout period is permitted during a long washout period provided all appropriate washout periods are met prior to Visit 2.) The washout duration will be dependent on the subject's pre-study ocular hypotensive therapy. The table below lists the applicable washout durations for various pre-study ocular hypotensive medications. (Note: This table may not be inclusive of all

ocular hypotensive medications. The Medical Monitor should be contacted for further information regarding the washout period of an ocular hypotensive not included in the table.) If the Investigator assesses an acceptable risk, subjects may extend washout up to 49 days to accommodate scheduling.

Table 2: Ocular Hypotensive Medication Washout Schedule

Ocular Hypotensive Generic/Trade Names	Washout period* (between Screening and Baseline Visit)
Muscarinic agonists (e.g., pilocarpine) and Oral or Topical Carbonic Anhydrase Inhibitors (CAI)	≥ 5 days
Beta-adrenoceptor antagonists	≥ 6 weeks
Alpha adrenoceptor agonists	≥ 5 weeks
Prostaglandin analogues, Combination Drugs (use longest wash-out period of individual components) *	≥ 6 weeks
Rho-associated protein kinase (ROCK) inhibitors	≥ 6 weeks

*The washout period of longest duration should be used when the subject is taking multiple ocular hypotensive medications from more than one class. Additional +1 week extended washout permitted to accommodate scheduling considerations (Stroman et al, 1997; Johnson and Jampel, 2021).

Following the applicable washout period, the subject will return for applicable inclusion/exclusion evaluations on the Baseline Visit (Day 1) and a subject meeting all inclusion/exclusion criteria at Pre-T_0 will be randomized to IP. Both eyes will be dosed and evaluated for safety throughout the trial. The study eye is 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 defined as the eye with the higher Pre-T_0 8 am IOP on Baseline (Day 1). If both eyes have the same Pre-T_0 8 am IOP on Baseline (Day 1), the study eye will be the right eye.

Dosing will be initiated on Day 1 in the office after measurement of the Pre-T_0 8 a.m. IOP and the completion of all examinations required prior to the Pre-T_0 8 a.m. IOP measurement. The subject will be dosed for up to 28 days during which time they will be monitored for safety, tolerability, and efficacy assessments according to the Schedule of Study Assessments and Procedures.

The duration of participation for subjects in each stage will be as follows:

Screening Visit: 1 day
Washout Period: up to 42 days (+ 7 days) depending on pre-study ocular hypotensive therapy
Treatment Period: 28 days ± 2 days

3.6 Drug Packaging and Labeling

H-1337 and timolol 5 mL low density polyethylene (LDPE) bottles will be similar but not identical. Each bottle will be concealed in an identical foil pouch. Each identical IP kit will contain 3 identical inner cartons, each containing 2 identical foil pouches (one a.m. and one p.m. pouch). The kits, inner cartons, pouches and bottles will be labeled in a format appropriate for the study.

Masking will be maintained by the appointment of an unmasked study coordinator not

participating in key endpoint data collection at each clinical site, solely responsible for subject IP dispensation and return.

3.7 Drug Accountability and Storage

All IP required for this study will be provided by D. Western Therapeutics, Inc., or its designee. The recipient will acknowledge receipt of IP, indicating shipment content and condition. Damaged supplies may be replaced upon notification to D. Western Therapeutics, Inc., or its designee. Accurate records of all IP dispensed from and returned to the study site should be maintained and recorded. A study monitor will periodically check the supplies of IP held at the site to verify accountability of all IP. All used and unused IP (non-dispensed) will be returned to D. Western Therapeutics, Inc., or its designee.

IP must be stored in a temperature monitored secure and restricted storage area with limited access. Temperature monitoring records must be maintained throughout the trial. IP should be stored at controlled refrigerated temperatures from 2° - 8° C and protected from light. Once dispensed to subjects IP bottles may be stored at room temperature, i.e., 15° - 25° C. Subjects must be instructed not to leave the IP in their car, near a window, or outdoors where it may be exposed to direct sunlight and/or heat for a prolonged period.

The IP must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply IP to other clinical sites, investigators or subjects, or allow the IP to be used other than as directed by this protocol without prior authorization from D. Western Therapeutics, Inc.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must fulfill all the inclusion and exclusion criteria and the investigator must obtain written approval from the Medical Monitor, to confirm any deviation from these ***prior to*** randomization of the subject.

4.1 Inclusion Criteria

1. 18 years of age or older.
2. Diagnosis of bilateral primary open angle glaucoma or ocular hypertension.
3. One qualifying IOP criteria after washout:
   - Baseline (Day 1) at T_0 (T_0 = 8 am ± 30 min [IOP time]) IOP ≥ 23 mmHg in the study eye.
4. IOP criteria after washout ≤ 32 mmHg OU at all qualifying time points/visits.
5. Best-corrected visual acuity (BCVA) in both eyes of 20/200 or better on Snellen, equivalent to + 1.0 log Mar at Visit 1 Screening.
6. Able and willing to sign informed consent, follow study instructions and complete all study visits.
7. As applicable, must be willing to discontinue the use of all ocular hypotensive medication(s) in both eyes prior to receiving the study medication and for the entire course of the study.
8. Able to self-administer or have a caretaker administer investigational product eye drops.

4.2 Exclusion Criteria

Exclusion criteria:
Investigators will exclude any subject who they consider unsafe for participation in this study or unlikely to complete the requirement of the protocol for any reason.

