Study Protocol

Official title：	**A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of HBM9036 Ophthalmic Solution 0.25% versus Placebo in Subjects with Moderate to Severe Dry Eye**
NCT number:	**NCT04092907**
Document date	**9 January 2019**

Clinical Trial Protocol

Study Title	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of HBM9036 Ophthalmic Solution 0.25% versus Placebo in Subjects with Moderate to Severe Dry Eye
Study Number	9036.1
Study Phase	II
Investigational Product	HBM9036 Ophthalmic Solution
Indications	Dry eye
Investigators	Multi-center
Sponsor	Harbour BioMed (Guangzhou) Co., Ltd
Sponsor Contact	Xiaoxiang Chen Harbour BioMed (Guangzhou) Co., Ltd

	Version No.	**Date**
Original Protocol	Version 1.0	7 November 2018
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Revised Protocol	Version 1.2	9 January 2019

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SYNOPSIS

Sponsor: Harbour BioMed (Guangzhou) Co., Ltd
Investigational Product: HBM9036 Ophthalmic Solution
Name of Active Ingredient: HBM9036
Study Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of HBM9036 Ophthalmic Solution 0.25% versus Placebo in Subjects with moderate to Severe Dry Eye
Study Number: 9036.1
Study Phase: II
Primary Objective: To compare the efficacy and safety of HBM9036 Ophthalmic Solution (0.25%) versus placebo in the treatment of dry eye
Study Design: A multicenter, randomized, double-blind, placebo-controlled, and parallel-group study.
Selection of Subjects: Subjects who are≥ 18 years of age; have a history of dry eye for ≥ 6 months; have a best corrected visual acuity of 0.7 logMAR or better in each eye; have in the study eye a Schirmer's test score of ≤10 mm and ≥1 mm; have at least in the study eye a corneal fluorescein staining score of ≥2 according to the Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale; have at least in the study eye a score of ≥2 according to the Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire in at least one of the dry eye symptoms; have in the study eye a conjunctival redness score≥ 1 according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale; and demonstrate in the study eye a response to the CAE® as defined by: a) Having at least a ≥1 point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure; b) Reporting an Ocular Discomfort score ≥3 at 2 or more consecutive time points in at least one eye during CAE® exposure (if a subject has an Ocular Discomfort rating of 3 at time = 0 for an eye, he/she must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye). Note: a subject cannot have an Ocular Discomfort score of 4 at time = 0).
Drug, Dose and Mode of Administration: Investigational Product: HBM9036 Ophthalmic Solution Dose: 0.25% Mode of Administration: eye drop

Dose Regimen: one drop per eye, twice a day in the morning and evening

Reference Therapy: placebo
Dose: not applicable
Mode of Administration: eye drop
Dose Regimen: one drop per eye, twice a day in the morning and evening

Duration of Treatment: Eight weeks

Primary Efficacy Endpoint:

- Changes from baseline in change from pre- to post-CAE inferior corneal staining (ICS) score of the study eye evaluated at Visit 6 (Day 57, Week 8) according to Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale

Secondary Efficacy Endpoints:

- Changes from baseline in change from pre- to post-CAE ICS score of the study eye evaluated at Visit 5 using Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale
- Changes from baseline in pre-CAE ocular discomfort of the study eye evaluated at Visit 6 according to Ora Calibra® Ocular Discomfort Scale
- Changes from baseline in pre-CAE ocular discomfort of the study eye evaluated at Visit 5 according to Ora Calibra® Ocular Discomfort Scale
- Changes from baseline in pre-CAE symptom score evaluated at Visit 6 according to Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- Changes from baseline in pre-CAE symptom score evaluated at Visit 5 according to Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- Changes from baseline in post-CAE TFBUT of the study eye evaluated at Visit 6
- Changes from baseline in post-CAE conjunctival redness score of the study eye evaluated at Visit 6 according to Ora Calibra® Conjunctival Redness Scale
- Changes from baseline in Schirmer's test (nonanesthetized) results at Visit 6
- Change from baseline in OSDI© scores at Visit 6
- Changes from baseline in pre-CAE burning sensation score evaluated at Visit 6 according to Visual Analogue Scale (VAS)
- Changes from baseline in average weekly burning sensation score in subject diary at Week 8

Safety Evaluation:

- Incidence and severity of ocular AEs
- Incidence and severity of non-ocular AEs
- BCVA at each visit
- Slit-lamp bio-microscopic results at each visit

- Evaluation of tolerance (at Visit 2)
- Intraocular pressure (at Visits 1 and 6)
- Fundus photography (at Visits 1 and 6)

Statistical Methods:

Primary Efficacy Analysis

ANCOVA models will be used to compare the change from baseline in the pre- to post-CAE® ICS staining at Day 57 (Visit 6), as measured on the Ora Calibra® scale, between 0.25% HBM9036 Ophthalmic Solution and placebo groups. The ANCOVA model will include the change from pre- to post-CAE inferior corneal fluorescein staining at baseline as a covariant.

Secondary Efficacy Analysis

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, min and max). All visit-based data will be analyzed at each visit and based on the change from baseline. T test, Wilcoxon rank sum test and ANCOVA adjusting for baseline will also be performed as appropriate and no imputation of missing values will be performed.

Safety Analysis

The frequency and percentage of subjects who report treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to premature discontinuation of study will be summarized. An AE is treatment emergent if 1) it occurs after the first dose of study treatment; or 2) exists before the first dose of study treatment and its severity worsens or frequency increases after first dose. The AEs will be coded using the MedDRA preferred term and system organ class and listed by severity and the causal relationship with the study drug. The AEs leading to discontinuation of the study will be listed. No hypothesis test will be performed. Separate analyses will be performed for ocular specific and all AEs (including systemic). Other safety endpoints including visual acuity, slit-lamp biomicroscopy, fundus color photography, and intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed on eyes, the data for study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized.

Data Monitoring and Clinical Endpoint Committee
Not applicable

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ANOVA	analysis of variance
APC	antigen presenting cell
API	active pharmaceutical ingredient
BCVA	best corrected visual acuity
BID	twice daily
CAE	controlled adverse environment
CD	optical disk
CDA	clinical data analyst
CDM	clinical data manager
CRA	clinical research associate
CRO	contract research organization
CTR	clinical trial report
DCF	data clarification form
DVM	data verification manual
EC	ethics committee
e-CRF	electric case report form
EDC	electronic data acquisition system
EDTA	ethylenediaminetetraacetic acid
ET	early termination
ETDRS	early treatment diabetic retinopathy study
FAS	full analysis set
GCP	Good Clinical Practice
ICF	informed consent form
ICH	international conference of harmonization
ICS	inferior corneal staining
IgG	immunoglobulin G
IgM	immunoglobulin M
IND	investigational new drug
IOP	intraocular pressure
IP	investigational product
ITT	intent-to-treat
IUD	intrauterine device
KCS	keratoconjunctivitis sicca
LASIK	laser-assisted in-situ keratomileusis
LDPE	low density polyethylene
LOCF	last observation carried forward
LogMAR	logarithm of the minimum angular resolution
MedDRA	Medical Dictionary for Regulatory Activities
MW	molecular weight
N	number
ODS	ocular discomfort score
OPI	ocular protection index

OSDI	ocular surface disease index
OTC	over-the-counter drugs
OU	oculus uterque (each eye or two eyes)
PI	principal investigator
PK	pharmacokinetic
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDC	Statistics and Data Corporation, Inc.
SEC	self-evident correction
STT	Schirmer tear test
TFBUT	break up time of tear film
TM	trademark
VA	visual acuity
VAS	Visual Analogue Scale

1 INTRODUCTION

1.1 Medical Background

Dry eye is a complex disease that results in symptoms of discomfort, visual disturbance, and tear film instability. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Estimates of the prevalence of dry eye vary considerably, depending on the criteria used to define the syndrome. In the US, as many as 3.2 million women and 1.7 million men over the age of 50 have dry eye, with a projected 40% increase in number of patients affected by 2030[1-3]. In China, the prevalence of dry eye is up to 13.55%[4]. With the dramatic increase of aging population in our country and the increase of computer use, dry eye is expected to become more prevalent and finding a treatment is becoming even more important[5].

Dry eye can be related to external factors, such as the low humidity of air-conditioned offices, winter heating, a dusty or windy outdoor environment, prolonged use of computers, or wearing of contact lenses, as well as to internal factors, such as hormonal imbalance, autoimmune disease, the use of many widely prescribed systemic medications, anatomical changes or trauma, and aging. Symptoms result in mildly decreased quality of life at a minimum, and with increasing severity, loss of function and productivity, pain, light sensitivity, and the misery that accompanies significantly impaired vision and decreased quality of life[6-8].

Dry eye is a multifactorial disorder that is directly linked to a disturbance in the production or properties of the tear film that protects and lubricates the ocular surface[9], and can be roughly categorized into two major subgroups, respectively aqueous-deficient dry eye and evaporative dry eye. Inflammation is primary in dry eye disease associated with Sjögren's Syndrome, sarcoidosis and chronic graft versus host disease, but is a secondary consequence of cell damage due to dessicating stress and hyperosmolarity in non-autoimmune dry eye[10-11]. The secreted inflammatory cytokines, especially TNF-α, interleukin (IL)-1, and IL-6, facilitate the activation and migration of antigen presenting cells (APCs) toward the draining lymph nodes[12]. In the lymph nodes, these APCs stimulate naïve T cells (Th0), leading to the expansion of Th1/Th17 cells, and antagonize the regulatory T cell (Treg) function.

Once these effectors are generated in the lymph nodes, they migrate to the ocular surface. Interaction of IL-17 with its receptors on the ocular surface leads to epithelial damage through increased secretion of matrix metalloproteinases and inflammatory cytokines[13]. These events lead to tear film instability which exacerbates ocular surface hyperosmolarity and completes the vicious circle.

1.2 Overview of Drug

HBM9036 is a molecularly engineered TNF receptor 1 (TNFR1) fragment. Molecule fragmentation and engineering techniques are applied for enhanced tissue distribution, increased stability and potency.

HBM9036 is composed of 171 amino acids, from 41-211 residues of TNFR1 outside domain and a methionine residue added at the N-terminal. HBM9036 is a protein molecularly engineered by amino acid substitution of the 29th leucine, 53rd histidine, 56th histidine, 58th arginine, 59th histidine, and 122nd lysine with valine, methionine, phenylalanine, proline, glycine, and asparagine respectively.

1.3 Non-clinical Studies

HBM9036 was found to significantly decrease the signs of dry eye disease induced in two studies implementing an established murine model of the disease, and in one study of spontaneous dry eye disease in dogs. In the murine dry eye models, keratitis scores and goblet cell number significantly improved in each study. In the dog study, Schirmer's scores showed significantly increased tear production, and scoring of signs demonstrated significantly decreased total signs, ocular discharge and hyperemia.

Pharmacokinetic profiles in blood and ocular tissues (cornea, aqueous humor, and vitreous humor) were evaluated with repeat ocular instillation of HBM9036 in male New Zealand white rabbits. HBM9036 1, 5, and 25 mg/mL was administered into both eyes three times per day in 3-hour intervals for 14 days. Results showed that systemic and ocular drug concentrations after ocular administration of 1 and 5 mg/mL HBM9036 were low or undetectable (<Lower level of Quantitation [LLOQ]). Drug was identified in the cornea and vitreous humor only at the high dose of 25 mg/mL. After topical administration of 25 mg/mL HBM9036, the concentration quickly decreased (α-phase) within two hours, and then remained at a constant level (β-phase) in the cornea. In the vitreous humor, the maximum concentration was found within one to two hours after the last administration of 25 mg/mL HBM9036. A gradual decrease until six hours and steady state after were then observed.

The toxicity of HBM9036 has been investigated in seven repeat-dose studies. Six of these studies involved ocular dosing: two ocular repeat-dose studies in mice for durations of 2 weeks and 28 days (with a 14-day recovery period in the latter study); two studies in rabbits with durations of 1-day and 8 weeks (with a 4-week recovery period in the latter study), and two in dogs with durations of 2 and 8 weeks (with a 2-week recovery period in the latter study). One 28-day study assessed the systemic toxicity and toxicokinetics of HBM9036 with repeat intravenous (IV) dosing in dogs. The results of these studies demonstrated no significant toxicity across all species. The results indicated that HBM9036 Ophthalmic Solution was well tolerated and caused no alterations in ocular tissues or other tissues examined.

