Title

Phase I/II, Double-Masked, Randomized, Vehicle-Controlled Study of H-1337 Ophthalmic Solution for Glaucoma and Ocular Hypertension

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Phase 1 / 2 Double-Masked Randomized Vehicle-Controlled Study H-1337 Ophthalmic Solution in Glaucoma and Ocular Hypertension

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Registered on clinicaltrials.gov as NCT03452033

Abstract

Purpose:

Phase 1 / 2 evaluation of H-1337 Ophthalmic Solution in Subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OHT)

Design:

This was a phase 1/2, randomized, double-masked, vehicle-controlled, dose-response study. conducted at 6 private practice sites in the United States.

Participants:

Enrolled were 87 subjects with bilateral POAG or OHT.

Methods:

After washout of ocular hypotensive medications as required, subjects were randomized to receive H-1337 Ophthalmic Solution 0.06%, 0.20% and 0.60% or its vehicle, BID unilaterally in the study eye for the first 3 days, then BID O.U. from Day 4 to Day 28.

Main outcome measures:

The primary efficacy endpoint was the mean change from Baseline (Day 0) IOP for each group on Day 14 at Hour 4 as compared to vehicle.

Results:

In the primary efficacy endpoint, mean change from baseline at Day 28 at Hour 4, the mean changes from baseline were -4.45 ± 3.801, -5.16 ± 3.114, -4.93 ± 3.110, and -0.39 ± 2.355 in the 0.06%, 0.2% and 0.6% H-1337 and vehicle groups, respectively. The difference between each active group and the vehicle was statistically significant ($p < 0.0001$). Treatment-emergent adverse events (TEAEs) occurred in 49% of subjects receiving H-1337 (range, 41% [0.2% arm] to 64% [0.6% arm] across H-1337 arms) and in 18% of subjects receiving vehicle. The majority of TEAEs were mild in severity; 3 subjects receiving H-1337 had a TEAE of moderate intensity (instillation site erythema, vision blurred, and muscle strain).

Conclusion:

H-1337 Ophthalmic Solution showed clinically and statistically significant ocular hypotensive activity and was well tolerated, with a relatively low incidence of hyperemia.

Introduction

Glaucoma is a chronic, degenerative optic neuropathy with a characteristic appearance of the optic nerve.[1] The primary method for the treatment of open-angle glaucoma (OAG) is the lowering of intraocular pressure (IOP) by either medical, surgical or laser therapy.[2, 3] The selection of treatment modalities for a given patient depends upon numerous factors, including patient preference.[4] With respect to medical therapies, there are several classes of topical treatments available for chronic therapy including prostaglandins, β-adrenoceptor antagonists, α-adrenoceptor agonists, carbonic anhydrase inhibitors, and the newest class, rho-kinase inhibitors (RKI's).[5] Each of these classes, and each agent within each class, has benefits and risks. In the most recent class of RKI's, one molecule is approved for topical ocular use in Japan (ripasudil), and another in the United States and Europe (netarsudil, also in a fixed-combination with latanoprost). While these agents are a welcome addition to the pharmacopeia in the treatment of OAG, they have limitations on efficacy and ocular safety.[6-8]

Isoquinoline sulfonamide derivatives have been known to inhibit selectively a variety of protein kinases.[9, 10] Previously, a series of molecules were evaluated in normotensive monkeys, and lowered IOP from 2 to 6 mmHg.[11] Isoquinoline sulfonamides such as fasudil, H-1152, ripasudil and H-1129 produce IOP-lowering and neuroprotective effects in preclinical models through Rho kinase inhibition.[12] H-1337, an isoquinoline sulfonamide, together with its major metabolite, H-1337M1, inhibits several kinases in vitro, including Leucine-Rich Repeat Kinase 2 (LRRK2).[13] LRRK2 molecular interactions and physiological function are closely related to the organization of the actin-based cytoskeleton.[14] Therefore, it is hypothesized that inhibition of LRRK2 might reduce IOP by disruption of actin cytoskeleton in trabecular meshwork cells, change of cell morphology and promoting aqueous humor outlfow. Administered topically to the eye, H-1337 demonstrated ocular hypotensive activity in normotensive rabbits and monkeys of 7.3 mmHg and 4.3 mmHg, respectively.[15]

Based upon this novel mechanism of action and in vitro and in vivo activity, an ophthalmic formulation of H-1337 was developed for clinical evaluation. H-1337 has not been previously evaluated in humans. In this report, we report a Phase 1 / 2 evaluation of H-1337 Ophthalmic Solution.