Ocular:
Exclude subjects with:

1. Closed or very narrow angles (Grade 0-1) (*see Section 5, gonioscopy*) or those the investigator judges as occludable and/or with evidence of peripheral anterior synechiae (PAS) ≥ 180 degrees by gonioscopy within 6 months prior to Screening Visit in either eye. (Patent laser iridotomy with Grade 1-2 angles is acceptable in either eye, providing the PAS criteria are still met).
2. Previous glaucoma intraocular surgery in either eye(including cyclodestructive procedures). Prior laser trabeculoplasty (ALT or SLT) in either eye is allowed if performed more than 6 months prior to Screening Visit.
3. Any non-glaucoma intraocular surgery within 3 months prior to Screening Visit in either eye.
4. Intraocular laser surgery such as laser capsulotomy, laser iridotomy, and/or retinal laser within 1 month prior to Screening Visit in either eye.
5. Significant media opacity in either eye that would impede adequate posterior segment examination.
6. Contraindications to pupil dilation in either eye.
7. Other forms of glaucoma such as primary congenital, juvenile onset, chronic angle closure, and secondary glaucoma of any type including corticosteroid-induced, inflammation-induced, or exfoliation glaucoma in either eye. Pigment dispersion syndrome/glaucoma is permitted in either or both eyes.
8. Clinically significant corneal dystrophy, epithelial or endothelial disease, corneal irregularities or scarring that, in the investigator's judgment, would impede an accurate measurement of IOP or visualization of intraocular anatomy in the study eye.
9. Prior netarsudil use in either eye which resulted in clinically significant adverse events leading to discontinuation of treatment including: conjunctival hyperemia, subconjunctival hemorrhage, cornea verticillata, or reticular bullous epithelial edema.
10. History of refractive surgery in either eye (i.e., radial keratotomy, PRK, LASIK).
11. History of corneal cross-linking procedure in either eye.
12. Unwillingness to be contact lens free during study participation.
13. Any history of uveitis, keratitis, or scleritis in either eye. Note: SPK associated with ocular surface disease is permitted.
14. Any history of penetrating ocular trauma in either eye.
15. History within 3 months prior to Screening Visit of clinically significant moderate or severe chronic or active blepharitis, ocular dermatitis, or recent ocular conjunctivitis and/or ocular inflammation in either eye. Mild blepharitis, hyperemia (due to prostaglandin use) and/or blepharitis, and/or mild or inactive seasonal allergic conjunctivitis and non-infectious dermatitis are acceptable.
16. Corneal thickness < 480 or > 620 µm in the study eye. Pachymetry measurement within 6 months prior to Screening Visit is acceptable.
17. Advanced or severe glaucoma with progressive visual field loss, NFL thinning documented by OCT, and/or optic nerve changes in either eye that, in the investigator's best judgment,

prevent safe withdrawal from treatment for the time periods required in this protocol. Notes: 1) Subjects may be switched to a different IOP lowering therapy with a shorter washout period as long as the appropriate washout is met prior to Visit 2. 2) Visual fields must be reliable, defined as those with a) fixation losses less than or equal to 33%, b) false positives less than or equal to 33% and c) false negatives less than or equal to 33%.

18. In the investigator's best judgment, progressive retinal (including, but not limited to worsening dry AMD, presence of active wet AMD, or unstable diabetic retinopathy) or optic nerve disease in either eye from any cause other than glaucoma. Mild BDR is permitted.
19. Any prior intravitreal corticosteroid injection in either eye.
20. Sub-tenon's, sub-conjunctival or periocular corticosteroid injections within the 6 months prior to Screening Visit in either eye.
21. Any use of ocular topical corticosteroids in either eye within 7 days, or chronic (as determined by the investigator) topical steroids within 28 days, prior to Baseline Day 1 and ensuing trial participation.
22. Known hypersensitivity to any component of the H-1337 formulation, including BAK, timolol maleate, or to topical anesthetics or diagnostic drops to be used during the study.
23. Any ocular condition that, in the investigator's judgment, could prevent the subject from safe participation the study.
24. Planned ocular surgery or intraocular injection procedure in either eye during study participation.

<u>General/Systemic:</u>

Exclude subjects with:

25. Participation in a clinical study with use of any investigational drug or treatment within 30 days prior to Baseline (Day 1).
26. Prior use of H-1337.
27. Clinically significant systemic, psychiatric or psychological disease (for example, renal, hepatic, uncontrolled diabetes, uncontrolled blood pressure, autoimmune disorders, psychiatric disorders, endocrine disorders, or any other disorders) or dependency which, in the investigator's judgment, would be unsafe and interfere with interpretation of the study results or the subject's ability to comply with the study requirements.
28. Contraindication to beta-blocker usage including: reactive airway disease, uncontrolled heart failure, or second as well as third degree cardiac block, myasthenia gravis.
29. Anticipated changes or initiation of medications which might affect IOP and/or systemic blood pressure within 7 days prior to Baseline/Day 1 (e.g., including, but not limited to: oral anti-hypertensives such as sympathomimetic agents, beta-adrenergic blocking agents, alpha agonists, alpha adrenergic blocking agents, calcium channel blockers, angiotensin converting enzyme inhibitors [diuretics are allowed]), and 2 months prior to Baseline/Day 1 for corticosteroids (i.e., oral, nasal, topical [dermal, mucosal], and/or inhaled corticosteroids). If there are no further anticipated changes in medications that could affect IOP and/or systemic blood pressure, then once the subject is stable on their new dose of medication for the required time period, the subject may complete the Baseline Visit, assuming that all other screening requirements are met. Medications used on an adjustable or sliding scale based on testing results are allowed. Note: Vaccines are permitted.
30. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of

childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at the Screening Visit and at Baseline (Day 1) prior to randomization in the study and must not intend to become pregnant during the study.

31. History of drug or alcohol abuse within the last 5 years.
32. Unwillingness to refrain from consumption of alcohol or cannabinoids, including tetrahydrocannabinol (THC) and cannabidiol (CBD), in any form by any delivery route, on the day prior to each study visit after Visit 1 Screening.
33. Related to site study staff and/or site employees.