1.4 Previous Clinical Studies

1.4.1 Phase I Study

A first-in-human study was completed in Korea in August 2016 aiming to assess the safety, local tolerance, and PK properties of HBM9036. A total of 77 subjects were screened and 20 subjects were randomized to Group A and Group B to receive topical ophthalmic instillation of HBM9036 0.5 mg/mL and 5 mg/mL twice in one day into left eyes, while right eyes received vehicle placebo.

Of the 20 subjects who received study drugs, 11 subjects reported 27 AEs. Twenty AEs were mild in severity and the subjects recovered without sequela. The remaining 7 AEs were moderate in severity, and all events were reported by one subject. Among the 7 moderate AEs, all symptoms except for corneal opacity resolved completely. The assessment of causal relationship between the study drug and the 7 AEs was determined to be "unlikely" for all events. The most frequently reported AE after administration of the study drug was conjunctival hyperemia, with 18 events reported. There were 5 AEs reported by 2 subjects from the HBM9036 0.5 mg/mL group and 6 AEs reported by 3 subjects from the HBM9036 5 mg/mL group. The remaining 7 AEs were reported by 3 subjects in the placebo group. There were 24 AEs reported by 9 subjects (45%) that may have been caused by the study drug (the causal relationship was possible, probable, or certain). Among the AEs thought to be caused by the study drug in each group, conjunctival hyperemia was the most frequently reported (17 AEs reported by 7 [35.0%] subjects). All conjunctival hyperemia events were mild, and the subjects recovered without sequelae. There was no serious AE or unexpected adverse drug reaction reported, and no clinically significant changes were observed in vital signs, physical examinations, and medical laboratory tests. Local tolerance was assessed and there were no moderate or severe ophthalmologic symptoms observed.

1.4.2 Phase II Study

The Phase II, dose range, and proof-of-concept study of HBM 9036 was completed in the US. This was a multicenter, randomized, double-blinded, placebo-controlled study. Subjects were randomly assigned to one of three treatment groups (HBM9036 Ophthalmic Solution 0.10%, 0.25% or placebo) to receive topical ophthalmic drops administered bilaterally BID. The study lasted for 8 weeks and included 6 visits. Although the primary sign of fluorescein staining at Visit 6 pre-CAE was not met with an ANCOVA analysis, analysis of the change in fluorescein staining score pre-CAE to post-CAE as well as post-CAE showed significant treatment differences from baseline starting as early as Visit 4 (Day 15) in total corneal and superior staining, and these significant treatment differences became consistent at Visit 5 (Day 29) and Visit 6 (Day 57). Significant improvements in burning and itching as assessed by the VAS were seen in favor of the HBM9036 0.25% group as early as Visit 4 (Day 15) and continued to Visit 6 (Day 57). Significant improvement was observed in total OSDI score in the HBM9036 0.25% treatment group compared with placebo group.

In the safety population, 44 (29.3%) subjects reported 64 AEs. Of them, 37 (24.7%) subjects reported 51 treatment-emergent adverse events (TEAEs), including 26 ocular TEAEs and 25 non-ocular TEAEs. All TEAEs were of mild or moderate severity. A total of 16 (10.7%) subjects reported at least one ocular TEAE related to the study drug. Of them 7 subjects were treated with HBM9036 (HL036) 0.10%, 8 subjects were treated with HBM9036 0.25%, and 1 subject was treated with placebo. The most common unexpected ocular TEAEs related to the study drug were installation site pain and allergic conjunctivitis. No deaths or SAEs were reported in the study. A total of 8 subjects withdrew from the study due to allergic conjunctivitis: 3 subjects were from HBM9036 (HL036) 0.10% group and 5 subjects were from HBM9036 (HL036) 0.25% group. No change of clinical significance was reported for other safety endpoints.

1.5 Rationale

Currently, mild dry eye is treated with artificial tears, which only provide temporary relief of symptoms. For moderate to severe cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®, Allergan, Inc) is administered. Recently, lifitegrast ophthalmic solution 5% (Xiidra®, Shire US, Inc) has been approved for targeting the inflammatory aspects of dry eye.[14-16] In China, the treatments for dry eye are very limited. The most common treatment is artificial tears. However, it can only alleviate symptoms and may induce drug dependency. No clinical trials on the two new drugs, Xiidra® and Restasis®, have been conducted in China and the approval for marketing in China for them has not been obtained. Therefore, a more effective and safe treatment for dry eye is urgently needed in China.

TNF is a cytokine that mediates various inflammatory diseases. It is secreted chiefly by activated macrophages, although it can be produced by many other cell types such as T helper cells, NK cells and neurons.

The primary role of TNF is the regulation of immune cells. TNF acts as an endogenous pyrogen, which induces fever, apoptotic cell death, sepsis via IL-1 and IL-6 producing cells, carchexia by stimulation of fat accumulation in liver, and inflammation, and inhibits tumorigenesis and viral replication.

TNF exists in soluble form (sTNF) or in transmembrane form (tmTNF). Transmembrane TNF elicits cytotoxicity and inflammation through cell-to-cell contact. From the transmembrane TNF form, soluble TNF is released by the TNF alpha-converting enzyme (TACE). TNF strongly binds two receptors, TNFR1 (p55) and TNFR2 (p75), and this induces pathologic activities including inflammation and disease promotion.[17]

TNF inhibitors (anti-TNF molecules), which block TNF-TNFR binding, are in development, and antibody-based therapeutics have proven the most effective. Anti-TNF molecules have been approved for rheumatoid arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis, and Crohn's diseases. They are also prescribed for off-label use for uveitis, dry eye disease, macular degeneration, sciatic neuralgia, chronic obstructive pulmonary diseases and asthma.

The role of TNF as a major cytokine in dry eye provides a rationale for use of TNF inhibitors in this disease.[18-20] However, the majority of TNF inhibitors are antibody-based with a large molecular size (~150 kDa) that limits tissue penetration. Considering the limited ocular distribution and excessive toxicity of TNF-inhibitor therapies administered systemically, there is a need for topical eyedrop forms of TNF-inhibitors with increased penetration and distribution and minimal systemic side effects.

HBM9036 (HL036) ophthalmic solution is a TNFR1 fragment developed as an eye drop formulation. HBM9036 (HL036) is molecularly engineered for enhanced stability, and TNF-neutralizing activity. Previous results showed that HBM9036 (HL036) significantly improved signs of dry eye in mouse and dog models. Toxicological studies showed that HBM9036 (HL036) exhibited no significant toxicity and was well tolerated (see Section 1.3). In the Phase I clinical trial, HBM 9036 (HL036) also showed good tolerance and neither SAEs nor unexpected adverse drug reactions were reported (see Section 1.4).

This study is a proof-of-concept study in Chinese population to explore whether the optimal dose (HMB9036 0.25%) in the US population is consistently effective and safe in Chinese population.

1.6 Clinical Risk/Benefits Assessment

The toxicity of HBM9036 (HL036) has been investigated in 7 repeat-dose studies. Six of these studies involved ocular dosing: 2 ocular repeat-dose studies in mice, 2 studies in rabbits, and 2 in dogs. One 28-day study assessed the systemic toxicity and toxicokinetics of HBM9036 (HL036) with repeat intravenous (IV) dosing in dogs. The results of these studies demonstrated no significant toxicity across all experimental species and HBM9036 (HL036) caused no alterations in ocular tissues or other tissues examined.

In the murine dry eye models, keratitis scores and goblet cell number significantly improved in each study. In the dog study, Schirmer's scores showed significantly increased tear production, and scoring of signs demonstrated significantly decreased total signs, ocular discharge and hyperemia. These results confirmed the effectiveness of HBM9036 (HL036) in animal models.

The Phase I study completed in Korea assessed the safety, local tolerance, and PK properties of HBM9036 (HL036). Healthy subjects received topical ophthalmic instillation of HBM9036 (HL036) (twice a day at 12-hour interval) into left eyes, while right eyes received vehicle placebo. Of the 20 subjects who received study drugs, 11 subjects reported 27 AEs. Twenty AEs were mild in severity and the subjects recovered without sequela. The remaining seven AEs were moderate in severity, and all events were reported by one subject. All symptoms except for corneal opacity resolved completely. The assessment of causal relationship between the study drug and the seven AEs was determined to be "unlikely" for all events. There was no serious AE or unexpected adverse drug reaction reported, and no clinically significant changes were observed in vital signs, physical examinations, and medical laboratory tests. Local tolerance was assessed and there were no moderate or severe ophthalmologic symptoms observed.

The Phase II, dose range, and proof-of-concept study of HBM9036 (HL036) completed in the US also showed that, after administration of HBM9036 (HL036) 0.25% BID, the change in fluorescein staining score (baseline correction value) pre-CAE to post-CAE as well as post-CAE showed significant differences compared with placebo group. Significant improvements in burning and itching were seen in favor of the HBM9036 (HL036) 0.25% group. Significant improvement was observed in total OSDI score in the HBM9036 (HL036) 0.25% treatment group compared with placebo group. A total of 44 (29.3%) subjects reported 64 AEs. Of them, 37 (24.7%) subjects reported 51 treatment-emergent adverse events (TEAEs). All TEAEs were of mild or moderate severity. No deaths or SAEs were reported in the study. A total of 16 (10.7%) subjects reported at least one ocular TEAE related to the study drug. Of them 7 subjects were treated with HBM 9036 0.10%, 8 subjects were treated with HBM9036 (HL036) 0.25%, and 1 subject was treated with placebo. No change of clinical significance was reported for other safety endpoints.

All data above indicate that HBM9036 (HL036) 0.25% (BID) was safe and well tolerated in previous clinical studies and could improve dry eye symptoms. The overall benefit-to-risk ratio is good.

2 OBJECTIVE

2.1 Primary Objective

The objective of this study is to compare the safety and efficacy of HBM9036 (HL036) 0.25% ophthalmic solutions with placebo for the treatment of the signs and symptoms of dry eye.

The primary objective is to evaluate the efficacy of 8-week continuous treatment with HBM9036 (HL036) ophthalmic solution (BID) in Chinese patients with dry eye and provide evidences for the Phase III trial.

2.2 Secondary Objective

The secondary objective is to evaluate the safety of 8-week continuous treatment with HBM9036 (HL036) ophthalmic solution (BID) in Chinese patients with dry eye.

3 STUDY ENDPOINTS

3.1 Primary Efficacy Endpoint

- Changes from baseline in change from pre- to post-CAE ICS score of the study eye evaluated at Visit 6 (Day 57, Week 8) according to Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale

3.2 Secondary Efficacy Endpoints

- Changes from baseline in change from pre- to post-CAE ICS score of the study eye evaluated at Visit 5 using Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale
- Changes from baseline in pre-CAE ocular discomfort of the study eye evaluated at Visit 6 according to Ora Calibra® Ocular Discomfort Scale
- Changes from baseline in pre-CAE ocular discomfort of the study eye evaluated at Visit 5 according to Ora Calibra® Ocular Discomfort Scale
- Changes from baseline in pre-CAE symptom score evaluated at Visit 6 according to Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- Changes from baseline in pre-CAE symptom score evaluated at Visit 5 according to Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- Changes from baseline in post-CAE TFBUT© of the study eye evaluated at Visit 6
- Changes from baseline in post-CAE conjunctival redness score of the study eye evaluated at Visit 6 according to Ora Calibra® Conjunctival Redness Scale
- Changes from baseline in Schirmer's test (nonanesthetized) results at Visit 6
- Change from baseline in OSDI© scores at Visit 6
- Changes from baseline in pre-CAE burning sensation score evaluated at Visit 6 according to Visual Analogue Scale (VAS)
- Changes from baseline in average weekly burning sensation score in subject diary at Week 8

3.3 Safety Evaluation

- Incidence and severity of ocular AEs
- Incidence and severity of non-ocular AEs

- BCVA at each visit
- Slit-lamp bio-microscopic results at each visit
- Evaluation of tolerance (at Visit 2) by Ora Calibra® Drop Comfort Scale and Ora Calibra® Drop Comfort Questionnaire
- Intraocular pressure (at Visits 1 and 6)
- Fundus photography (at Visits 1 and 6)

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This study is a multicenter, randomized, double-blinded placebo-controlled, parallel-group Phase II study. Subjects will be randomized at Visit 2 to one of following treatment groups:

- HBM9036 (HL036) 0.25% Ophthalmic Solution
- Placebo

Subjects will receive either HBM9036 (HL036) Ophthalmic Solution (0.25%) or placebo solution as topical ophthalmic drops administered bilaterally BID. Subjects, Sponsor, and site personnel will be masked to treatment assignment.