Materials and Methods

Study design

This was a phase 1/2, randomized, double-masked, vehicle-controlled, dose-response study. conducted at 6 private practice sites in the United States. This study was conducted under an IND in accordance with Good Clinical Practice as required by US Food and Drug Administration regulations. The study was approved by an Institutional Review Board, adhered to the Declaration of Helsinki, and all subjects provided written informed consent before enrollment in the study. This study was registered on clinicaltrials.gov as NCT03452033

All drug products were packaged in the same container/closure system (bottle, tip and cap). Thus, all subjects, clinical staff and investigators were masked as to treatment."An unmasked statistician generated the randomization codes. Other study statisticians, investigators, medical monitor and other study personnel were masked to the identity of the treatments until all data was entered into the database and locked.

Consenting subjects who met the applicable inclusion/exclusion criteria at the Screening Visit discontinued use of any current ocular hypotensive therapy during the washout period. The washout duration was dependent on the patient's pre-study ocular hypotensive therapy (Muscarinic agonists, oral or topical carbonic anhydrase inhibitors (CAI): ≥ 5 days; β-adrenoceptor antagonists: ≥ 6 weeks; α- adrenoceptor agonists: ≥ 5 weeks; prostaglandin analogues: ≥ 6 weeks; fixed dose combination products used the component with the longest washout period). The study eye was the eye that met the entry IOP criteria after washout. If both eyes met the criteria, then the study eye was the eye with the higher 8:00 am IOP at the Baseline Visit. If both eyes had the same 8:00 IOP, the study eye was the right eye.

Following the washout period (if applicable), subjects meeting all inclusion/exclusion criteria were randomized to 1 of 4 dosing arms in a 1:1:1:1 ratio: H-1337 at concentrations of 0.06%, 0.2%, or 0.6%, or vehicle (control). Randomization was stratified by baseline IOP (23-26 mm Hg and 27-32 mm Hg at 8:00 AM).

Study drug was to be taken twice daily (BID), with dosing initiated in the office on Day 0. As a first in human study, on Day 0 to Day 3, only the study eye was dosed. For the remainder of treatment (Days 4-28), both eyes were dosed.

Subjects were monitored for safety, tolerability, and efficacy assessments during visits at Baseline (Day 0), Day 1, Day 4, Day 14, and Day 28. At each visit, subjects had safety assessments, measurement of best-corrected visual acuity (BCVA), slit-lamp eye examination, and Goldmann applanation tonometry. Goldmann applanation tonometry was performed to assess IOP at T_0 (pre-dose), T_0+1h, T_0+2h, T_0+4h, T_0+8h, and T_0+12h during the Baseline, Day 14, and Day 28 visits and at T_0 at Day 1 and Day 4 visits.

Subject eligibility

Subjects (18 years or older) with a diagnosis of bilateral POAG or OHT were eligible if they had baseline IOP (after washout of any ocular hypotensive drugs) ≥23 mm Hg at 8:00 AM in the study eye and ≤32 mm Hg in both eyes at all baseline time points. Subjects also had to meet the following key criteria: (1) BCVA in both eyes of 20/200 or better Snellen equivalent; (2) no refractive surgery, corneal cross-linking, intravitreal steroid injection, or glaucoma intraocular surgery in either eye (laser trabeculoplasty was permitted if more than 6 months prior to screening); (3) no intraocular laser surgery within 1 month in either eye (e.g., laser capsulotomy, laser iridotomy, and/or retinal laser); (4) no non-glaucoma intraocular surgery within 3 months in either eye; (5) no Sub-Tenon's, subconjunctival, or periocular steroid injections within 6 months in either eye; (6) no history of uveitis, keratitis, scleritis, or penetrating ocular trauma in either

eye; (7) no advanced or severe glaucoma in either eye; (8) no progressive retinal or optic nerve disease in either eye from any cause other than glaucoma; (9) no clinically significant moderate or severe chronic or active blepharitis, ocular dermatitis, or recent ocular conjunctivitis and/or ocular inflammation within 3 months in either eye; and (10) no use in either eye of ocular topical corticosteroids within 7 days or chronic topical corticosteroids within 28 days.

Study drugs

H-1337 Ophthalmic Solution is a benzalkonium chloride-preserved, isotonic, sterile ophthalmic solution buffered at pH 6.5 and was supplied at 3 concentrations (w/v: 0.06%, 0.2%, and 0.6%). Vehicle was identical in formulation to the H-1337 study drug product but without H-1337.