4.3 Subject Withdrawal and/or Discontinuation

Subjects are free to discontinue their participation in the study at any time without prejudice to further treatment. The investigator must withdraw any subject from the study at their request. Subjects should provide the reason for withdrawal and confirm whether they are withdrawing consent or withdrawing from IP treatment. The investigator or D. Western Therapeutics, Inc. designee, may withdraw the subject from IP treatment for any reason or if the subject meets any of the following criteria.

- Experiences a serious or intolerable AE that is judged by the investigator to preclude further study participation.
- Develops a clinically significant laboratory or other abnormality that is judged by the investigator to be potentially related to IP.
- Requires a medication that is prohibited by the protocol. Contact the Medical Monitor to discuss exiting a subject due to use of a prohibited medication before exiting the subject.
- Does not follow the protocol procedures, including noncompliance.
- Is lost to follow-up; every effort should be made to contact the subject.
- Administrative reasons, including termination of the trial by the Sponsor, unavailable for follow-up procedures.
- Experiences glaucomatous progression and/or unacceptable IOP elevation, per the discretion of the investigator.

Should a subject's medical or mental condition change or become unstable during the study, such that the ability of the subject to continue in this study becomes compromised or, in the investigator's judgment, their health is jeopardized, or further continuation is unadvisable, the subject may be withdrawn from study treatment.

If a subject withdraws or is withdrawn from IP treatment, every effort should be made to ensure the subject continues to participate in the remaining trial visits.

If a subject withdraws or is withdrawn from IP treatment, either at her/his request or at the discretion of the investigator or D. Western Therapeutics, Inc. the reason for withdrawal should be recorded. All subjects withdrawing or withdrawn from IP dosing, regardless of cause, will return within 14 days from their last dose of IP to complete Early Termination visit assessments; consult the Medical Monitor to determine which diurnal measurements, if any, are required for the ET visit.

It is vital to obtain follow-up data for any subject withdrawn due to an AE. In any case, every effort must be made to undertake safety follow-up procedures.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. If every effort is made to contact the subject (including two telephone calls and a traceable letter sent to the subject) and these attempts are unsuccessful, the subject is considered lost to follow-up.

4.4 Medication

During the washout period between Visits 1 and 2 from prior IOP-lowering therapy, topical carbonic anhydrase inhibitors (CAI) (i.e., Dorzolamide (Trusopt®) or Brinzolamide (Azopt®) will be permitted, but will not be provided by the Sponsor. Should a topical CAI be employed during the washout period, the applicable washout for CAIs should be implemented and the CAI should be discontinued 5 days prior to Baseline (Day 1).

Current systemic mediations which may influence intraocular pressure should be stable without anticipated changes over the course of the trial. Should a subject's medical condition change or become unstable during the study, such that the change in non-ocular medication that can or may affect IOP are added or altered (i.e., steroids, systemic beta blockers, etc.), the subject's condition should be reviewed with the study Medical Monitor. If the subject is withdrawn from IP treatment, the subject will continue to be followed during routine trial visits or until he/she returns within 14 days from the last dose of IP to complete the Early Termination visit.

If, during the study, an investigator determines the IOP is inadequately controlled such that the safety of the subject is compromised, the PI may withdraw the subject from IP treatment and institute IOP treatment.

4.5 Monitoring for Subject Compliance

Subjects or their caretakers will administer study medications according to the IP dosing instructions and training provided, ie; as close as possible to 8 a.m. and 8 p.m. Compliance will be assessed at each visit by asking the subject for their recollection about any missed doses. Confirmation of compliant IP dosing the evening prior to a study visit must be confirmed or the visit should be rescheduled. If the subject reports missing more than 4 doses since the prior visit, a Protocol Deviation will be documented and the subject will be counseled on IP compliance.

4.6 Lifestyle Guidance

During the study, subjects of childbearing potential (who are menarchal) must use reliable precautions to prevent pregnancy. These restrictions should be followed throughout the duration of the study and maintained for 30 days after trial completion.

Acceptable contraceptive methods for subjects of child-bearing potential:

- Abstinence

- Hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin sub-dermal implants, progesterone-releasing IUDs)
- Placement of a copper-containing intrauterine device (IUD)
- Condom with spermicidal foam/gel/film/cream/suppository
- Male partner who has had a vasectomy for at least 4 months
- Tubal ligation
- Hysterectomy

5. STUDY VISIT PROCEDURES

All study visit procedures should be conducted in the order listed in Section 5.1.

Informed Consent: Properly executed informed consent (written and verbal) is to be obtained prior to completion of any study-related procedures. Subjects must review, sign, and date the informed consent document and receive a copy. The original document should be retained in the Investigator's Site File (ISF) or with the Subject's source documents.

Medical and Ocular History: Relevant and clinically significant medical and ocular history must be recorded. This includes reported changes between Screening Visit 1 and first IP administration.

Concomitant Medications/Procedures: All prescription and over-the-counter (OTC) medications and nutritional supplements taken during the study and 30 days prior to the Screening Visit will be recorded. Additionally, all ocular hypotensive medications taken within 45 days prior to the Screening Visit will be recorded. Diagnostic and anesthetic eye drops do not need to be recorded. All procedures occurring during the study and 30 days prior to the Screening Visit will be recorded.

Randomization: Randomization will be accomplished using an Interactive Web Response System (IWRS). Site personnel will receive instruction about IWRS access and use.

Adverse Events: Any events occurring after the first dose of IP will be recorded as an adverse event. At each visit, the subject should be asked questions such as, "How are you feeling? How are your eyes feeling today? Have you had any changes since the last exam?"

IP Administration and Compliance: The first dose of study IP will be administered by study staff after the IOP measurement at T_0 on Day 1. Subjects will self-dose for the remainder of the trial except on study visit days when subjects will be instructed to refrain from self-dosing prior to the visit and the study morning IP will be administered by the unmasked dosing coordinator after the related IOP measurements; evening IP will be self-dosed (out of view of study staff) after the related IOP measurements. Compliance will be assessed at applicable visits by asking the subject their recollection of any missed doses. Confirmation of compliant IP dosing the evening prior to a study visit must be confirmed or the visit should be rescheduled. If the subject reports missing more than 4 doses since the prior visit, a Protocol Deviation will be documented and the subject will be counseled on IP compliance.