Controlled adverse environment (CAE) is an environmental chamber used to improve the accuracy for measuring signs and symptoms (such as corneal staining and ocular discomfort) of dry eye by regulating indoor humidity, temperature, air flow and visual tasks. The introduction of CAE® can improve the accuracy of predicting the efficacy of the investigational product by fewer patients, fewer study sites and less time. This environmental chamber has a reliable record of use under conditions of standard test design.

During the screening period, 90-minute exposures to the CAE® (at Visits 1 and 2, two times) will be conducted to ascertain eligibility to enter the study by assessing the change of signs and symptoms during the 90-minute period and post-CAE exposure. Those who qualify will be randomized to receive study drug in a double-blinded manner for 56 days. Subjects will self-administer drops twice daily and will complete daily diary assessments.

At Visits 1, 2, 5 (Day 29), and 6 (Day 57), CAE® exposure will occur, with pre-CAE®, during CAE® (symptoms only) and post-CAE® assessments of ocular signs and symptoms. At Visits 3 and 4, no CAE® exposure will occur but signs and symptoms will be assessed.

The total number of expected participants, including screen failures, is approximately 200 subjects. A total of 100 subjects are expected to be randomized.

A study flow chart appears below:

Visit 1 (Day -13 ± 2): Subject screening (CAE®)	Informed Consent Demographics, Medical/Medication & Ocular History Urine Pregnancy Testing (as needed) Symptom Questionnaire, Visual Acuity Eye evaluations before entering the CAE® CAE® Exposure Eye evaluations after leaving the CAE® Safety Assessments (IOP and Fundus Color Photography) Run-in & Subject Daily Diary Dispensed
↓	
Placebo Run-in Period (Day 14/7±2)	
↓	
Visit 2 (Day 1): Subject Confirmation (CAE®)/Baseline	Collection of Run-in Placebo/Diary Medical/Medication Update: AE Query Symptom Questionnaire, Visual Acuity Eye evaluations before entering the CAE® CAE® Exposure Eye evaluations after leaving the CAE® Randomization On-Site Dose & Drop Comfort Questionnaire Study Drug & Subject Daily Diary Dispensed
↓	
Visit 3 (Day 8 ±1): 1-Week Follow-up	Collection of Study Drug/Diary Medical/Medication Update: AE Query Symptom Questionnaire, Visual Acuity Eye Evaluations On-Site Dose Subject Daily Diary Dispensed
↓	
Visit 4 (Day 15 ±2): 2-Week CAE® Follow Up	Collection of Study Drug/Diary Medical/Medication Update: AE Query Symptom Questionnaire, Visual Acuity Eye Evaluations Study Drug & Subject Daily Diary Dispensed
↓	
Visit 5 (Day 29 ±2): 4-Week CAE® Follow Up	Collection of Study Drug/Diary Medical/Medication Update: AE Query Symptom Questionnaire, Visual Acuity Eye evaluations before entering the CAE® CAE® Exposure Eye evaluations after leaving the CAE® Study Drug & Subject Daily Diary Dispensed
↓	

Visit 6 (Day 57 ±3): 8-Week CAE® Follow-up and Study Exit	Collection of Study Drug/Diary Medical/Medication Update: AE Query Urine Pregnancy Testing (as needed) Symptom Questionnaire, Visual Acuity Eye evaluations before entering the CAE® CAE® Exposure Post-CAE® Eye Evaluations Safety Assessments (IOP and Fundus Color Photography) Study Exit

Subjects who terminate early during the treatment period will be asked to complete safety assessments prior to commencement of any alternative dry eye therapy.

4.2 Rationale of Study Design

The expectation of this study is to observe that compared with the placebo, HBM9036 (HL036) 0.25% Ophthalmic Solution can significantly improve the tolerance of dry eye patients to environment, which is consistent with the results from the Phase II clinical trial conducted in the US. The primary endpoint of this study is:

- Changes from baseline in change from pre- to post-CAE® ICS score evaluated at Visit 6 according to Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale

Considering the mechanism of action, a randomized, double-blinded, parallel-group study design will be used. Details are provided in Section 9.2.

4.3 Rationale of Dose/Regimen and Duration of Treatment

Ocular topical administration is the best route of administration for dry eye treatment. The proposed 8-week treatment period is also based on the results from non-clinical studies, current clinical study data and the anti-inflammatory mechanism of action.

5 SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1. Provide written informed consent;
2. Be at least 18 years of age at Visit 1;
3. Have a patient-reported history of dry eye for≥ 6 months prior to enrollment;
4. Have a history of use eye drops for dry eye symptoms within 6 months of Visit 1 or desire to use eye drops;
5. Have a best corrected visual acuity of 0.7 logMAR or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1;
6. Report in the study eye a score of ≥ 2 according to the Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visits 1 and 2;
7. Have in the study eye a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm at Visits 1 and 2;
8. Have at least in the study eye a corneal fluorescein staining score of≥ 2 for at least one subregion (inferior cornea, superior cornea or central cornea) according to the Ora Calibra® Corneal and Conjunctival Fluorescein Staining Scale at Visits 1 and 2;
9. Have at least in the study eye a conjunctival redness score ≥ 1 according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale at Visits 1 and 2;
10. Demonstrate in the study eye a response to the CAE® at Visits 1 and 2 as defined by:
    a) Having at least a ≥1 point increase in fluorescein staining in the inferior region in at least the study eye following CAE® exposure;
    b) Reporting an Ocular Discomfort score ≥3 at 2 or more consecutive time points in at least the study eye during CAE® exposure (if a subject has an Ocular Discomfort rating of 3 at time = 0 for an eye, he/she must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye). Note: a subject cannot have an Ocular Discomfort score of 4 at time = 0);
11. Be willing and can adjust current treatment for dry eye according to the protocol, judged by the Investigator;
12. Must be willing to complete all study assessments required by the protocol.

5.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters; have meibomian gland dysfunction requiring local or systemic treatment with antibiotics;

2. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;

3. Be diagnosed with Sjogren's syndrome, Steven-Johnson syndrome, or dry eye secondary to chronic graft-versus-host disease;

4. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study;

5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months, or had femtosecond small incision lenticule extraction (SMILE) within the last 12 months, or had phacoemulsification within the last 3 months, or had dry eye or aggravation of dry eye caused by other ocular operations has not been stable;

6. Have any planned ocular and/or lid surgeries over the study period;

7. Be using or anticipate using temporary punctal plugs during the study, or anticipate having permanent punctal occlusion, or have used permanent punctal occlusion and had complications such as extrusion or shifting;

8. Have used ophthalmic cyclosporine A, tacrolimus or Xiidra® within 60 days prior to Visit 1;

9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the study (excluding medications allowed during the study); the respective wash-out periods are required for the following medications, otherwise the subjects will be excluded:

    a) Antihistamines (including ocular): 72 hours prior to Visit 1

    b) Oral aspirin or aspirin–containing products allowed if dose has been stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study period

c) Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1

d) Any medication (oral or topical) known to cause ocular drying that has not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study

e) All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to Visit 1

10. Be a woman who is pregnant, nursing or planning to be pregnant, or be a woman of childbearing potential who is not using an acceptable means of birth control;

11. Be a man who does not take one or more acceptable contraceptive methods;

12. Have severe cardiovascular diseases, liver diseases, nervous system diseases and malignant tumors, or other diseases that the Investigator believes may interfere significantly with the subject's participation in the study and follow-up, or may cause diseases leading to hospitalization during the study;

13. Drug allergy: patients who are allergic to drugs similar to study drugs or allergic to excipients of study drugs;

14. Drug abuse: subjects who have obvious alcohol and drug abuse judged by the Investigator;

15. Have other remarkable diseases, traumas, or other conditions except for dry eye, which the Investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study;

16. Have connection with the study sites: investigators, sub-investigators, study coordinators or employers of investigators, or direct relatives of those listed above cannot participate in the study;

17. Cannot provide valid informed consent: have mental disorders, mental retardation, bad intentions or a history of other illnesses that limit the validity of informed consent in this study;

18. Study drugs or devices: have used an investigational drug or device within 30 days of Visit 1 (screening) or 5 half-lives, whichever longest.

    Note: subjects who participate in an observational study (i.e. no change in treatment or no other interventions is required) are not excluded.

5.3 Subject Identification

At screening visit (Visit 1), each subject will be assigned a unique screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. If all inclusion criteria are met and no exclusion criteria are met at Visits 1 and 2, each subject will then be assigned a randomization number at the end of Visit 2 and block randomization will be conducted by IWRS system.

All the subjects, the Sponsor, and investigators will not know the treatment assigned to each subject and will be masked throughout the study.

5.4 Previous, Concomitant and Prohibited Medications

The use of any prescription or over-the-counter medications within 30 days before Visit 1 is to be recorded on the previous/concomitant page in electronic case report form (eCRF). Any increase or decrease in drugs or dosage change during the study should also be recorded on eCRF. Any drugs currently in use, including OTC medications and Chinese herbal medicines, are permitted if they are not prohibited in the protocol and are approved by investigators. Subjects will be told that they should contact investigators in case of any disease occurring.

All concomitant medications used during the study and their indications, doses, route of administration and dates of administration will be recorded on the concomitant page in eCRF.

5.4.1 Other Medications for the Treatment of Dry Eye

Other medications for the treatment of dry eye other than the study drugs are not permitted during the study.

5.4.2 Prohibited Medications

Prohibited medications/treatments during the study are outlined in the exclusion criteria (Section 5.2).

5.4.3 Other Prohibited Medications

Not applicable.

5.5 Other Restrictions, Illicit Drugs or Drug Abuse

5.5.1 Illicit Drugs

See the exclusion criteria for details (Section 5.2).

5.5.2 Dietary Restriction

There is no dietary restriction in this study.

5.6 Reasons for Discontinuation of Treatment or Study Withdrawal

Subjects may withdraw their consent to participate in the study at any time. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and/or Sponsor and in accordance with his/her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out.

The Investigator must notify the Sponsor of all subject withdrawals as soon as possible. The Sponsor also reserves the right to terminate the study at any time for either clinical or administrative reasons and to discontinue participation of the individual Investigator or study site for slow enrollment or noncompliance.

Reasons for which the Investigator may withdraw a subject from the study include, but are not limited to, the following:

- Subject experiences a serious or intolerable AE;
- Subject requires medication prohibited by the protocol;
- Subject does not adhere to study requirements specified in the protocol;
- Subject was erroneously admitted into the study or does not meet entry criteria;
- Subject is lost to follow–up;
- Subject becomes pregnant;
- Death;
- Investigator's decision;
- Termination of the study by the sponsor;
- Subject's willingness.

If a subject fails to return for scheduled visits, efforts must be made to determine the reason. If the subject cannot be reached by telephone after two attempts, he will be discontinued from the study. The date of last visit will be recorded in the study records and CRF. For subjects who are reached again after lost to follow-up and have missed the visit, supplementary medications should be provided as soon as possible for them to continue the study.

If a female subject is pregnant during the study, she should withdraw from the study and be followed up until childbirth or pregnancy outcome.

5.7 Removal of Subjects from Treatment or Assessment

5.7.1 Removal of Individual Subjects

Subjects who meet any of the following criteria will withdraw from the trial:

- Withdraw the ICF for any reason;
- No longer able to continue to participate in the study for medical reasons (e.g. pregnancy, surgery, AEs or other diseases);
- Administrative reasons (protocol violation, lack of compliance);
- Harbour BioMed decides to terminate the trial early for one or all subjects (previous positive benefit-risk assessment is not supported by new toxicological findings or SAEs).

Subjects should not be discontinued from the trial due to protocol violations before discussion with the clinical research associate.

The data of the subjects who discontinue from the study before enrollment will be recorded in the study database and listed. The data of the subjects who discontinue from the study after enrollment must be recorded, and the reasons must be recorded in the source documents as well as in eCRF. These data must be included in the study database and be reported.

The procedures after early withdrawal from the trial are presented in Section 8.2.

Pregnancy

If a subject is pregnant during the study, the study drug needs to be discontinued, and the subject should be followed up until childbirth or termination of pregnancy. The data of the subject until completion of the last visit will be collected and reported in the clinical trial report (CTR); and any subsequent events will be reported in the Drug Safety Database of Harbour BioMed. Detailed information about reporting of the pregnancy events is presented in Section 7.2.9.