IOP assessment

Intraocular pressure was taken and read by Goldmann applanation tonometry by a single person. Two consecutive IOP measurements were taken at each IOP time point, with the right eye being measured first. The applanation probe was withdrawn between measurements. The average of the 2 measurements was used for analysis. If the 2 measurements differed by more than 4 mm Hg, a third measurement was taken, and the median value was used for analysis.[16]

Conjunctival hyperemia assessment

Conjunctival hyperemia was assessed and recorded separately from biomicroscopy through direct visual observation prior to fluorescein instillation and IOP measurement. The hyperemia was graded on a scale of 0 to 3 using a photographic reference scale and the following guidance: 0 (normal – few vessels of bulbar conjunctiva easily observed; 0.5 (trace) – trace flush, reddish-pink color of the bulbar conjunctiva; 1 (mild) – mild flush, reddish-pink color of the bulbar conjunctiva; 2 (moderate) – bright reddening of the bulbar conjunctiva; 3 (severe) – deep, severe, bright, and diffuse reddening of the bulbar conjunctiva. Adverse events were initially evaluated upon subject presentation to the clinic. However, any observation made by the investigator upon ophthalmic examination could also be considered an adverse events.

Statistics

The sample size was driven by interest in the IOP-lowering effect of H-1337. The study was designed to test whether 1 or more concentrations of H-1337 were superior to the vehicle control in the reduction of IOP. With 22 subjects per group, this protocol was powered at 94% to detect a difference in IOP reduction of 4.0 mm Hg between groups against a standard deviation (SD) of 3.5 mm Hg (2-sided t-test, alpha=0.05). The study also had the power to detect a difference in adverse event rates of 15%, and a hyperemia score difference of 1 (range of 0 to 4).

The primary efficacy analyses were performed using the study eyes of the intent-to-treat (ITT) population, which included all randomized subjects. *A priori*, the primary efficacy measure as registered in clinicaltrials.gov was the mean change from baseline IOP at Day 28 at Hour 4. Other a priori measures included: mean change in IOP from Baseline (Day 0) IOP (mmHg) for each group on Days 14 at each matched time point and Day 28 at the other diurnal time points.

Secondary/supportive efficacy endpoints included: (1) the observed IOP, mean percent change from Baseline IOP at each matched time point at each visit and (2) the mean observed, mean change from Baseline and mean percent change from Baseline for the mean diurnal IOP at each visit, and (3) the proportion of subjects reaching a target IOP (< 18 mmHg) at each time point and with the mean diurnal IOP for each visit. For the IOP, diurnal IOP, and the change from baseline, each of the active treatment groups was compared to the vehicle group using the analysis of covariance (ANCOVA) model, separately for each time point. Baseline value was used as a covariate and the stratum to which the subject was randomized was included in the model. Randomization and all statistical analyses were programmed using SAS® software version 9.3 or later (SAS Institute, Cary, NC).

Bioanalytical methodology

Blood samples were taken at two pre-selected sites from study subjects pre-dose at Days 0 and 28 and approximately 2 and 8 hours (± 10 min) post- morning dose on Day 28. Samples were centrifuged on site, plasma aliquoted, and shipped, on dry ice, to a bioanalytical facility. Plasma samples were analyzed for H1337 using an ultra-high performance liquid chromatography with tandem mass spectrometry method in the positive electrospray ionization mode. The method was validated in a previous study over the concentration range of 1.0 to 1000 ng/mL using a 0.025-mL sample.

Results

Disposition, demographics and baseline characteristics

Enrolled into the study were 87 subjects, all of whom completed the study. The mean age of the treatment groups ranged from 61 to 67 years. Overall, 59% to 64% of each treatment group was female, 82% to 95% was White, and 64% to 68% had baseline IOP ≤26 mm Hg. All demographics and baseline characteristics appeared similar between treatment arms.

Pharmacokinetics

Ninety six human plasma samples were analyzed for H-1337 concentrations. This represents 24 subjects from two sites at 4 time points – pre-dose on Day 1, and pre-dose, and hours 2 and 8 on Day 28. All samples were below limit of quantitation (1 ng/mL).

Ocular hypotensive efficacy

At unmedicated baseline, mean IOP at 8:00 AM was 25.8 ± 2.3 to 26.3 ± 2.6 mm Hg in each treatment group, decreasing throughout the day to 20.3 ± 2.6 to 21.5 ± 3.7 mm Hg at 8:00 PM. In the primary outcome measure as registered with clinicaltrials.gov, mean change from baseline at Day 28 at Hour 4, the mean changes from baseline were -4.45 ± 3.801, -5.16 ± 3.114, -4.93 ± 3.110, and -0.39 ± 2.355 in the 0.06%, 0.2% and 0.6% H-1337 and vehicle groups, respectively. The difference between each active group and the vehicle was statistically significant ($p < 0.0001$).