Heart Rate and Blood Pressure (BP) Measurements: Both systolic and diastolic blood pressure should be recorded. The same type of device and cuff must be used throughout the study on the same subject. An appropriate cuff size with a bladder encircling at least 80% of the upper arm should be used to ensure accurate measurements.

Blood pressure will be measured using the most ideal conditions possible given the subject's medical condition and age. If possible, the same arm should be used throughout the study. Blood pressure should be measured after sitting in a seated position for 5 minutes.
Heart rate measurements will be measured by radial pulse for at least 30 seconds. The subject should be in a seated and relaxed state. An automated blood pressure unit may be used to measure the heart rate.

Best-Corrected Visual Acuity (ETDRS): Visual acuity will be performed before implementing any procedure that can affect vision (i.e., pupil dilation, tonometry, and gonioscopy). The most current refraction within 6 months prior to the Screening Visit will be recorded unless changes in refraction are suspected. If changes are suspected since the most current refraction, refraction should be repeated at the Screening Visit. The same optotype should be used throughout the study for a specific subject, and the right eye should be tested first. Best corrected visual acuity (BCVA) should be recorded using the ETDRS chart (or a modified ETDRS chart). If a change in BCVA is noted, pinhole may be used to test for the BCVA, but a formal refraction prior to dilation should be performed during that visit and/or on the next visit. The logarithm of the minimum angle of resolution (LogMAR) scores will be calculated according to the standard scoring methodology. A change of ≥ 10 letters may indicate an adverse event and should be investigated further by the investigator and the refraction should be rechecked.

ETDRS Scoring Methodology: The best-corrected visual acuity will be measured using an ETDRS (Early Treatment Diabetic Retinopathy Study) chart. The test distance must be at the distance specified on the ETDRS chart.

Position the ETDRS chart at the approximate eye level of an average-height seated subject. Mark a spot on the floor (e.g., with tape) that is the appropriate test distance from the ETDRS chart. The test distance and lighting for the chart must be kept constant throughout the study. The subject should be seated comfortably, directly in front of the chart, so that the eyes remain at the appropriate distance specified by the ETDRS chart. Testing always begins with the right eye, followed by the left eye. The fellow eye should be occluded.

Do not point to specific letters on the chart during the test. Ask the subject to read each letter slowly, line by line, left to right, beginning with Line 1 at the top. Tell the subject that the chart has letters only, no numbers. If the subject reads a number, remind him/her that the chart contains no numbers, and request a letter in lieu of the number. The subject should be told that only one chance is given to read each letter, but he/she may change his/her mind before moving to the next letter. Do not allow the subject to proceed to the next letter until he/she has given a finite answer. If the subject is unsure about the identity of the letter, then the subject should be encouraged to guess. The subject should be encouraged to continue reading even if making

mistakes. When a subject reaches a level where he/she cannot guess, the examiner may stop the test.

Each letter read correctly is counted. The examiner will total each line and the whole column (0 if no letters are incorrect) on the data collection form and record in the format specified.

Slit Lamp Biomicroscopy: This will be performed by the investigator's usual clinical technique and must be performed prior to pupil dilation OU. Changes and/or abnormalities of the anterior segment in the lids, conjunctiva, cornea, anterior segment, and lens will be graded. Iris color will be recorded at screening. Magnification, lighting, and examiner should be consistent for each subject throughout the study. Findings will be graded according to the following scales:

LID

Erythema

None (0)	Normal, without any redness, or less than mild
Mild (1+)	A low grade flushed reddish color
Moderate (2+)	Diffused redness encompassing the entire lid margin
Severe (3+)	Deep diffused reddish color of lid margins and superior or inferior eyelid

Edema

None (0)	Normal, no swelling of the lid tissue, or less than mild
Mild (1+)	Slight diffuse swelling above normal
Moderate (2+)	General swelling
Severe (3+)	Extensive swelling of the eyelid(s), with or without eversion of upper and/or lower lids.

CONJUNCTIVA

Hyperemia

None (0)	Normal: few vessels of bulbar conjunctiva easily observed
Minimal (0.5+)	Trace flush, reddish-pink color of the bulbar conjunctiva
Mild (1+)	Mild flush – Reddish pink of the bulbar conjunctiva
Moderate (2+)	Moderate, Bright reddening of the bulbar conjunctiva
Severe (3+)	Deep, severe, bright and diffuse reddening of the bulbar conjunctiva

Edema

None (0)	Normal, no swelling of the conjunctiva or less than mild
Mild (1+)	Slight diffuse or regional swelling of the conjunctiva
Moderate (2+)	General swelling of the conjunctiva
Severe (3+)	Extensive swelling of the conjunctiva

CORNEA

Edema

None (0)	Transparent and clear or less than mild
Mild (1+) =	Dull glassy appearance
Moderate (2+)	Dull glassy appearance of epithelium with large number of vacuoles
Severe (3+)	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

ANTERIOR CHAMBER

Cells

None (0)	No cells seen or less than mild
Mild (+ 1)	1-5 cells
Moderate (2+)	6-10 cells
Severe (3+)	11-20 cells
Hypopyon (4+)	> 20 cells, Hypopyon Formation (indicate size of hypopyon)

Flare

None (0)	No Tyndall effect or less than mild
Mild (1+)	Tyndall beam in the anterior chamber has a mild intensity
Moderate (2+)	Tyndall beam in the anterior chamber is of strong intensity
Severe (3+)	Tyndall beam is very intense. The aqueous has a white, milky appearance