5.7.2 Termination of the Trial by the Sponsor

Harbour BioMed reserves the right to terminate the trial or a study site for any reason listed below at any time:

- The overall enrollment or enrollment at a study site does not meet the target;
- Any efficacy/safety information that can significantly affect the implementation of this trial and does not support the initial positive benefit-risk assessment;
- Violations against GCP, CTP or the contract and interfere with normal implementation of the trial.

If the trial is terminated, investigators/study sites will be compensated reasonably (except in the third case listed above).

6 LABELING, PACKAGING, STORAGE, DISPENSE AND RETURN OF STUDY DRUGS

6.1 Subject Information

The packaging for the study drugs needs to meet the study requirements. Study staffs will use IWRS to assign subjects to treatment groups, dispense study drugs, and manage the drug dispense. The study drugs need to be packaged according to the drug package plan made by the Sponsor. A unique personal identification number (PIN) must be assigned to the persons who access the IWRS system. These personnel must use the PIN allocated to them to enter the system and not share their PIN with anyone else.

6.2 Product Description

Study drug will be supplied as a sterile, clear, colorless liquid solution containing 0.25% API (HBM9036) in 0.5 mL low-density polyethylene (LDPE) unit dose vials with a fill volume of approximately 0.25 mL. Each mL of the 0.25% solution contains 2.5 mg of the API. In addition to HBM9036, the components of the drug solution are: sodium chloride (tonicity adjusting agent), citric acid monohydrate (buffering solution), sodium hydroxide solution and hydrochloric acid 1% (both for pH adjustments), and sterile water for injection as a solvent.

The placebo solution consists of all components of the drug product solution except for HBM9036.

6.3 Packaging and Labeling Information

Batch #(ID for tracing packaging ID) Drug # Composition ID # Specification and Formulation	Storage Conditions Protocol # Regulatory Requirements Sponsor's Contact Information

ID= identification number; #=number

6.4 Emergent Unblinding of Treatment Assignment

The IWRS should be used to unblind subjects and to unmask drug identity. When the Investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. Harbour BioMed will not provide a disclosure envelope with the clinical supplies.

The Investigator or treating physician may unblind a subject's treatment assignment only **in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.

Whenever possible, the Investigator must first discuss options with the clinical research associate (CRA) or appropriate study personnel before unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify the Sponsor as soon as possible,

but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

6.5 Storage Requirements

HBM9036 and placebo solution must be refrigerated (2-8°C). Subjects will be told to store HBM9036 and placebo solution in the fridge (at 2-8℃).

6.6 Preparation and Dispensing of Study Treatments

Study drugs will be packaged and labeled into study kits. Both sterile drug and placebo solutions are packaged in disposable 0.5 mL LDPE vials with a dose of about 50 μL per drop. Each two vials are placed in a nitrogen-filled aluminum foil bag, providing the dose for one day. Each study kit contains enough medications until the next study visit.

For the screening visit (Visit 1), drugs will be dispensed according to the schedule of assessments and visit window.

For the treatment period, drugs are distributed according to requirements of each study visit considering visit window.

Subjects will be suggested to put 1 vial of HBM9036 or placebo solution at room temperature 1±0.5 hours before drug administration.

At study sites, all IPs must be stored safely under the storage conditions specified in the protocol and only accessed by qualified personnel designated by the study site. All IPs must be stored and managed in accordance with local regulations, ICH GCP and study procedures, and inventory must be carefully and accurately recorded.

6.7 Treatment Compliance

Subjects will be required to record the use of study drugs in their diaries every day which will be used for evaluation of subject's treatment compliance. Drug usage of 80% to 125% will be evaluated as good compliance.

Treatment compliance will be calculated as: (actual drug use/ planned drug use) × 100%. The actual drug use is the amount of drug used by subjects between the drug dispensing and next study visit (based on the records of drug use reviewed by the Investigator); and the planned drug use is calculated as (daily drug use specified in the protocol) × (the optimum interval between two study visits). The decrease in drug dose caused by the treatment interruption or dose decrease because of AEs is not considered as poor compliance.

6.8 Drug Accountability/Return of Study Drugs

The study drug is not allowed to be used by investigators in any case, unless specified in the protocol.

A staff will be authorized by the study site to receive, safely and appropriately manage and preserve and store study drug in a safe place. The study drug can be inspected only by authorized staff. The storage conditions of the study drugs should be observed, monitored and recorded carefully, and study drugs should be distributed according to the protocol. Investigators or other authorized personnel will be responsible for accurately recording the amount of drugs received from Harbour BioMed, delivered to subjects, returned by subjects, and the amount of drugs remaining at the end of study. The study drug should be disposed according to Good Supply Practice for Pharmaceutical Products. In case of any problems requiring special or protective handling, the clinical research associate should be contacted. All study drugs, including partially used or empty containers, must be returned at the end of the study as required by Harbour BioMed.

Staff at study sites will check the records for drug accountability together and the records will be monitored by the Sponsor's CRA regularly.

Before the completion of all pre-dose evaluations and confirmation of subjects' eligibility for randomization/participation in the study, authorized staff will not be allowed to open the package of study drug. Any action that violates the requirements listed above must be discussed with the CRA.

All used drug package used by subjects and unused study drugs will be collected. The study drugs used by subjects will be stored in safety locker at room temperature before being returned to Harbour BioMed or its authorized personnel.

Note: the used drug package and unused study drugs should be stored separated from the study drugs not dispensed.

All complaints related to product quality (including package problems) must be reported to Harbour BioMed using the Product Complaint Form in the folders of each site. Harbour BioMed will contact study sites to assess the nature of the complaints and decide the further measures that need to be taken.

7 SAFETY

7.1 Safety Assessments

The safety of the investigational product will be evaluated according to adverse reactions and all ophthalmologic findings (see details in Section 3.3).

7.1.1 Medical/Surgical History and Ophthalmologic Examination

See Section 8 Study Plan and Section 3.3 Safety Endpoints for detailed information.

7.1.2 Pregnancy Test

Urine pregnancy tests will be conducted for premenopausal women without surgical contraception in the laboratories of all study sites at Visit 1 (screening visit) and Visit 6 (Week 8) or at study discontinuation/withdrawal.

7.1.3 Drop Tolerance Assessed Using Ora Calibra® Drop Tolerance Scale and Ora Calibra® Drop Tolerance Questionnaire

Drop tolerance will be assessed using the Ora Calibra® Drop Tolerance Scale and Ora Calibra® Drop Tolerance Questionnaire at each study site at Visit 2.

7.2 Adverse events

7.2.1 Definition of AEs

An AE refers to all untoward medical occurrence after the use of an IP. An AE can be any sign, symptom or abnormal clinical laboratory results, but may not necessarily have a causal relationship with the IP.

An AE includes, but are not limited to:

- Any symptom or condition (medical history) not reported previously by subjects;
- An aggravation of existing symptoms or conditions;
- Significantly increased frequency or intensity of existing events or conditions;
- Conditions discovered or diagnosed for first time after the administration of the investigational product, even if they may already exist prior to initiation of the study.

An AE does not include:

- Routine medical or surgical procedures caused by non-disease factors (e.g., plastic surgery, endoscopy, biopsy);
- Planned surgical procedures before enrollment (e.g., cataract surgery) or hospitalization due to social factors (e.g., medical insurance);

- Overdose of either study drug or concurrent medication without any clinical signs or symptoms;
- Non-clinically significant abnormal laboratory values. (If accompanied by signs/symptoms, the signs or symptoms are considered an AE.).

7.2.2 Collection of Adverse Events

Adverse events that occur between the time subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as a treatment-emergent adverse event unless the event meets the definition of an SAE or AE related to protocol specific procedures.

Adverse events that occur between the time when subject is randomized and last visit should be reported through CRF. All SAEs should be reported to Harbour BioMed within 24 hours of awareness.

Any SAE between last visit and study completion that has a causal relationship with investigational product should be immediately reported to Harbour BioMed and recorded in CRF.

Post-study AE/SAE that investigators judge its occurrence related to investigational product should be reported to Harbour BioMed PV through spontaneous reporting.

7.2.3 Assessment of Adverse Events

The Investigator should immediately record and report all AEs via CRF and AE report forms during the study. All SAEs (see Section 7.2.7) must be reported to Harbour BioMed or designee within 24 hours after the Investigator recognizes/classifies the event as an SAE.

When a SAE occurs, the subject may be discontinued from the treatment after investigators have thorough discussion with medical monitors.

The Investigator will categorize the severity of each AE according to the following criteria:

Mild: Associated with no limitation of daily activities or only slight discomfort; generally not requiring change or interruption of study drugs; and/or not needing therapeutic intervention;

Moderate: Associated with limitation of daily activities or obvious discomfort; generally requiring change or interruption of study drugs; and/or requiring therapeutic intervention;

Severe: Associated with inability of subject to carry out daily activities or obvious discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

7.2.4 Causality

The relationship of each AE to the administration of study drug will be assessed by the Investigator after careful consideration, and according to the following guidelines:

Definitely: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered;

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; but it could also be reasonably explained by other factors such as underlying disease, complications, concomitant medications or treatments;

Possibly unrelated: A reaction that does not follow a reasonable temporal sequence from administration of study drug; that does not follow a known or expected response pattern to the study drug; it could be reasonably explained by other factors such as underlying disease, complications, concomitant medications or treatments;

Unrelated: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered;

Inaccessible: A reaction for which current data is too insufficient to assess its relationship with the study drug.

7.2.5 Recording of Symptoms, Signs and Scale/Questionnaire Evaluation Results

During the study period, not all symptoms, signs, and scale/questionnaire assessment will be recorded as AEs, and the following conditions will not be recorded as AEs:

- Symptoms and signs due to fluctuation in dry eye disease. Symptoms and signs of dry eye disease will be analyzed as the efficacy endpoint and will not be recorded as AEs;
- The assessment of tolerance to eye drops will be analyzed as a safety endpoint, and will not be recorded as AEs;
- The CAE simulates daily adverse environment and triggers the symptoms and signs which will be evaluated as the efficacy endpoint. Therefore, dry eye symptoms and signs triggered by CAE will not be recorded as AEs unless the dry eye symptoms and signs triggered by CAE exceed the expected range of dry eye.

7.2.6 Clinical Laboratory Abnormalities Reported as Adverse Events

Clinical laboratory tests will not be required during the study. However, some subjects may be asked to take clinical laboratory tests.

Not all laboratory abnormalities observed during the study will be reported as AEs unless one of the following criteria is met:

- A laboratory abnormality that leads to a dose adjustment (e.g., an abnormality that results in dose decrease, treatment interruption, or discontinuation of study);

- A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or non-drug therapy is needed);

- Other laboratory abnormality judged by the Investigator to be of any clinical significance (e.g., significant decrease in hemoglobin not requiring transfusion);

For laboratory abnormalities that do not meet the above criteria but are outside of normal range (e.g., < or > normal reference range), the Investigator should indicate whether the value is clinically significant or not for the subject.

7.2.7 Serious Adverse Events

A SAE refers to the event meeting one of the following criteria:

- Results in death;

- Is life-threatening (i.e., in the view of the Investigator, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.);

- Results in hospitalization or prolongation of hospitalization;

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

- Results in congenital anomaly/birth defect;

- Important medical events that may require intervention to prevent one of the outcomes listed above (e.g. allergic bronchospasm requiring intensive treatment in an emergency room or at home, dyscrasias or convulsions that do not result in hospitalization, or drug dependency or drug abuse.).

When a SAE occurs, the Investigator should immediately provide appropriate treatments to the subject for their safety and benefit.

7.2.7.1 Reporting Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to Harbour BioMed. All SAEs must be reported to Harbour BioMed within 24 hours after the Investigator recognizes/classifies the event as an SAE. At a minimum, the term of the event and the causality determined by the Investigator must be provided at the time of the initial report. The Investigator should follow up the event and report to Harbour BioMed within 24 hours after he/she receives the follow-up information.

7.2.7.2 Post-Study Follow-Up of Adverse Events

Any AEs that are unresolved at the subject's last study visit need to be followed up by the Investigator until clinical signs/symptoms disappear or return to baseline level, or become stable at the Investigator's discretion, or refusal to follow-up by subjects, or lost to follow-up. Harbour BioMed reserves the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.2.7.3 Reporting Serious Adverse Events to Ethics Committees

The Investigator is responsible for notifying the Ethics Committee of all SAEs, including any follow-up information. Documentation of the safety report submitted to the EC must be retained. The Investigator is also responsible for notifying Harbour BioMed if the EC requires revisions to the ICF or other measures based on its review of the SAE report.