As noted in methods, several secondary/supportive analyses of IOP were conducted. At Day 14, for diurnally adjusted mean change from baseline, there was a decrease of 4.1 ± 2.7 to 5.2 ± 3.5 mm Hg (15 to 20% decrease) at the presumed trough on Day 14 at 8:00 hours, and 4.4 ± 3.1 to 5.7 ± 3.9 mm Hg at the presumed peak at 10:00 hours (18 to 22% decrease). The vehicle effect was 2.0 ± 2.0 mm Hg (8% decrease). At Day 28, the higher concentrations of H-1337 appeared to have a longer duration of action. The mean reduction in IOP was statistically significant in all three active treatment groups at all times (range, -3.95 ± 2.4 to -5.14 ± 2.3 mm Hg; $P < 0.0001$, 17 to 22% decrease). In the vehicle group, the change was not statistically significant at most time points, Table 2). . The difference between each active group and the vehicle was statistically significant at all time points ($p < 0.05$).

For mean IOP, at the first on-drug visit (study eye only, Day 4 at 8:00 AM, 12 hours since last dose, presumed trough), IOP was 20.3 ± 3.4 to 21.3 ± 2.7 mmHg in the active groups, and 24.0 ± 2.6 in the vehicle group. On Day 14 at 08:00 AM, IOP was similar to Day 4. Two hours later, after in-office treatment (presumed peak), IOP decreased to 17.1 ± 2.3 to 18.8 ± 2.6 mm Hg in the active groups, and was 22.8 ± 3.2 mm Hg in the vehicle group. A similar peak and trough effect was seen on Day 28 (Figure 1).

For mean diurnal IOP, calculated as the average of IOP measures over 12 hours) for each subject for the study eye, there was a decrease from unmedicated baseline values of 22.0 ± 2.2 to 22.9 ± 1.8 mm Hg to 17.6 ± 2.1 to 18.9 ± 2.3 at Day 14 and to 17.5 ± 3.3 to 18.6 ± 3.8 at Day 28 in the active groups. This represented a mean decrease of 3.6 ± 2.3 to 4.8 ± 2.6 mm Hg ($p < 0.0001$). Mean diurnal IOP in the vehicle group decreased by 0.6 ± 1.7 to 0.8 ± 1.8 mm Hg on these days. Each active group was statistically significantly different from vehicle at both Day 14 and Day 28 ($p < 0.001$; Figure 2). The proportion of subjects with IOP ≤ 18 mm Hg in diurnal IOP at 12 hours after morning dose was 38% (8/21), 50% (11/22) and 55% (12/22) at Day 14 and 29% (6/21), 45% (10/22), and 59% (13/22) at Day 28 in the 0.06%, 0.2% and 0.6% groups, respectively. The proportion of subjects reaching this criterion in the vehicle group was 5% (1/22) and 9% (2/22), respectively. For both measures of diurnal IOP, there was a dose-associated trend towards greater ocular hypotensive efficacy with increasing H-1337 concentration.

Safety

All subjects completed the study and there were no drug discontinuations due to AEs. Treatment-emergent adverse events (TEAEs) occurred in 49% of subjects receiving H-1337 (range, 41% [0.2% arm] to 64% [0.6% arm] across H-1337 arms) and in 18% of subjects receiving vehicle (Table 3). The majority of TEAEs were mild in severity; 3 subjects receiving H-1337 had a TEAE of moderate intensity (instillation site erythema, vision blurred, and muscle strain).

The most frequently reported TEAEs among subjects receiving H-1337 were instillation site pain (31%, 20/65), instillation site erythema (22%, 14/65), and vision blurred (9%, 6/65). There was a dose-related trend in the proportion of subjects experiencing instillation site pain (all mild), but no apparent trend in the proportion of subjects reporting conjunctival hyperemia. Most ocular-

associated AEs were judged by the investigator to be treatment related, while none of the non-ocular AEs were considered treatment related.

The mean change from baseline in conjunctival hyperemia in the study eye at Day 28 increased no more than 0.2 units (0 to 3 scale) in any study arm at any time point, from pre-treatment through 12 hours after treatment. A slight increase was observed 2 hours after dosing among the treatment groups but was not observed by 4 hours after dosing. There were no dose-related trends in hyperemia noted.