LENS

Phakic	Yes/No
Aphakic	Yes/No
Pseudophakic	Yes/No

For phakic only

Crystalline Lens	
Normal (0)	No opacity in the lens
Abnormal	
Nuclear Cataract	
None (0)	
Minimal (1+)	Minimal changes in nuclear zone
Mild (2+)	Mild opacity with central zone still distinguishable
Moderate (3+)	Moderate opacity
Severe (4+)	Dense opacity
Cortical Cataract	
None (0)	
Minimal (1+)	<1/8 of the circumference
Mild (2+)	<1/8, but less than 1/4 of the circumference
Moderate (3+)	<1/4, but less than 1/2 of the circumference
Severe (4+)	≥1/2 of the circumference
Posterior Subcapsular Cataract	
None (0)	
Minimal (1+)	
Mild (2+)	
Moderate (3+)	
Severe (4+)	

For pseudophakic only

Posterior capsular opacification (PCO)	
None (0)	
Trace/Mild (1+)	<2 mm
Moderate (2+)	≥2 mm, but <3 mm
Severe (3+)	≥3 mm
Clear central axis (s/p YAG Capsulotomy)	

Conjunctival Hyperemia: Hyperemia will be assessed and recorded separately from biomicroscopy through direct visual observation using photographic reference scale prior to fluorescein instillation and IOP measurement. The hyperemia will be graded on a 0 to 3 scale using the photographic reference scale provided by the Sponsor for use in this protocol.

0	Normal: few vessels of bulbar conjunctiva easily observed
0.5	Trace flush, reddish-pink color of the bulbar conjunctiva
1	Mild flush – Reddish pink of the bulbar conjunctiva
2	Moderate, Bright reddening of the bulbar conjunctiva
3	Deep, severe, bright and diffuse reddening of the bulbar conjunctiva

Tonometry (Intraocular Pressure): All IOP measurements must be measured by Goldmann applanation tonometry. The tonometer calibration should be checked for accuracy within one month before screening the first subject for the study. A Tonometer Calibration Form must be completed and filed before the first subject is screened and calibration must be checked monthly throughout the study. Variation within ± 2 mm Hg is acceptable. The fluorescein and anesthetic agents should remain consistent throughout the study. IOP will be measured following slit lamp biomicroscopy and always prior to dilation.

Two consecutive IOP measurements should be taken for each IOP time point, with the right eye being measured first. The applanation probe should be withdrawn between measurements. Intraocular pressure will be measured 2 times and the average will be used for analysis. If the two measurements differ by more than 2 mmHg, a third measurement will be taken and the median value will be used for analysis. Mean IOP values should be rounded up to the next whole number if the value is equal to or greater than 0.5 mmHg, and rounded down if less than 0.5 mmHg (e.g., 24.5 should be rounded to 25, 24.4 should be rounded to 24). The same procedure will be repeated on the contralateral eye.

In order to minimize confounding variables, every effort should be made to acquire all IOP measurements for each subject using the same tonometer and approximately at the same time at all visits. Every effort should be made to use the same examiner for each unique timepoint.

Pachymetry: Pachymetry will be performed OU at the Screening Visit; results obtained within the prior 6 months may be used if no change is suspected. Central corneal thickness (central zone) will be measured with a calibrated ultrasound pachymeter in both eyes after topical anesthetic has been applied. The subject will be in a seated position and fixating on a target straight ahead. Three measurements will be taken in the right eye first, and the average will be recorded in micrometers (μm). The same procedure is then performed on the left eye.

Gonioscopy: The gonioscopy examination will be performed OU at the Screening Visit; results obtained within the prior 6 months may be used if no change is suspected. Gonioscopy should be performed prior to instillation of dilating or miotic drops, with high magnification, and with dim illumination to potentiate visualization of the angle in its natural configuration. The angular width of the angle recess will be graded as an average score representative of all 4 quadrants using the grading criteria below.

Grade Description (Shaffer System, based on the angular width of the angle recess [Marsh & Cantor, 2005])

4	45 to 35° angular approach, wide open
3	35 to 20° angular approach, wide open
2	20° angular approach, narrow
1	≤ 10° angular approach, extremely narrow
Slit	0° angle, narrowed to slit

Visual Field Examination: A visual field will be performed OU at the Screening Visit; reliable results obtained within the prior 6 months may be used if no change is suspected. Visual fields must be automated threshold visual fields (i.e., Humphrey [30-2 or 24-2] or Octopus equivalent).

SITA Standard (24-2 or 30-2) is preferred, SITA fast is also allowed. The subject's best correction at 33 cm is to be used. Visual fields must be reliable, defined as those with a) fixation losses less than or equal to 33%, b) false positives less than or equal to 33% and c) false negatives less than or equal to 33%. Visual fields are to be performed with a non-dilated pupil unless, in the opinion of the investigator, the pupil is so miotic (i.e., < 3 mm) that dilation is required. If the visual field examination was conducted using dilation at the Screening Visit, dilation should be used for any subsequent visual field examinations (i.e., if performed at an unscheduled visit; visual field testing should be performed during the trial if glaucomatous progression is suspected). Visual field interpretation must be documented and reviewed by the investigator, including an assessment of whether the results are normal or abnormal and the clinical significance of abnormalities.

Dilated Ophthalmoscopy: Posterior segment exam will be performed according to the investigator's preferred procedure. Magnification, lighting, and examiner should be consistent for each subject throughout the study. Ophthalmoscopy should be performed after pupil dilation (e.g., 1% tropicamide or cyclopentolate and/or 2.5% phenylephrine). The examination should include an evaluation of the vitreous, retina, macula, choroid, and optic nerve (including the absence or presence of notches and/or disc or peripapillary hemorrhages). Abnormalities and pathologic findings will be graded. Ocular structures will be graded according to the following scale.

Vitreous, Retina, Macula and Choroid: Examination emphasizes the visual axis.