7.2.7.4 Safety Reports to the Health Authority

The Investigator must report the SAE to National Medical Products Administration (NMPA) and its local affiliates, and National Health Commission (NHC) within 24 hours after he receives the SAE information. The report also needs to be sent to the pharmacovigilance team at Harbour BioMed. The follow-up report should be reported within the same time frame as the initial SAE report.

Harbour BioMed or its representatives will submit a safety report to NMPA and NHC, for any suspected adverse reaction that is both serious and unexpected (SUSAR) within the appropriate time frame (initial report: 7 days for death or life-threating case, 15 days for other SUSAR; follow-up report: 8 days for death or life-threating case, 15 days for other SUSAR). Other SAEs will be reported in annual report.

Harbour BioMed or its representatives will send the investigators who are participating in the clinical studies sponsored by Harbour BioMed the copies of each safety report submitted to NMPA. Safety reports must be submitted to the appropriate EC as soon as possible. Documentation of the safety report submitted to the EC must be retained.

7.2.8 Overdose

An overdose is defined as a dose greater than the dose specified in this study protocol. In the event of an overdose of study drug, the Investigator should treat the overdose based on clinical judgement and contact the medical monitor. The overdose information needs to be recorded in the drug overdose form. Any overdose which results in AE should be reported on AE page in CRF. Any case which meets the definition of SAE should be reported per SAE reporting procedures. The Investigator should refer to Investigator's Brochure for detailed information of study drug(s) being used in this study. Investigator should take appropriate actions to treat the event to ensure the safety and benefit of subject.

7.2.9 Pregnancy

To ensure subject safety, pregnancy occurring in female subjects from Visit 1 to study completion must be reported to Harbour BioMed within 24 hours of awareness of the event. The pregnancy should be followed up to determine outcome. Outcomes include spontaneous or voluntary termination of pregnancy, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Pregnancy Report Form and reported to Harbour BioMed by the Investigator. Any AE occurring during pregnancy must be reported on the AE page in CRF; any event meeting the criteria of SAE should be reported per SAE reporting procedures.

The pregnancy occurring in female partner of male subjects during the study should be collected and reported following the pregnancy reporting procedures.

7.2.10 Clinical Endpoint Committee

No Clinical Endpoint Committee will be used for this study.

7.2.11 Data Monitoring Committee

No Data Monitoring Committee will be used for this study.

8 STUDY PLAN

8.1 Schedule of Study

See Table 1.

Table 1. Schedule of Study

Procedure	**Visit 1 Day -13 ± 2**		**Visit 2 Day 1**		**Visit 3 Day 8 ± 1**	**Visit 4 Day 15 ± 2**	**Visit 5 Day 29 ±2**		**Visit 6 Day 57 ±3**		**EOT[4]**	**FU[2]**
	Before CAE	**After CAE**	**Before CAE**	**After CAE**	**No CAE**	**No CAE**	**Before CAE**	**After CAE**	**Before CAE**	**After CAE**		
Informed consent	X											
Medical/medication history and demographics	X											
Medical/Medication history update			X		X	X	X		X			
Placebo run-in dispensation		X										
Placebo run-in collection			X									
Randomization				X								
Study drug dispensation				X		X		X				
Study drug instillation				X	X							
Study drug collection					X	X	X		X		X	
Diary dispensation		X		X	X	X		X				
Diary collection			X		X	X	X		X		X	
Review of inclusion/exclusion criteria	X	X	X	X								
Adverse event Query	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X[1]								X[1]		X[1]	
Drop tolerance assessment				X								
Ora Calibra® Ocular Discomfort Scale	X	X	X	X	X	X	X	X	X	X		
Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire	X	X	X	X	X	X	X	X	X	X		
VAS Discomfort Scale	X	X	X	X	X	X	X	X	X	X		

Procedure	**Visit 1 Day -13 ± 2**		**Visit 2 Day 1**		**Visit 3 Day 8 ± 1**	**Visit 4 Day 15 ± 2**	**Visit 5 Day 29 ±2**		**Visit 6 Day 57 ±3**		**EOT**[4]	**FU**[2]
	Before CAE	**After CAE**	**Before CAE**	**After CAE**	**No CAE**	**No CAE**	**Before CAE**	**After CAE**	**Before CAE**	**After CAE**		
OSDI© Questionnaire	X		X		X	X	X		X			
Visual acuity (ETDRS)	X		X		X	X	X		X		X	
Slit-lamp bio-microscopy	X	X	X	X	X	X	X	X	X	X	X	
Conjunctival redness	X	X	X	X	X	X	X	X	X	X		
TFBUT	X	X	X	X	X	X	X	X	X	X		
Fluorescein staining	X	X	X	X		X	X	X	X	X		
CAE exposure	X		X				X		X			
Discomfort grading during CAE exposure	X		X				X		X			
Schirmer's test		X		X		X		X		X		
Intraocular pressure		X								X	X	
Fundus color photography [3]		X								X	X	
Subject withdrawal from the study										X		

EOT: End of Treatment

1. Applies to females of child bearing potential. See the definition for details.
2. A telephone follow-up will be made 7 days after the last dose of study drugs to collect safety information. See Section 8.4 for details.
3. If retinopathy is detected, or if it is impossible to take clear photos of both optic dics and mucula lutea simultaneously, the indirect ophthalmoscope or preset lens should be inspected under the pupil dilation conditions.
4. The examination that a subject who withdraws the study must receive. See Section 8.3 for details.

Before any study-related procedure is performed, subjects, investigators or specified persons and witnesses (if necessary) must sign and date the ICF.

The following procedure should be performed in sequence. For detailed information about the related methods and grading system, see Annex 1.

8.1.1 Visit 1: Day -13±2 to Subject Screening (CAE)

All subjects will be screened and assessed as follows.

Before entering the CAE

- Informed consent. Before change of drug treatment and/or invasive procedures (such as CAE), this study will be discussed with each subject, and those subjects who are willing to join this study must provide written informed consent.

- Demographics, medical/medication/ophthalmological history. All the demographic data, medical history, use of medications and underlying diseases will be collected and recorded. Only the serious non-ophthalmological medical history in the past one year and the medication history in the past 30 days are collected. The medications that subjects are receiving and have used but stopped within 30 days before screening will be recorded.

- Review of inclusion/exclusion criteria

- Urine pregnancy test (for females of childbearing potential). The result of urine pregnancy test for females of childbearing potential must be negative before participation in the study.

- Ora Calibra® Ocular Discomfort Scale

- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire Ocular Discomfort Score

- Ocular discomforts assessed by Visual Analog Scale (VAS)

- OSDI©

- BCVA assessed by the ETDRS Charts. At Visit 1, the score for each eye of a subject must be 0.7 logMAR or better (Snellen equivalent score is 20/100 or better)

- Slit-lamp bio-microscopy. Slit-lamp bio-microscopy will be performed at the start of visit and be re-performed after CAE exposure to exclude any subjects with undesirable eye diseases.

- Conjunctival redness score. It is an objective index that assesses conjunctival redness through the Ora Calibra® Dry Eye Conjunctival Redness Scale. For an increment, half a point may be used (0.5 points).

- TFBUT
- Corneal staining (fluorescein), assessed by the Ora Calibra® Fluorescein Staining Rating Scale for cornea and conjunctiva
- AE query. All the AEs that occur after signing of ICF will be reported.

Screening Challenge (CAE # 1)

Subjects meeting all of the above evaluation (Pre–CAE® #1) criteria will undergo further screening evaluation in the CAE®. Subjects will be exposed to the CAE® for 90 ±5 minutes. Ocular discomfort self-assessment scores (ODS) will be obtained just prior to entering, during and just after the CAE® exposure. During the CAE® exposure, ODS will be collected at time 0 and every 5 minutes thereafter throughout the 90 ±5 minutes.

After leaving the CAE

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit-lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal staining (fluorescein)
- Schirmer's test
- IOP
- Fundus color photography
- Review of inclusion/exclusion criteria
    - Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting all of the following criteria in the same eye:
        - Having at least a ≥1 point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure;
        - Reporting an Ocular Discomfort score ≥3 at 2 or more consecutive time points in at least one eye during CAE® exposure (if a subject has

an Ocular Discomfort rating of 3 at time = 0 for an eye, he must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye). Note: a subject cannot have an Ocular Discomfort score of 4 at time = 0);

- If both eyes are equal, the right eye (OD) will be designated as the study eye.

- Following the screening procedures at this visit, all subjects who meet all eligibility criteria and have a positive response (as defined above) will self-administer their initial dose of placebo drops (open–label, single drop, OU), for training purposes, at the study site under supervision of trained study personnel following the last Post– CAE® #1 study assessment. Only a single dose of placebo drops will be administered OU on Day –13.

- Placebo and diary dispensation and administration. Prior to discharge from the study site on Day –13, subjects will be dispensed sufficient placebo supply to last until Visit 2 and will be educated in study drug diary recording and self-administration of placebo. Subjects will be instructed to self–administer one drop BID in each eye in the morning and the evening until screening Visit 2. Subjects will be instructed not to instill study drug on the morning of their next scheduled study visit (Visit 2, Day 1).

- Monitoring and query of AEs. Report any AEs that occur after signing the ICF.

- Schedule next visit. Subjects will be scheduled for Visit 2.

8.1.2 Day -13 to Day 0

- From Day -13 to Day 0, subjects will self-administer one drop of placebo eye drop into both eyes in open-label status every morning and evening (BID). The placebo eye drop will be provided in disposable vials. Subjects need to report any AEs and record drug administration information in subject diary.

8.1.3 Visit 2：Day 1- Subject Confirmation (CAE) and Baseline

Before entering the CAE

- Study diary/placebo collection. Subject study diaries and all used/unused placebo vials dispensed for Days –13 to 1 should be collected and reviewed by a trained study technician.

- Site staff must confirm subjects have not administered their morning placebo dose at home.

- Review of inclusion/exclusion criteria

- Monitoring and query of AEs

- Record all changes in concomitant medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- OSDI
- BCVA Utilizing an ETDRS Chart
- Slit-lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal staining (fluorescein)

Re-confirmation of Screening Challenge (CAE # 2)

Subjects will be exposed to the CAE® for 90 ±5 minutes. Ocular discomfort se lf–assessment scores (ODS) will be obtained just prior to entering, during and just after the CAE® exposure. During the CAE® exposure, ODS will be collected at time 0 and every 5 minutes thereafter throughout the 90 ±5 minutes.

After leaving the CAE

- Inclusion/exclusion evaluation
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit-lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal staining (fluorescein)
- Schirmer's test

- Review of inclusion/exclusion criteria

    - Eligible subjects must replicate a positive response at this visit in the same eye as was elicited in Visit 1. A positive response is defined as meeting all of the following criteria in the same eye:

        - Having at least a ≥1 point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure;

        - Reporting an Ocular Discomfort score ≥3 at 2 or more consecutive time points in at least one eye during CAE® exposure (if a subject has an Ocular Discomfort rating of 3 at time = 0 for an eye, he must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye). Note: a subject cannot have an Ocular Discomfort score of 4 at time = 0);

        - If both eyes are equal, the right eye (OD) will be designated as the study eye.

Randomization

- Study drug instillation at the study site. All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria after Visit 2 will be randomized to one of two treatment arms. Randomized subjects will self-administer their initial study drug dose bilaterally at the study site.

- Drop comfort assessment. A drop tolerance evaluation will be performed by using the Ora Calibra® drop tolerance scale immediately and then at 1 and 2 minutes following initial dosing. A drop tolerance evaluation will be performed by using the Ora Calibra® drop tolerance questionnaire at 3 minutes following initial dosing.

- Monitoring and query of AEs

- Subject diary/study drug dispensation. Prior to discharge from the study site on Visit 2 (Day 1), randomized subjects will be educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 4 (Day 15) and will be instructed not to self-administer study drug on the morning of their next scheduled study visit (Visit 3, Day 8).

- Schedule next visit. Subjects will be scheduled for Visit 3.

8.1.4 Day 1 to Day 7±1

Subjects will self-administer the study drug (BID) in the morning and evening of Day 1 and continue to take the study drug till Day 7. The study drugs are provided in disposable vials. Subjects must instill a drop of the study drug to each eye when they are awake in the morning

and evening. Subjects need to report any AEs and record drug administration information in subject diary.

8.1.5 Visit 3 (Day 8±1)

There is no CAE® evaluation at Day 8, Visit 3.