There were no clinically significant changes in visual acuity, biomicroscopy, ophthalmoscopy, or pupil size as judged by the investigators.

Discussion

In this Phase 1 / 2 study of a new chemical entity, H-1337, in a preserved ophthalmic solution, there was a clinically and statistically significant ocular hypotensive effect with a relatively rapid onset. Relative to vehicle, and adjusted for baseline diurnal IOP, the twice-daily dosing regimen appeared to be adequate. Further, the ocular hypotensive effect, at least by some measures, appeared to be dose-related, with the 0.20% and 0.60% concentrations more effective than the 0.06% concentration. Some of the observations might be explained by the circadian nature of IOP. In this study, mean IOP in the vehicle group was approximately 3 to 4 mm Hg lower at 8:00 pm relative to 8;00 AM. The potential for an ocular hypertensive agents to further lower IOP is thus less – that is, the lower the IOP, the lower the apparent ocular hypotensive effect. This has been reported for prostaglandins, β-adrenoceptor antagonists and some RKI's. In patients with normal tension glaucoma or normal IOP, the ocular hypotensive effect of approved agents may be only 1-2 mmHg.[17-21]

From a safety perspective, no subjects discontinued from the study. The most frequent adverse events were mild instillation site pain and erythema, followed by blurred vision. Conjunctival hyperemia, previously reported for RKI's,[6-8] was reported in one subject in the 0.2% and 0.6% H-1337 groups. Conjunctival hyperemia, also previously reported for RKI's,[6-8] was reported in only one subject, who was in the vehicle group.

It may be that some of the hyperemia was related to the relatively frequent applanation. The lack of systemic exposure, as determined by a sensitive bioanalytical method, is consistent with the systemic safety profile.

As a pilot, Phase 1 / 2 study, this study was designed to include 87 subjects to limit exposure. In addition to the three concentrations of H-1337, a vehicle control group was included. We considered a positive control group, but with the selected sample size, the power to detect a difference from a positive control would be limited. This is consistent with the design of previous pilot studies of agents in this class.[22, 23] It is also tempting to compare the results of H-1337 in this study with other studies, or to propose potential differences in efficacy, safety,

dosing regimen or the benefit-risk ratio of H-1337 due to its multi-kinase inhibitor effects. However, given the lack of a concurrent positive control in this study, or comparative data in preclinical studies, we suggest it is inappropriate to make these comparisons at this time.

The findings of this study are limited due to its sample size, lack of Asians in the study, single observer measurement of IOP, and potential for unmasking due to the adverse events in the active groups. The potential for H-1337 Ophthalmic Solution as an ocular hypotensive therapeutic agent will require additional studies including comparison to an active control, and further exploration of dose-response and frequency-response.

In conclusion, 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.

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Disclosures:

Paul J. Hartman: None.

David L. Cooke: None

Henry Hsu: Employee and stockholder in Allysta, Inc.

Jeanette Stewart: Consultant to Allysta, Inc.

Kengo Sumi: Employee of D. Western Therapeutics Institute, Inc. and Mie University

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Gary D. Novack: Consultant to several medical device and pharmaceutical firms. Separate disclosure list provided.

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Figure Legends

Figure 1 Intraocular Pressure: Mean (± SEM) (ITT population, mm Hg)

Figure 2 Mean change (± SEM) in 12-Hour Diurnal Intraocular Pressure in the Study Eye

Each active group was statistically significantly different from vehicle at both Day 14 and Day 28 ($p < 0.001$).

Table 1 Demographics and Baseline Characteristics

Characteristic	*H-1337 0.06% (n=21)*	*H-1337 0.2% (n=22)*	*H-1337 0.6% (n=22)*	*Vehicle (n=22)*
Age, years				
Mean (SD)	61.1 (13.58)	64.1 (10.02)	67.4 (11.72)	65.0 (14.44)
Median	64.0	64.5	70.5	68.5
Minimum, maximum	25, 80	42, 86	49, 87	26, 87
Gender, n (%)				
Male	8 (38)	9 (41)	8 (36)	10 (45)
Female	13 (62)	13 (59)	14 (64)	12 (55)
Ethnicity, n (%)				
Hispanic/Latino	2 (10)	3 (14)	3 (14)	1 (5)
Not Hispanic/Latino	19 (90)	19 (86)	19 (86)	21 (95)
Race, n (%)				
Black/African American	1 (5)	2 (9)	3 (14)	4 (18)
White	20 (95)	20 (91)	19 (86)	18 (82)
Iris color, n (%)				
Brown	9 (43)	8 (36)	11 (50)	11 (50)
Blue	6 (29)	6 (27)	4 (18)	7 (32)
Green	2 (10)	2 (9)	1 (5)	1 (5)
Hazel	4 (19)	6 (27)	6 (27)	2 (9)
Other/Mixed	0	0	0	1 (5)
Screening IOP, mm Hg				
Mean (SD)	22.90 (4.323)	21.11 (3.097)	20.75 (3.572)	22.07 (3.707)
Median	23.00	21.00	20.50	22.25
Minimum, maximum	15.0, 31.5	15.5, 27.5	14.0, 28.0	16.0, 29.5
Baseline Unmedicated IOP, mm Hg				
Mean (SD)	26.33 (2.619)	25.98 (2.107)	25.80 (2.282)	25.98 (1.899)
Median	25.50	25.75	25.00	26.00