0 Normal
1 Abnormal, describe.

Optic Nerve

0 Normal. No damage
1 Mild optic nerve damage, secondary to glaucoma including any rim loss (sloping or thinning)
2 Moderate optic nerve damage, including cupping to disc margin at one or more points
3 Severe optic nerve damage, nearly total cupping, only nasal rim or less present

Any new findings (i.e., notch and/or peripapillary hemorrhage) or deterioration occurring after the first IP dose will be reported as an adverse event. The cup/disc ratio will be recorded horizontally and vertically for each examination, and reported in 0.1 increments. Changes observed between Screening Visit 1 and prior to the first IOP dose will be reported as ocular history.

Pregnancy Test:
Urine pregnancy testing will be required at the Screening Visit for subjects of child-bearing potential and at Day 0. Pregnancy test results must be negative for subjects to continue in the study. On Day 28, a urine pregnancy test will be administered.

5.1 Study Visits

Perform study procedures as referenced in the Schedule of Study Assessments and Procedures (see protocol synopsis) in the order specified below.

5.1.1 Screening

- Informed consent
- Medical/ocular and concomitant medication history, with review of inclusion/exclusion criteria
  - Any unfavorable medical occurrence should be reported as medical or ocular history
- BCVA
- Biomicroscopy
- Goldmann tonometry
- Gonioscopy
- Pachymetry
- Dilated ophthalmoscopy
- At any time during the visit after informed consent:
  - Urine pregnancy test (if applicable); result must be negative
  - Visual field testing

5.1.2 Day 0

- Medical/ocular and concomitant medication history, with review of inclusion/exclusion criteria
- Urine pregnancy test (if applicable, at any time during the visit); result must be negative
- Any unfavorable medical occurrence should be reported as medical or ocular history
- Heart rate/blood pressure at all required timepoints
- BCVA (may be performed prior to heart rate/blood pressure)
- Biomicroscopy
- Conjunctival hyperemia grading at all required timepoints
- Goldmann tonometry at all required timepoints

5.1.3 Day 1

- Medical/ocular and concomitant medication history, with review of inclusion/exclusion criteria (and again after Pre-T_0 Goldmann tonometry)
- Any pre-dose unfavorable medical occurrence should be reported as medical or ocular history
- Heart rate/blood pressure at all required timepoints
- BCVA(may be performed prior to heart rate/blood pressure)
- Biomicroscopy at all required timepoints
- Conjunctival hyperemia grading at all required timepoints
- Goldmann tonometry at all required timepoints
- Randomization and IP administration immediately after 8 AM T_0 IOP timepoint
- Any post-dose unfavorable medical occurrence should be reported as an Adverse Event

5.1.4 Days 7 and 14

- Concomitant medications

- Adverse events
- IP compliance
- BCVA(may be performed prior to heart rate/blood pressure)
- Biomicroscopy at all required timepoints (i.e., Pre-T_0)
- Conjunctival hyperemia grading at all required timepoints (i.e., Pre-T_0)
- Goldmann tonometry (Pre-T_0)
- IP administration (8 AM only)

5.1.5 Day 28

- Concomitant medications
- Adverse events
- IP compliance
- Heart rate/blood pressure at all required timepoints
- BCVA(may be performed prior to heart rate/blood pressure)
- Biomicroscopy at all required timepoints
- Conjunctival hyperemia grading at all required timepoints
- Goldmann tonometry at all required timepoints
- IP administration (8 AM only)
- Urine pregnancy test (if applicable) at any time during the visit
- Dilated ophthalmoscopy after final Goldmann tonometry – may be performed on following day for scheduling convenience.

6. ASSESSMENT OF EFFICACY

6.1 Efficacy Parameters

Primary Efficacy Endpoints:
The primary efficacy measure will be the mean change in IOP from Baseline (Day 1) IOP (mmHg) for each group on Day 28 at each matched time point as compared to timolol. IOP will be measured according to the Schedule of Assessments and Procedures Table.

Secondary efficacy endpoints:
1. The observed IOP, mean change from Baseline, and % change from Baseline IOP at each matched time point at each visit, and
2. The mean observed, mean change from Baseline and mean % change from Baseline for the mean diurnal IOP at each visit, and
3. The proportion of subjects with IOP $\leq$ 18 mmHg at each time point at each visit, and with the mean diurnal IOP $\leq$ 18 mmHg for each visit.

6.2 Method and Timing

The efficacy parameter for this study is IOP as measured by Goldman applanation tonometry. The timing of the IOP measurements is based on standard diurnal measurements, and data from the previous clinical study of H1337.

7. ASSESSMENT OF SAFETY

7.1 Adverse Event Reporting

The investigator is responsible for monitoring the safety of subjects who have entered the study. Subjects should be asked at each visit about any changes in their health status. Any changes in health status after informed consent has been obtained, but prior to the first dose of IP, will be reported as medical history. Changes will be reported as AEs after the subject receives the first dose of IP (Day 1). Ongoing AEs at study completion (Day 28) or the final study visit will be followed until the event resolves, stabilizes, or for 30 days, whichever comes first.

All adverse events (serious and non-serious) must be documented regardless of the causal relationship to the study medication. The severity, frequency, seriousness, duration, relationship to IP(s), treatment of event, action taken with IP, and outcome for every adverse event should be documented.

Non-clinically significant incremental < 2 unit grade changes in conjunctival hyperemia (according to the photographic reference scale provided for the trial) are not required to be reported as adverse events; changes ≥2 unit grade changes must be reported as an Adverse Event and tracked until returning to baseline.

To capture the most potentially relevant safety information during a clinical study, it is important that investigators record accurate AE terms. Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE.

Investigators are required to report to D. Western Therapeutics, Inc. or its representative all observed and/or volunteered AEs occurring during the clinical trial (21 CFR §312.64[b]) regardless of treatment group or suspected causality to the investigational drug.