- Subject diary/study drug collection. Subject diaries and all used study drug vials dispensed for Days 1 to 7 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have not administered their morning placebo dose at home.
- Monitoring and query AEs
- Recording of all changes in concomitant medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- VAS discomfort scale
- OSDI
- BCVA Utilizing an ETDRS Chart
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Study drug instillation at the study site. Subjects will self-administer study drug dose bilaterally at the study site following the last study assessment. The evening dose will be administered at home by the subject.
- Monitoring and query AEs
- Subject diary. Prior to discharge from the study site on Visit 3 (Day 8), subjects will be educated in study drug diary recording and self-administration of study drug. Subjects will be instructed not to self-administer study drug on the morning of their next scheduled study visit (Visit 4, Day 15).
- Schedule next visit. Subjects will be scheduled for Visit 4 and will be instructed not to self-administer study drug on the morning of their next scheduled study visit (Visit 4, Day 15).

8.1.6 From Day 8 to Day 14±2

Subjects will self-administer the study drug (BID) in the morning and evening of Day 8 and continue to take the study drug till Day 14±2 . The study drugs are provided in disposable vials.

Subjects need to report any AEs and record drug administration information in subject diary.

8.1.7 Visit 4: Day 15±2

There is no CAE® evaluation at Day 15, Visit 4.

- Subject diary/study drug collection. Subject diaries and all used study drug vials dispensed for Days 8 to 15 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have not administered their morning placebo dose at home.
- Monitoring and query AEs
- Recording of all changes in concomitant medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- VAS discomfort scale
- OSDI
- BCVA Utilizing an ETDRS Chart
- Slit-lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal staining (fluorescein)
- Schirmer's test
- Subject diary. Prior to discharge from the study site on Visit 4 (Day 15), subjects will be educated in study drug diary recording and self-administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 5 and will be instructed not to self-administer study drug on the morning of their next scheduled study visit (Visit 5, Day 29).

- Schedule next visit. Subjects will be scheduled for Visit 5.

8.1.8 From Day 15 to Day 28±2

Subjects will self-administer the study drug (BID) in the morning and evening of Day 15 and continue to take the study drug till Day 28±2. The study drugs are provided in disposable vials. Subjects must instill a drop of the study drug to each eye when they are awake in the morning and evening. Subjects need to report any AEs and record drug administration information in subject diary.

8.1.9 Visit 5: Day 29±2

Before entering the CAE

- Subject diary/study drug collection. Subject diaries and all used study drug vials dispensed for Days 15 to 29 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have not administered their morning study drug dose at home.
- Monitoring and query of AEs
- Record all changes in concomitant medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- VAS discomfort scale
- OSDI
- BCVA Utilizing an ETDRS Chart
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal staining (fluorescein)

CAE

- During the CAE® exposure, ODS will be collected at time 0 and every 5 minutes thereafter throughout the 90 ±5 minutes.

After leaving the CAE

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal staining (fluorescein);
- Schirmer's test;
- Monitoring and query of AEs
- Study Drug Diary/Study Drug Dispensation Prior to discharge from the study site on Visit 5 (Day 29), subjects will be educated in study drug diary recording and self-administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 6 and will be instructed to not self–administer study drug on the morning of their next scheduled study visit (Visit 6, Day 57).
- Schedule next visit. Subjects will be scheduled for Visit 6.

8.1.10 From Day 29 to Day 56±3

Subjects will self-administer the study drug (BID) in the morning and evening of Day 29 and continue to take the study drug till Day 56±3. The study drugs are provided in disposable vials. Subjects must instill a drop of the study drug to each eye when they are awake in the morning and evening. Subjects need to report any AEs and record drug administration information in subject diary.

8.1.11 Visit 6: Day 57±3

Before entering the CAE

- Subject diary/study drug collection. Subject diaries and all used/unused study drug vials dispensed for Days 29 to 57 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have not administered their morning study drug dose at home.

- Monitoring and query of AEs
- Record all changes in concomitant medications
- Urine pregnancy test (for females of childbearing potential)
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire
- VAS discomfort scale
- OSDI
- BCVA Utilizing an ETDRS Chart
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal staining (fluorescein)

CAE

- During the CAE® exposure, ODS will be collected at time 0 and every 5 minutes thereafter throughout the 90 ±5 minutes.

After leaving the CAE

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal Staining (fluorescein)
- Schirmer's test

- Intraocular Pressure
- Fundus color photography
- Monitoring and query of AEs, and a telephone follow-up will be made 7 days later
- Study Exit

8.2 Discontinuation of Treatment and Premature Withdrawal from Study

Subjects may be discontinued before their completion of the study due to:

- Adverse events;
- Unblinding when medically necessary;
- Protocol violations;
- Administrative reasons (e.g., inability to continue, lost to follow up);
- Termination of study by sponsor;
- Subject choice (e.g. Withdrawal of consent); and
- Other.

Note: In addition, any subject may be discontinued for any sound medical reason at the discretion of the Investigator.

Notification of a subject discontinuation and the reason for discontinuation will be made to the Sponsor and will be clearly documented on the eCRF.

Subjects who discontinue treatment should switch to proper maintenance treatment at the discretion of the Investigator. For subjects who discontinue treatment and do not finish at least one post-treatment data collection, a telephone follow-up should be made at least 7 days after the last dose of study drug.

Discontinued subjects will not be replaced.

8.3 Unscheduled Visits and End of Treatment/Study Exit Visit

Repeat assessments, if needed, will be captured in unscheduled visits.

End of treatment/study exit visits will be captured as unscheduled visits. At least the following procedures will be completed at these visits:

- Record AEs and SAEs (if any);

- Review concomitant medications;
- Urine samples will be collected from women of childbearing potential for pregnancy tests；
- All the study drugs/subject diaries will be collected；
- Subjects will resume pre-study treatment or receive appropriate medication treatment;
- Subjects will be told to report all the SAEs that occur within 7 days after the last dose of study drug；
- Collect the reasons for discontinuation of study. These visits may be made to ensure safety of subjects. All the procedures performed at unscheduled visits must be recorded in the source documents and the eCRF page for unscheduled visits. For any procedure indicated in the eCRF, "unperformed" should be indicated if they have not been performed；
- Assessment that may be performed at unscheduled visits：

1. Slit-lamp biomicroscopy;
2. Visual acuity;
3. Intraocular pressure;
4. Urine pregnancy test;
5. Fundus color photography or mydriasis fundus examination；
6. Any other assessment needed in the judgement of the Investigator.

8.4 End of Study

All subjects will be followed up by telephone call 7 days after last dose of study drug. The following procedures will be completed:

- Review ongoing AEs and SAEs (if any)；
- Collection of new SAEs (if any)；
- Review of concomitant medications.

Note: For the subjects who withdraw the informed consent, a telephone follow-up will be made at least 7 days after last dose of study drug.

8.5 Termination of Study

According to the contract signed with Harbour BioMed, investigators may choose to discontinue the study for any reason on a fully-informed basis.

Harbour BioMed reserves the right to terminate the study at any time due to clinical or administrative reasons. If Harbour BioMed decides to terminate the study, the termination process must be implemented by investigators within a time frame that is favorable to subjects' health conditions.

8.6 Completion of Study

Investigators will record the reasons for study completion or early withdrawal on the eCRF. The events will be classified as follows on the eCRF：

- Subjects' decision (record the reasons);
- For subjects' best benefit in the judgement of the Investigator;
- Adverse events;
- Administrative reasons (e.g. premature termination of the study);
- Lost to follow-up;
- Lack of efficacy;
- Major protocol deviations;
- Death;
- Study completion;
- Specific criteria specified in protocol (see Section 5).

9 STATISTICAL METHODS

9.1 Analysis Populations

The analysis populations in this study are defined as follows:

- **Full Analysis Set (FAS)** includes all the randomized subjects who have received at least one dose of study drug according to the principle of intention-to-treat (ITT). Subjects will be analyzed as randomized.

- **Per Protocol Set (PPS)** is a subset of the FAS population including all the subjects who do not have major protocol deviations and who complete the study. Subjects in the PP population will be analyzed as treated. Protocol deviations will be assessed before database lock and unblinding. For the subjects who have major protocol deviations (protocol violations), all their data should be eliminated from the PPS data, or the data of specific time points and/or subsequent time points should be eliminated.

- **Safety Set (SS)** includes all randomized subjects who have received at least one dose of the investigational product. The SS will be analyzed for all safety assessments. Subjects in the SS will be analyzed as treated.

In this study, the baseline data analysis will be based on the FAS. The efficacy analysis will be based on both FAS and PPS. The PPS will be used for main analysis. For the FAS, the missing data after dropout will be imputed using the Last Observation Carried Forward (LOCF) method. The observed and imputed data will be used for the analysis of FAS to assess the robustness of study results. The SS will be used for analysis of laboratory examination data, adverse events, and adverse reactions.

9.2 Determination of Sample Size

This study is expected to enroll 50 subjects in each treatment group so a total of 100 subjects will be randomized. Assuming a 20% drop out rate, 40 subjects per group are expected to complete the study.

According to the results from the US Phase II study, assuming the standard deviation is 0.7 unit for the change from baseline in the pre- to post-CAE® inferior corneal fluorescein staining (ICSS) score and the mean of the change from baseline in the pre- to post-CAE ICSS score is about 0.65, the efficacy results will be very promising if the difference in the mean of ICSS change for the placebo and treatment groups are greater than 0.3. If the difference< 0.1, the efficacy may not be promising.

If 40 subjects in each group will complete the study, the probability for observing the efficacy< 0.1 in this study will be about 74% if the study drug is not effective in the treatment group. If the difference in the efficacy between the treatment and placebo groups is >0.4, the probability for observing the efficacy> 0.3 in this study will be at least 75%. Other possibilities are summarized in the table below.

ICSS Actual Mean Difference	Ideal Region Mean difference >=0.3	Consideration Region Mean Difference [0.1, 0.3)	Unsatisfactory Region Mean difference <0.1
0.0	*3.0%*	*23.3%*	*73.8%*
0.1	*9.9%*	*40.1%*	*50.0%*
0.2	*26.2%*	*48.6%*	*25.2%*
0.3	*50.0%*	*40.2%*	*9.8%*
0.4	*74.8%*	*22.7%*	*2.6%*

9.3 Blinding and Randomization

Random numbers will be generated at a ratio of 1:1 (treatment group to control group) using the randomized block method by independent biostatisticians responsible for the data management and statistical analysis of this study. The selected block size and random seeds will be kept confidential. Statisticians unrelated to this study will label study drugs with the random number. Each study site will use the assigned code according to the sequence of enrollment.

This study will use the centralized randomization method and each study site will enroll subjects competitively. For each eligible subject, the study staff at study sites will log into the IWRS system, complete screening information, and obtain the random number and corresponding drug number. Investigators will dispense study drugs according to the random number and drug number.

9.4 General Considerations for Statistical Analysis

The quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The qualitative variables will be summarized using counts and percentages. All summaries will be presented by treatment group. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

Medical history, concurrent therapies, and AEs will be coded to MedDRA and WHO Drug dictionaries.

Baseline measures are defined as the last measure before the initiation of study treatment, usually at Visit 2. If a measure is taken both pre-CAE® and post-CAE®, the baseline will be the time point matched value at Visit 2. For measures from daily subject diaries, baseline is defined as the average of all days during the run-in period. For changes from pre-CAE® to post-CAE® post first treatment, the change from pre-CAE® to post-CAE® at Visit 2 will be considered the baseline value.

All analyses for primary and secondary efficacy outcomes will be tested 2-sided at a significance level of 0.05.

Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the study eye, or the "worst eye," as defined by the following:

Worst Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria. In the case that both eyes are eligible for analysis, the worst eye will be the eye with worse (higher) inferior corneal staining pre-CAE® at Visit 2. If the inferior corneal staining is the same in both eyes, then the worst eye will be the eye with the highest ocular discomfort pre-CAE® at Visit 2. If the ocular discomfort is the same in both eyes, then the right eye will be selected as the worst eye.

9.5 Efficacy and Safety Analysis

9.5.1 Efficacy Analysis

9.5.1.1 Primary Efficacy Analyses

For primary efficacy endpoints, the pre- to post-CAE ICSS change will be calculated as post-CAE ICSS score-pre-CAE ICSS score. The change from baseline will be calculated as visit (post-CAE-pre-CAE)-baseline (post-CAE-pre-CAE) such that a positive difference indicates the change at study visit is larger than that at baseline. In addition, treatment comparisons between treatment and placebo groups will be calculated as treatment – placebo, such that a negative result indicates a better score for the treatment group (i.e., the treatment group have a smaller increase in dry eye signs or symptoms than the placebo group).