Characteristic	*H-1337 0.06% (n=21)*	*H-1337 0.2% (n=22)*	*H-1337 0.6% (n=22)*	*Vehicle (n=22)*
Minimum, maximum	23.5, 32.0	23.0, 31.0	23.5, 31.0	23.5, 32.0
Randomization stratum for IOP, n (%)				
≤26 mm Hg	14 (67)	14 (64)	15 (68)	15 (68)
>26 mm Hg	7 (33)	8 (36)	7 (32)	7 (32)
Pre-study ocular hypotensive medications				
Prostaglandins				
Latanoprost	4 (19.0%)	12 (54.5%)	8 (36.4%)	12 (54.5%)
Bimatoprost	1(4.8%)	1(4.5%)	2(9.1%)	2(9.1%)
Carbonic anhydrase inhibitors				
Brinzolamide	2(9.5%)	3(13.6%)	1(4.5%)	---
Dorzolamide	---	1(4.5%)	2(9.1%)	2(9.1%)
Timolol	---	1(4.5%)	2(9.1%)	2(9.1%)
Glaucoma diagnosis				
Ocular hypertension	16 (76.2%)	10 (45.5%)	17 (77.3%)	16 (72.7%)
Open angle glaucoma	7 (33.3%)	13 (59.1%)	9 (40.9%)	11 (50.0%)

Note: Glaucoma diagnosis adds up to more than 100% due to different diagnosis in eyes within a subject.

IOP, intraocular pressure; SD, standard deviation.

Table 2 Mean (± SD) change from diurnally adjusted baseline: ITT population (mm Hg)

Day	*Hour*	*H-13370.06% (n=21)*	*H-13370.2% (n=22)*	*H-13370.6% (n=22)*	*Vehicle(n=22)*
4	8:00 am	-5.00 (2.881)*	-5.57 (2.352)	-5.52 (2.714)*	-1.95 (2.143)*
14	8:00 am	-4.14 (2.684)*	-4.75 (2.318)*	-5.18 (3.463)*	-1.95 (1.957)*
	9:00 am	-4.93 (3.018)*	-5.32 (2.491)*	-4.59 (3.504)*	-0.18 (3.138)
	10:00 am	-4.40 (3.121)*	-5.73 (3.878)*	-5.34 (4.316)*	-0.73 (2.975)
	12:00 pm	-3.40 (3.734)*	-5.11 (3.284)*	-5.20 (3.801)*	0.09 (2.562)
	4:00 pm	-3.07 (2.772)*	-4.43 (3.091)*	-4.14 (2.707)*	-1.36 (2.937)*
	8:00 pm	-2.19 (3.516)*	-2.70 (3.591)*	-2.55 (3.186)*	-0.77 (3.341)
28	8:00 am	-4.60 (3.652)*	-5.27 (3.042)*	-5.18 (3.322)*	-2.30 (3.344)*
	9:00 am	-5.17 (4.255)*	-5.25 (2.759)*	-4.43 (2.611)*	-0.77 (3.146)
	10:00 am	-4.86 (3.525)*	-5.07 (3.547)*	-5.86 (3.907)*	-1.50 (2.734)*
	12:00 pm	-4.45 (3.801)*	-5.16 (3.114)*	-4.93 (3.110)*	-0.39 (2.355)
	4:00 pm	-3.31 (2.804)*	-4.66 (2.962)*	-3.82 (3.235)*	-0.84 (3.375)
	8:00 pm	-1.90 (3.338)*	-3.77 (2.923)*	-2.86 (2.829)*	-0.48 (3.045)

* Mean reduction in IOP was statistically significant in all three active treatment groups (P = 0.0166 to <0.0001). In the vehicle group, the change statistically significant only at the asterisked time points.
The difference between each active group and the vehicle was statistically significant ($p < 0.05$) at each time point.