7.2 Definition of Adverse Event

An AE is any unfavorable medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. All AEs, including observed or volunteered problems, complaints, or symptoms, must be recorded. This definition also includes AEs which are reported up to 30 days after a subject has completed a clinical study. Therapeutic failures during clinical trials are not considered to be AEs.

Examples of adverse events include, but are not limited to:

- Abnormal test finding judged clinically significant by PI, and/or induces clinical signs or symptoms and/or requires active intervention and/or requires interruption or discontinuation of IP

- Clinically significant symptoms and signs
- Hypersensitivity
- Progression/worsening of underlying disease (not therapeutic failure of IP)
- Loss of > 3 lines BCVA
- Clinically significant change in pachymetry

Additionally, they may include the signs and symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Exposure in utero (i.e., pregnancy within 30 days of study completion)

7.3 Definitions of Non-Serious Adverse Events

Adverse events that do not meet the definitions for serious adverse events (SAEs) are non-serious AEs. Subjects should be instructed to report any AE that they experience to the investigator.

7.4 Definition of Serious Adverse Event

An SAE is any experience that suggests a significant hazard, contraindication, side effect, or precaution. This includes any experience that:

- Results in death
- Is acutely life-threatening
- Requires in-patient hospitalization or prolongs the existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires medical or surgical intervention to prevent one of the outcomes listed above

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse. This definition includes concurrent illness or injuries, exacerbation of pre-existing conditions and AEs occurring as a result of drug withdrawal, abuse or overdose. Serious adverse events observed during all periods of a clinical study after the first dose of IP (Day 1) have been administered, are to be recorded, including those occurring during a period without study medication and whether or not the AE is judged to be related to the study medication.

7.5 Hospitalization

Reported adverse events associated with hospitalization or prolonged hospitalizations are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility

meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care facility.

Hospitalization does not include the following:

- Rehabilitation facility
- Hospice facility
- Respite care (caregiver relief)
- Skilled nursing facility
- Nursing homes
- Routine emergency admission
- Same day surgeries

Hospitalization or prolongation in the absence of a precipitating, clinical adverse event (e.g., for work-up of persistent pre-treatment abnormality) is not in itself a serious adverse event.

Diagnostic and therapeutic noninvasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as an adverse event and the resulting surgical intervention should be recorded as a treatment of that adverse event.

7.6 Pregnancy

If a subject becomes pregnant during the study or up until 30 days after the last dose of IP (i.e., the final clinical visit), the Investigator must notify D. Western Therapeutics, Inc. or its representative immediately and within 24 hours of learning of its occurrence by completing a Pregnancy Report Form and forwarding to D. Western Therapeutics, Inc. or its representative. The pregnancy should be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Any complications during pregnancy should be recorded as an AE and may constitute an SAE if they fulfill any of the specified criteria for an SAE. If upon outcome, the pregnancy meets one of the serious criteria (e.g. spontaneous miscarriage, congenital anomaly, or birth defect), it will then be considered an SAE and full details will be requested. These events will not be included in the clinical study report, but will be maintained in the clinical study files.

7.7 Definition of Unexpected Adverse Events

An AE is considered an unexpected AE if it is not mentioned in the Investigator's Brochure (IB), or if it is of greater frequency and/or severity than that mentioned in the IB, in the judgment of the Medical Monitor.

7.8 Definition of Relationship of Adverse Event to IP

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). The investigator must record the relationship and report such an assessment in

accordance with the serious AE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to the adverse event. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by D. Western Therapeutics, Inc. If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented in study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable. The categories are as follows:

0=Unrelated:	No temporal association, or the cause of the event has been identified, or the drug, biological, or device cannot be implicated.
1=Possibly Related:	Temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biological, or device cannot be excluded.
2=Probably Related:	Temporal association, other etiologies are possible, but unlikely.
3=Definitely Related:	Temporal association and no other etiologies possible.

7.9 Documentation of Severity of Adverse Events

All adverse events will be examined to determine severity. The categories are as follows:

Mild:	Awareness of sign, symptom, or event, but easily tolerated. Does not interfere with subject's usual function.
Moderate:	Discomfort enough to cause some interference with usual activity and may warrant intervention.
Severe:	Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.
Life-threatening:	Immediate risk of death.

7.10 Reporting Serious Adverse Events

SAEs (this refers to any AE that meets one or more of the aforementioned serious criteria) occurring after the subject receives the first dose of IP (Day 1) will be reported to D. Western

Therapeutics, Inc. or its representative, followed until the event resolves or stabilizes, the subject's final visit or study completion (Day 28), or within 30 days of the last administration of IP, whichever comes first.

SAEs, and all deaths occurring within the study population, whether considered to be drug-related or not, will be reported using the SAE Report Form within 24 hours of knowledge of the occurrence to D. Western Therapeutics, Inc. or its representative.

This can be done by emailing a completed SAE Report Form to:

Name: Ashley Hehr
Title: Drug Safety Specialist Consultant
Company: Safety Sphere, LLC (www.safety-sphere.com)
Email: H1337-202sae@safety-sphere.com
Office Phone: 844-965-1070
Office Fax: 855-805-2406

When the initial report is made verbally or by telephone to D. Western Therapeutics, Inc. or designee, the SAE Report Form must be emailed within 24 hours according to the instructions above.

The investigator will be requested to supply detailed information regarding the event at the time of the initial contact. All SAEs (initial and follow-up information) must be reported to the reviewing Institutional Review Board/Ethics Committee, according to their reporting requirements, and a copy of that report must be forwarded to D. Western Therapeutics, Inc. or its representative. D. Western Therapeutics, Inc. (or designee) will report all Suspected Unexpected Serious Adverse Reactions (SUSARs) to Regulatory Authorities within 7/15 days of receipt depending on reporting requirements.

SAEs that come to the attention of the investigator within 30 days following the final study visit or Day 28 will be reported to D. Western Therapeutics, Inc. or its representative within 24 hours of knowledge of the occurrence.