ANCOVA models will be used to compare the change from baseline in the pre- to post-CAE® inferior corneal fluorescein staining at Day 57 (Visit 6) (measured by the Ora Calibra® scale), between 0.25% HBM9036 Ophthalmic Solution and Placebo. The ANCOVA models will include the change in pre- to post-CAE ICSS at baseline as a covariate. The primary analysis will use LOCF imputation to have a full accounting of the FAS at the Day 57 visit, as described in Section 9.7.

9.5.1.2 Secondary Efficacy Analysis

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, min and max), and analyzed with two-sample t-tests comparing the treatment group with placebo. All visit-based data will be analyzed at each visit and change from baseline. Change scores from pre- to post-CAE® will be calculated as post-CAE® score – pre--CAE® score. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline will also be assessed where appropriate. No imputation will be performed for secondary efficacy variables.

Two-sample t-tests and Wilcoxon rank sum tests will be used for ANCOVA model adjusting for baseline: the change from baseline in the pre- to post-CAE® change of the ICS fluorescein staining at Visit 5; the change from baseline in post-CAE® TFBUT and conjunctival redness; the change from baseline in unanesthetized Schirmer's test results and OSDI scores at Visit 6; the change from baseline in pre--CAE® ocular discomfort (including

the Ora Calibra Dry Eye Ocular Discomfort Scale, Ora Calibra Ocular Discomfort and Dry Eye 4-Symptom Questionnaire) at Visits 5 and 6; the change from baseline in pre--CAE® burning sensation score assessed by VAS scale at Visit 6; and the change from baseline in the mean score of burning sensation by week assessed according to subject diaries.

The worst symptom for each subject will be identified as the symptom with the highest average score during the run-in period (Days -13 to 0) as recorded in the subject diary. The worst symptom and each individual symptom will be analyzed per day using a two-sample t-test. Additionally, the average score for the worst symptom and each individual symptom will also be analyzed separately using a Wilcoxon rank sum test.

9.5.2 Safety Analysis

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it 1) occurs after the first dose of randomized study treatment or 2) if it is present prior to receipt of randomized study treatment but worsens in severity or increases in frequency after the first dose of randomized study treatment. Frequencies and percentages of subjects with AEs, SAEs, and AEs causing premature discontinuation will be provided by treatment group. The AEs will be listed by MedDRA SOCs and PTs and the AE listings will be categorized by severity, the causal relationship with study drug, and whether the AEs leading to discontinuation of study. No hypothesis test will be performed. Separate analyses will be performed for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, fundus color photography, drop tolerance, and intraocular pressure, will be summarized by treatment group and visit using descriptive statistics. Changes from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value will be summarized.

The exposure time (number of days) and drug administration times will be summarized by treatment group. The number and percentage of subjects with compliance will be calculated. The total exposure of the safety population will be summarized based on actual treatment received.

9.6 Subgroup Analyses

The four subgroups below are considered for subgroup analyses of primary efficacy outcome：

- Baseline subcorneal fluorescent staining score <2, ≥2；
- Baseline conjunctival redness score <2, ≥2；
- The course of disease is longer than average level, shorter than average level；

- The baseline CAE screening <20 minutes, ≥20 minutes.

The subgroup analyses above will be performed for secondary efficacy outcomes as appropriate.

9.7 Handling of Missing Data

The primary efficacy analyses will be performed using the Last Observation Carried Forward (LOCF) imputation method for missing values. For the analysis of ICSS at Day 57 (Visit 6), the last value from the previous visits will be carried forward, matching pre-CAE® or post-CAE® time points. A pre-CAE® time point will never be imputed for a post-CAE® value, and vice versa.

For the primary efficacy variables, the measured data will be used to assess the robustness of the study results.

No secondary efficacy endpoints or safety endpoints will be imputed.

9.8 Interim analysis

No interim analysis will be conducted in this study.

9.9 Multiplicity Adjustment

No multiplicity adjustment is considered in this study.

9.10 Statistical Analysis Plan and Analysis Software

All the analyses will be described in detail in the Statistical Analysis Plan (SAP), and the shells of tables, data listings and figures will be attached. The SAP will be signed for approval before database locking and unblinding.

The SAS9.4 will be used for data processing, statistical screening, descriptive reporting and efficacy and safety analyses. The R3.5.1 software may also be used for plotting.

10 STUDY MANAGEMENT

10.1 Regulatory Authority Approval

Harbour BioMed will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before a study site initiates the study.

10.2 Ethical Conduct of the Study and Institutional Review Board/Independent Ethics Committee Approval

The study will be conducted in accordance with Good Clinical Practice (GCP). These standards respect the following guidelines:

- Guideline for Good Clinical Practice E6 (R1);
- Good Clinical Practice in China in current use;
- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects);
- Any additional regulatory requirements.

The Investigator (or Harbour BioMed, where applicable) will be responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the ICF) will be reviewed and approved by the appropriate EC. The Investigator agrees to allow the EC direct access to all relevant documents. The EC must be constituted in accordance with all applicable regulatory requirements.

Harbour BioMed will provide the Investigator with relevant document(s)/data that are needed for EC review and approval of the study. If the protocol, the ICF, or any other information approved by EC and provided to potential subjects is amended during the study, the Investigator will be responsible for ensuring the EC reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining EC approval of the amended form before new subjects consent to take part in the study using this version of the form. The EC approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to Harbour BioMed promptly.

10.3 Subject Information and Informed Consent

The study will be conducted in accordance with applicable subject privacy requirements. The proposed ICF, which must be in compliance with applicable regulations, must be reviewed and approved by the EC and Harbour BioMed prior to initiation of the study.

The Investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific screening and enrollment. A copy of the signed ICF will be provided to the subject. The original will be retained by the Investigator.

10.4 Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations. Reference values and/or normal ranges for the test results must be provided to Harbour BioMed. Sponsor must be notified promptly in writing of any changes occurring in reference values during the course of the study.

10.5 Confidentiality

10.5.1 Data Confidentiality

By signing this protocol, the Investigator affirms to Harbour BioMed that information provided to the Investigator by Harbour BioMed will be maintained in confidence and such information will be disclosed to the EC, or similar organizations or expert committee; affiliated institution and employees only after confirming the confidentiality of such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential except those included in a publication.

10.5.2 Confidentiality of Subject / Patient Records

By signing this protocol, the Investigator agrees that Harbour BioMed (or representative), EC, or Regulatory Agency representatives may review and/or copy study documents to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked before sending the document to Harbour BioMed. In addition, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable laws (such as the Health Insurance Portability and Accountability Act), rules and regulations.

10.6 Quality Control and Assurance

Harbour BioMed will be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that the study will be conducted and data will be generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable local laws relating to the conduct of the clinical study.

10.7 Data Management

Data management procedures and information for this protocol will be provided by Harbour BioMed or its designee.

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Harbour BioMed procedures, clinical research associates (CRAs) will contact the site prior to subject enrollment to review the protocol and data collection procedures with site staff. In addition, the CRA will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these procedures, the CRA will:

- Check the progress of the study;
- Review study data collected;
- Conduct source document verification;
- Identify and address any issues.

The work above is to verify that:

- The data are authentic, accurate, and complete;
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The Investigator agrees to allow the CRA direct access to all relevant documents and to allocate his/her time to the CRA to discuss findings and any relevant issues.

Upon completion of the study, the CRA will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

- Return of all study data to Harbour BioMed;
- Data queries;
- Accountability, reconciliation, and arrangements for unused study drugs;
- Review of site study records for completeness.

After the final review of the study files, the files should be secured for the appropriate time period. The Investigator will also permit inspection of the study files by Quality Assurance auditors from Harbour BioMed, and authorized representatives of the NMPA or other applicable regulatory agencies.

10.9 Data Retention

Documents that individually and collectively being evaluable for the conduct of the study and the quality of the data must be maintained for review by quality assurance auditors from Harbour BioMed and by all applicable regulatory authorities. The period of time for which these documents must be maintained is determined by applicable regulations. Harbour BioMed or its designee will inform the Investigator when these documents may be destroyed. Harbour BioMed or its designee must be notified in writing prior to the intended date of disposal of any study record related to this protocol for making alternate storage arrangements.

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed.

10.11 Publication Policy

All the clinical study results will be published according to the Declaration of Helsinki. The drafts, publications or reports related to this study must be submitted to Harbour BioMed for review and approval before submission for publication or being reported, so as to ensure consistency with the policy of this protocol. All the communications between the investigators and Harbour BioMed and any third party should be carried out according to the confidentiality agreement.

11 List of References

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12 APPENDICES

12.1 APPENDIX 1：EXAMINATION PROCEDURE, TESTS, EQUIPMENTS AND TECHNIQUES

Visual Acuity Procedures (ETDRS Chart)

LogMAR visual acuity (VA) must be assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. VA should be evaluated at the beginning of each visit in the study (ie, prior to slit-lamp examination). VA testing should be done with most recent correction.

Equipment

The VA form used is the ETDRS Charts. If a small wall chart (18 "x 18", such as blindness prevention) is used, the measuring distance for subjects should be as accurate as 10 feet (or as per manufacturer instructions). In all cases, all the study sites can only use the same target form and should first test the right eye in order to standardize the test conditions during the study. For reflection-type wall charts, they should be placed right ahead, good lighting should be provided.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each number target, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has numbers only, no letters. If the subject reads a letter, he or she should be reminded that the chart contains no letters, and the examiner should then request a number in lieu of the letter. The subject should be asked to read slowly, so as to achieve the best identification of each number. He/she is not to proceed to the next number until he/she has given a definite response.

If the subject changes a response (e.g., 'that was a "9" not an "3"') before he has read aloud the next number, then the change must be accepted. If the subject changes a response having read the next number, then the change is not to be accepted. The examiner should never point to the chart or to specific numbers on the chart during the test.

A maximum effort should be made to identify each number on the chart. When the subject says he or she cannot read a number, he or she should be encouraged to guess. If the subject identifies a number as 1 of 2 numbers, he or she should be asked to choose 1 number and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as number difficulties vary and the last may be the only one read correctly. The targets missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a number is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of number targets missed up to and included in the last line read. This total sum represents the logMAR VA for that eye.

For Example: Subject correctly reads 4 of 5 numbers on the 0.2 line, and 2 of 5 numbers on the 0.1 line.

Base logMAR	= 0.1
N (total number of targets incorrect on line 0.2 as well as 0.1)	= 4
N×T （T=0.02）	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR VA	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of VA during the study, all VA assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (ie, a subject forgets his glasses), the reason for the change in correction should be documented.

Slit Lamp Biomicroscopy Procedures

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the investigator) or not clinically significant (NCS). The following will be examined:

- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens
- Eyelid

External magnification and biomicroscopy will be performed using a slit-lamp. Magnification will be consistent with standard clinical practice. The subject will be seated.

Fundus Color Photography

The fundus color camera will be used to take photos of the patients' fundus, and the photos will be kept. Pupil dilation is not a must, but the photos must be clear and include optic dics and macula lutea. The Investigator will examine the vitreous body, retina, macula lutea, choroid, and optic nerves.

Observations will be graded as Normal or Abnormal. Abnormal findings that are clinically significant (as determined by the Investigator that may interfere with study parameters or otherwise confound the data) and those that are not clinically significant will be described. An indirect ophthalmoscope or preset lens examination should be performed if retinal disease is detected or optic dics and macula lutea can't be photographed simultaneously.

- Vitreous: Examination should emphasize the visual axis.
- Retina, Macula, Choroid: Include an observation of the retina and its blood vessels. Eyes should be excluded from the study if active inflammation is present.
- Optic Nerve: Significant damage or cupping to the optic nerve should be noted.

It is recommended that tropicamide 1% ophthalmic solution be used to dilate subjects. The use of cyclopentolate 1% ophthalmic solution is recommended as secondary dilating medication, should the need arise.

Intraocular Pressure

Intraocular pressure (IOP) will be measured in each eye by non-contact tonometry by the examiner and the results will be recorded in mmHg. The measurement of intraocular pressure will be repeated three times to calculate the mean value. If the variation is large, the measurement will be repeated as appropriate to calculate the mean value.