Table 3 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

TEAEs	*H-1337 0.06% (n=21)*	*H-1337 0.2% (n=22)*	*H-1337 0.6% (n=22)*	*All H-1337 (n=65)*	*Vehicle (n=22)*
Subjects reporting any TEAEs, n (%)	9 (43)	9 (41)	14 (64)	32 (49)	4 (18)
Eye disorders, n (%)	5 (24)	3 (14)	5 (23)	13 (20)	2 (9)
Vision blurred	3 (14)	1 (5)	2 (9)	6 (9)	0 (0)
Conjunctival hyperaemia	0 (0)	1 (5)	1 (5)	2 (3)	0 (0)
Eye pain	0 (0)	1 (5)	1 (5)	2 (3)	0 (0)
Foreign body sensation in eyes	1 (5)	0 (0)	1 (5)	2 (3)	0 (0)
Blepharospasm	1 (5)	0 (0)	0 (0)	1 (2)	0 (0)
Eyelid oedema	0 (0)	1 (5)	0 (0)	1 (2)	0 (0)
Lacrimation increased	0 (0)	0 (0)	1 (5)	1 (2)	0 (0)
Punctate keratitis	1 (5)	0 (0)	0 (0)	1 (2)	0 (0)
Conjunctival haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Vitreous floaters	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
General disorders and administration site conditions, n (%)	6 (29)	8 (36)	13 (59)	27 (42)	2 (9)
Instillation site pain	3 (14)	5 (23)	12 (55)	20 (31)	2 (9)
Instillation site erythema	5 (24)	6 (27)	3 (14)	14 (22)	0 (0)
Eye pain	0 (0)	0 (0)	1 (5)	1 (1)	0 (0)
Instillation site foreign body sensation	0 (0)	1 (5)	0 (0)	1 (1)	0 (0)
Infections and infestations, n (%)	1 (5)	0 (0)	0 (0)	1 (1)	0 (0)
Tinea pedis	1 (5)	0 (0)	0 (0)	1 (1)	0 (0)
Injury, poisoning and procedural complications, n (%)	0 (0)	0 (0)	1 (5)	1 (1)	0 (0)
Muscle strain	0 (0)	0 (0)	1 (5)	1 (1)	0 (0)
Musculoskeletal and connective tissue disorders, n (%)	1 (5)	0 (0)	0 (0)	1 (1)	0 (0)
Intervertebral disc protrusion	1 (5)	0 (0)	0 (0)	1 (1)	0 (0)

TEAEs=treatment-emergent adverse events.