7.11 Serious Adverse Event Follow-Up

For all SAEs, the investigator must submit follow-up reports to D. Western Therapeutics, Inc. or designee, regarding the subject's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the subject dies, or within 30 days of the last administration of IP, whichever comes first.

8. STATISTICAL PLAN

8.1 Sample Size

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 ITT population, a total of 50 subjects per group is required.

8.2 Statistical Methods

Continuous and ordinal measures will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum values). Qualitative measures will be tabulated by counts and percentages. Selected safety measures may be summarized by the use of shift tables. Summary tables will show the data for each time point (visit and/or time of day as appropriate) and will display the observed and change from baseline value. In addition, percentage change from baseline will be summarized for IOP measurements.

Baseline is defined as the last non-missing measurement prior to first IP administration.

A statistical analysis plan will be finalized prior to unmasking the treatment assignments.

An analysis of results will be conducted when the database has been locked and the treatment assignments have been revealed. No interim analyses are planned.

8.3 Subject Population(s) for Analysis

All subjects who receive IP and at least one dose will be evaluable for the safety analysis. For efficacy considerations, the primary analysis population will be the intent-to-treat (ITT) population. All randomized subjects will be evaluable for the ITT analyses. Subjects who receive study medication, satisfy pre-randomization inclusion/exclusion criteria, and who complete at least one on-therapy study visit will be evaluable for a per protocol (PP) population analysis. 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.

8.4 Significance and Adjustment for Multiple Comparisons

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 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 LSmean, SE, and 2-sided 95% CI for the between treatments differences.
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 3. First, the primary endpoint is tested for non-inferiority at all 4 time points at Day 28 (excluding +12 hours) and all 3 on-treatment time points at Day 1 (excluding +12 hours) for the first pre-defined Group comparison listed in Table 3. 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 7 timepoints, then testing of the second listed Group Comparison in Table 3 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 3.

Table 3 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 7 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 7 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 7 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

8.5 Accountability Procedure

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. There are no plans to impute values for missing data. With regard to the primary efficacy variable, IOP, there are steps taken in the procedure for collecting these data that minimize the likelihood of spurious data.

8.6 Deviation Reporting

Any deviations from the statistical plan enumerated in the final statistical plan will be described and justified in the clinical study report.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Study visits will be conducted by an authorized D. Western Therapeutics, Inc., representative to inspect study data, subjects' medical records, and CRFs in accordance with current US Good Clinical Practices (GCP) and the respective local, national government and international regulations and guidelines.

The investigator will permit authorized representatives of D. Western Therapeutics, Inc., or its representative, the Food and Drug Administration (FDA), and any appropriate health authorities to inspect facilities and records relevant to this study.

10. DATA REVIEW AND ANALYSIS

Masked data will be continually monitored on an ongoing basis, according to the safety plan, as subjects are enrolled and complete the study. During the study, investigators, site personnel except the unmasked dosing coordinator, and D. Western Therapeutics, Inc. personnel responsible for the daily conduct of the study will remain masked to the results to maintain the scientific rigor and credibility of the trial. D. Western Therapeutics, Inc. personnel and selected external consultants will be unmasked once the data is locked. Data will then be reviewed, the safety and efficacy for each dose determined.

11. QUALITY CONTROL AND QUALITY ASSURANCE

Each investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by D. Western Therapeutics, Inc., prior to seeking approval from the IRB/Ethics Committee. Each investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. During study conduct, D. Western Therapeutics, Inc. and/or its representative will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. These representatives may review source documents to confirm that the data recorded in CRFs is accurate. The investigator and institution will allow D. Western Therapeutics, Inc., representatives, or agents and appropriate regulatory authorities direct access to source documents and CRFs to perform this verification.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

12. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with current US FDA regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki, and local ethical and legal requirements. The Principal Investigator must sign the protocol signature page to indicate acceptance of the protocol.

12.1 Informed Consent

The subject must sign the Informed Consent Document before his or her participation in the study. A copy of the Informed Consent Document must be provided to the subject or the subject's legal guardian. If applicable, it will be provided in a certified translation of the subject's first or native language. The original signed informed consent document for each participating subject shall be filed with records kept by the investigator (ISF) and must be available for verification by study monitors at any time; a copy will be given to each subject.

12.2 Institutional Review Board/Ethics Committee

This protocol, the informed consent document, relevant supporting information and all types of subject recruitment or advertisement information must be submitted to the IRB/Ethics Committee for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB/Ethics Committee prior to implementing changes in the study. The investigator is responsible for keeping the IRB/Ethics Committee apprised of the progress of the study, any SAEs, and any changes made to the protocol according to the requirements of the site's IRB.

12.3 Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is strictly prohibited. Information obtained during the conduct of this study will be used by D. Western Therapeutics, Inc., in connection with the development of the IP. The study investigator is obliged to provide D. Western Therapeutics, Inc., or designee with complete test results and all data developed in this study. This information may be disclosed to other physicians who are participating in this trial, and to the FDA as deemed necessary by D. Western Therapeutics, Inc. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission.

12.4 Early Sponsor Discontinuation of the Trial

All clinical investigational data will be reviewed by the Medical Monitor on a regular basis. Reports of all data may be made available to the appropriate IRB/Ethics Committee and to the FDA. The clinical investigation may be suspended if the Medical Monitor, upon review and evaluation of the clinical data, finds the severity or incidence of single or total complications unacceptable for continuation of the investigation.

13. DATA HANDLING AND RECORD KEEPING

The investigator must retain all study records according to ICH guidelines and according to the record retention policies of the country where the study is being conducted. FDA requires that records be retained for at least 2 years after a marketing application is approved for the drug, or if an application is not approved, until 2 years after FDA has been notified of the discontinuation of the investigational use of the drug (21CFR312.57).

14. APPENDICES

14.1 References

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