Ora proprietary scales – Not for distribution without permission

Ora Calibra® Ocular Discomfort Scale for Dry Eye

Ocular discomfort scores will be subjectively graded by the subjects according to the following scale, rating each eye separately.

0	**No discomfort**
1	**Intermittent awareness**
2	**Constant awareness**
3	**Intermittent discomfort**
4	**Constant discomfort**

Ora Calibra® Eye Discomfort and 4-Symptom Dry Eye Questionnaire

At each day during the at-home dosing period, subjects will grade the severity of their dry eye syndrome symptoms in their diary in the morning and in the evening, before instilling the study drug.

Subjects will rate the severity of each of the following symptoms, with regards to how both their eyes feel, in general – overall ocular discomfort, burning, dryness, grittiness and stinging according to the following 6-point (0 to 5) scale where 0 = none and 5 =worst.

0	1	2	3	4	5
(None)					(Most)

Visual Analog Scale (VAS)

The subject will be asked to rate each ocular symptom due to ocular dryness by placing a vertical mark on the horizontal line to indicate the level of discomfort. 0% corresponds to "no discomfort" and 100% corresponds to "maximal discomfort."

Burning/Stinging	0% ——————————— 100%
Pruritus	0% ——————————— 100%
Foreign body sensation	0% ——————————— 100%
Blurred vision	0% ——————————— 100%
Eye dryness	0% ——————————— 100%
Photophobia	0% ——————————— 100%
Pain	0% ——————————— 100%

Ocular Surface and Disease Index (OSDI)© for Dry Eye

Ocular Surface Disease Index® (OSDI®)[2]

Ask the patients the following 12 questions, and circle the number that best represents the answer of each question. Then fill in the boxes A, B, C, D and E according to the instructions beside each.

Have your experienced any of the following *during the last week*?	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**
1.Eyes that are sensitive to light?	**4**	**3**	**2**	**1**	**0**
2. Eyes that feel gritty?	**4**	**3**	**2**	**1**	**0**
3.Painful or score eyes?	**4**	**3**	**2**	**1**	**0**
4. Blurred vision?.....	**4**	**3**	**2**	**1**	**0**
5. Poor vision?	**4**	**3**	**2**	**1**	**0**

Subtotal score for answers 1 to 5 **(A)**

Have problems with your eyes limited you in performing any of the following *during the last week*?	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**	**N/A**
6. Reading?	**4**	**3**	**2**	**1**	**0**	**N/A**
7.Driving at night?	**4**	**3**	**2**	**1**	**0**	**N/A**
8.Working with a computer or bank machine (ATM)?.....	**4**	**3**	**2**	**1**	**0**	**N/A**
9. Watching TV?.....	**4**	**3**	**2**	**1**	**0**	**N/A**

Subtotal score of answers 6 to 9 **(B)**

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	**All of the time**	**Most of the time**	**Half of the time**	**Some of the time**	**None of the time**	**N/A**
10.Windy conditions?	**4**	**3**	**2**	**1**	**0**	**N/A**
11.Places or areas with low humidity (very dry)?	**4**	**3**	**2**	**1**	**0**	**N/A**
12.Areas that are air conditioned?.....	**4**	**3**	**2**	**1**	**0**	**N/A**

Subtotal score of answers 10 to 12 **(C)**

Add the subtotals A, B and C to obtain D (D = sum of scores for all questions answered)	**(D)**

Total number of questions answered (do not include questions answered N/A)	**(E)**

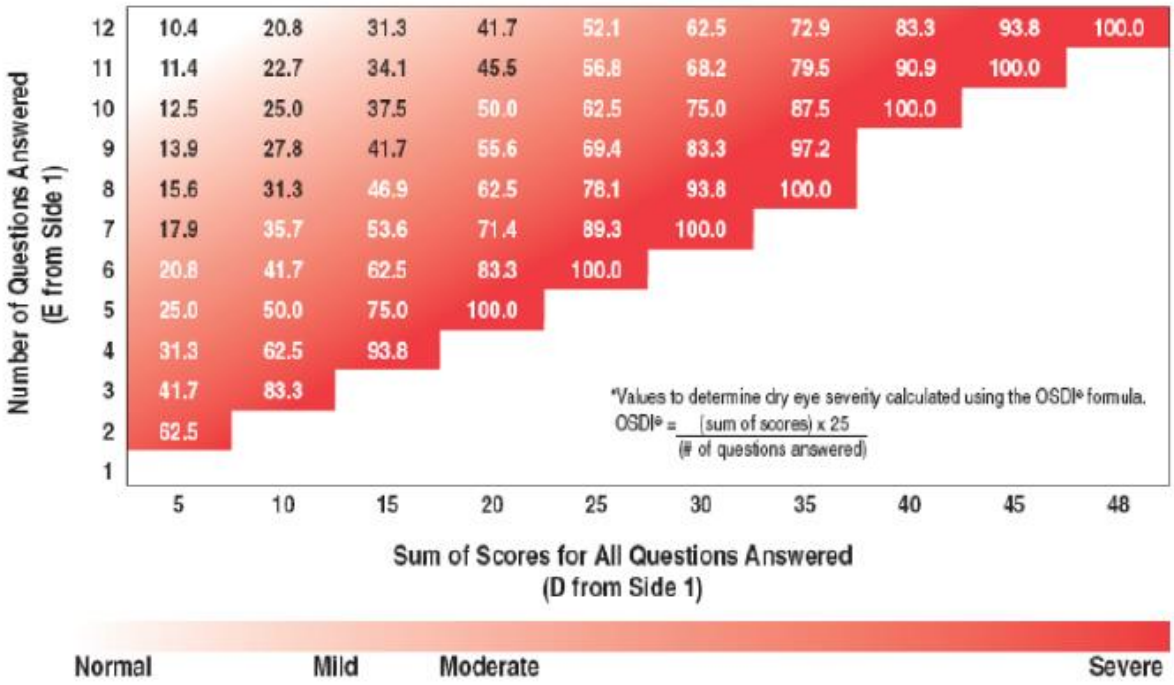
Please turn over the questionnaire to calculate the patient's final OSDI score.

Evaluating the OSDI© score[1]

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dye eye disease. The OSDI© is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1,2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Ora Calibra® Conjunctival Redness Scale for Dry Eye

None	0 = Normal, no vascular dilation
Trace	1 = Trace ciliary or conjunctival vasodilation
Mild	2 = Broad ciliary vasodilation;
Moderate	3 = Broad ciliary and slight, horizontal conjunctival vasodilation
Severe	4 = Broad ciliary and prominent, horizontal conjunctival vasodilation
Half (0.5) unit increments are allowed.	

Tear Film Break-Up Time (TFBUT)

The examiner will instill 5 μL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye or use the sodium fluorescein test strips for staining (moisturized in saline). To thoroughly mix the fluorescein with the tear film, the subject will be instructed to blink several times. In order to achieve maximum fluorescence, the examiner should wait approximately 30 seconds after instillation before evaluating TFBUT.

With the aid of a slit-lamp, the examiner will monitor the integrity of the tear film, noting the time it takes to form micelles from the time that the eye is opened. TFBUT will be measured in seconds using a stopwatch for the right eye followed by the left eye. A Wratten #12 yellow filter will be used to enhance the ability to grade TFBUT.

For each eye, 2 measurements will be taken and averaged unless the 2 measurements are > 2 seconds apart and are each < 10 seconds, in which case, a third measurement would be taken and the2 closest of the 3 would be averaged.

Fluorescein Staining

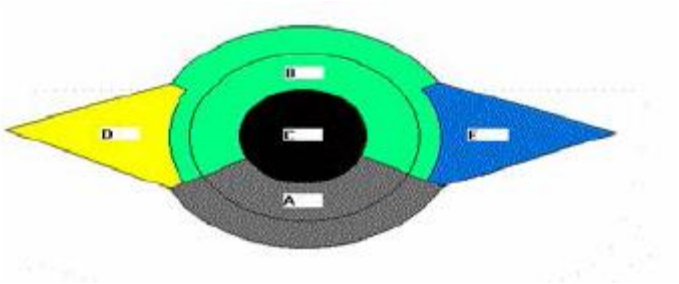
The examiner drips 5μL of 2% preservative-free sodium fluorescein solution or use the sodium fluorescein test strip for staining (moisturized in saline).to the subconjunctival posterior fornix of each eye. In order to maximize fluorescent staining, the examiner should wait for about 3-5 minutes after dripping the dyes, and then assess fluorescein staining. Use the Wratten #12 yellow optical filter to enhance rating of fluorescein staining, and the Ora Calibra® corneal and corneal fluorescein staining scale to rate staining (the NEI scale may be used for re-assessment after assessment with this scale).

Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining

The following scale will be used to grade staining of the ocular surface (areas A, B, C, D, and E). Half (0.5) grade increments may be used.

None	0 = No staining
Slight	1 = Occasional
Mild	2 = Countable
Moderate	3 = Uncountable, but unfused
Severe	4 = Fusion

Staining areas:



Staining Areas	Ocular Structure	Position
A – Inferior	Cornea	4-8 o'clock, extending 2 mm onto the conjunctiva
	Limbus/conjunctiva	4-8 o'clock, extending 2 mm towards the center
B – Superior	Cornea	8-4 o'clock, extending 3 mm onto the conjunctiva
	Limbus/Conjunctiva	8-10 o'clock and 2-4 o'clock, extending 1 mm onto the conjunctiva; 10-2 o'clock, extending 2 mm onto the conjunctiva
C - Central	Cornea	Central cornea
D – Temporal	Conjunctiva	Triangular wedge of temporal conjunctiva
E = Nasal	Conjunctiva	Triangular wedge of nasal conjunctiva

Unanesthetized Schirmer's Test

Schirmer Tear Test will be performed according to the following procedure:

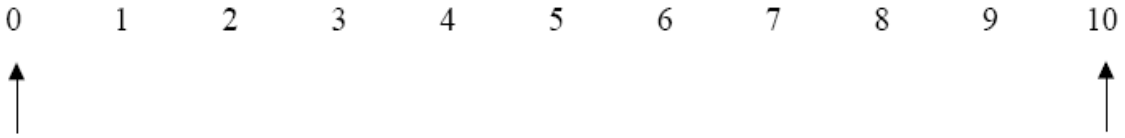
- Using a sterile Schirmer test strip, a bend in the strip will be made in line with the notch in the strip
- The subject will be instructed to gaze up and in
- The Schirmer test strip will be placed in the lower temporal lid margin of each eye such that the strip fits tightly. Subjects will be instructed to close their eyes
- After 5 minutes have elapsed, the Schirmer strip will be removed. The length of the moistened area will be recorded (mm) for each eye

Drop Comfort Assessments

Subject-Reported Drop Comfort Scale

Drop comfort will be assessed for each eye immediately upon instillation, and at 1 and 2 minutes following initial dosing at Visits 2, 3, 4, 5 and 6 using the Ora Calibra™ Drop Comfort Scale.

Ora Calibra® Drop Comfort Scale



Subject-Reported Drop Comfort Questionnaire

Description of drop comfort will be assessed at 3 minutes following initial dosing at Visits 2-6 using the Ora Calibra™ Drop Comfort Questionnaire:

Ora Calibra® Drop Comfort Questionnaire

The subjects will be asked to choose 3 words that best describe how each eye drop feels in both of his/her eyes:

Burning	**Refreshing**
Comfortable	**Smooth**
Cool	**Soothing**
Filmy	**Sticky**
Gritty	**Stinging**
Irritating	**Thick**
Others:_____	

Appendix Sponsor's Signature Page

Study Title:
Study Number:
Version Date:

This clinical protocol is reviewed and approved by the sponsor. The following personnel are involved in writing and approving this protocol.

Signature:_____ Date:_____

Name/title:_____

Signature:_____ Date:_____

Name/title:_____

Appendix Investigator's Signature Page

Title of Study:

Study Number:

Version Date:

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with the protocol and with any other study conduct procedures provided by Harbour BioMed. (hereafter referred to as Sponsor).
- Not to implement any changes to the protocol without agreement from Sponsor and prior review and written approval from the Ethics Committee, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of, and will comply with Good Clinical Practices and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by Sponsor including, but not limited to, the following: the protocol and the current Investigators Brochure (IB).
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions.
- To supply Sponsor with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Sponsor may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Sponsor.
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties.
- To accurately transfer all required data from each subject's source document to the electronic case report forms (eCRFs).
- To allow authorized representatives of Sponsor or regulatory authority representatives to conduct on-site visits to review, audit, and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature:_____ Date:_____

Name: _____

Study Site:_____