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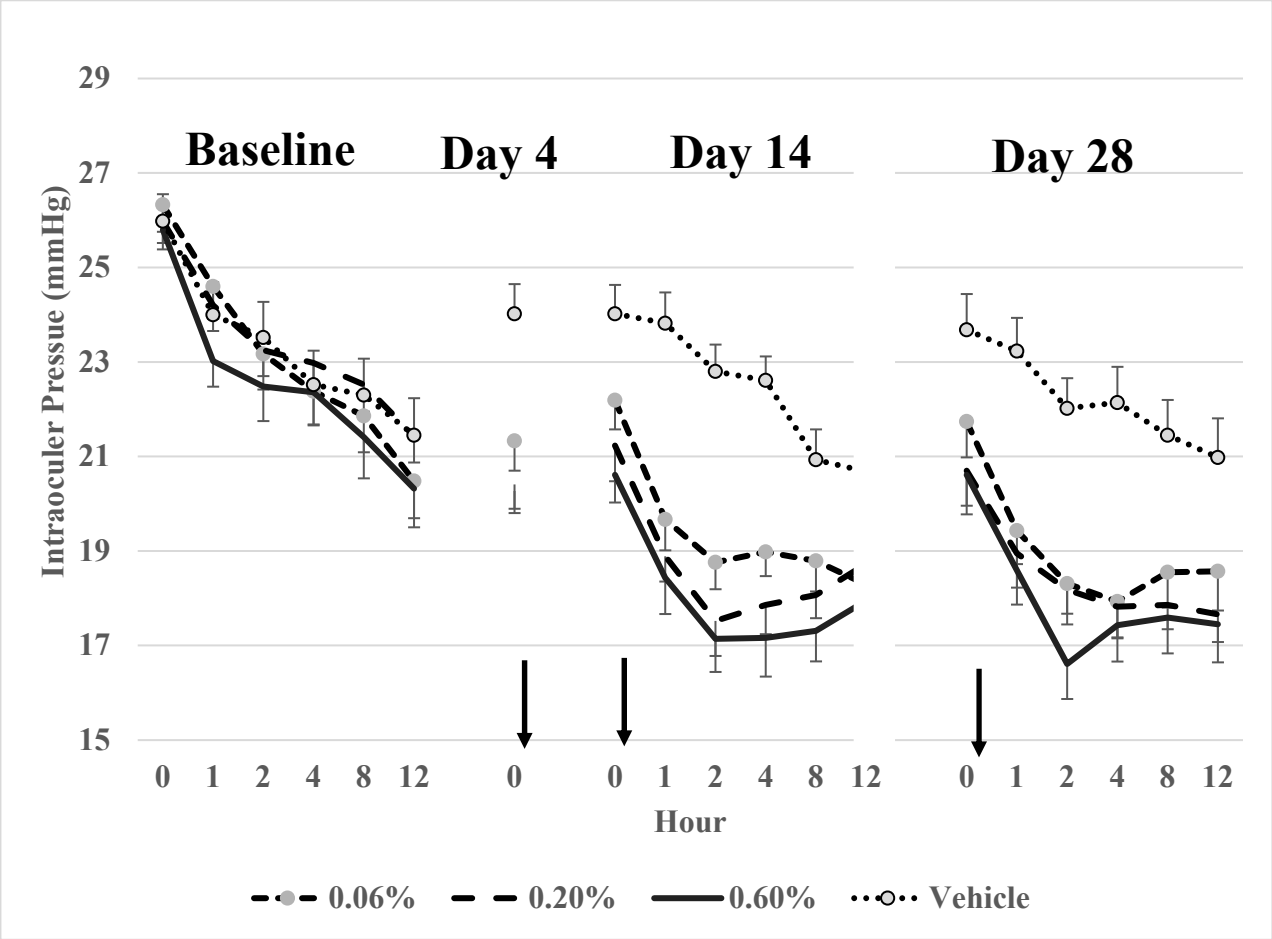
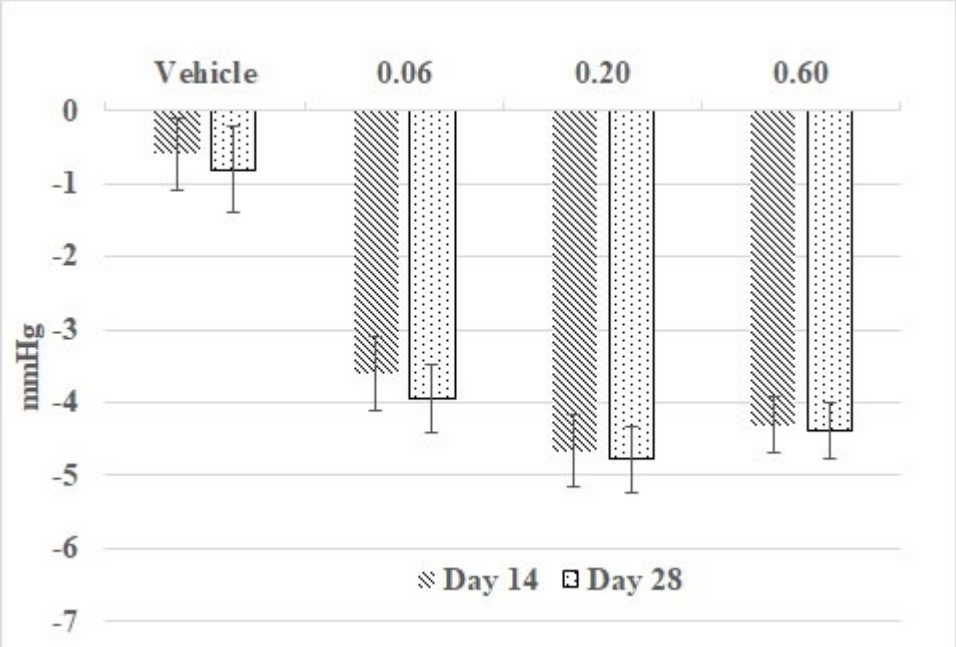
Figure 1 Intraocular Pressure: Mean (± SEM) (ITT population, mm Hg)



Arrow indicates dosing of masked product

Day 4 was study eye dosing only

Figure 2 Mean change (± SEM) in 12-Hour Diurnal Intraocular Pressure in the Study Eye



Each active group was statistically significantly different from vehicle at both Day 14 and Day 28 ($p < 0.001$).