CLOUDBREAK THERAPEUTICS

Protocol-short

A Phase 2 multicenter, double-masked, randomized, vehicle-controlled, parallel study to evaluate the safety, efficacy and pharmacokinetics of CBT-008 ophthalmic solution in patients with Meibomian Gland Dysfunction associated Dry Eye Disease (MGD-DED)

Protocol Number:	**CBT-CS105**
ClinicalTrials.gov Identifier	**NCT05261386**
Name of Investigational Product:	**CBT-008 Ophthalmic Solution**
Governing IRB/IEC:	**Sterling IRB**
Sponsor:	**ADS Therapeutics, LLC**
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Emergency Phone Numbers:	**1-949-678-9752**
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Date: **March 29, 2023**

Study Number: CBT-CS105
Name of Sponsor: ADS Therapeutics Inc
Name of Finished Product: Ophthalmic Solution of CBT-008
Name of Active Ingredient: CBT-008
Title of Study: A Phase 2 multicenter, double-masked, randomized, vehicle-controlled, parallel study to evaluate the safety, efficacy and pharmacokinetics of CBT-008 ophthalmic solution in patients with Meibomian Gland Dysfunction associated Dry Eye Disease (MGD-DED)
Study Period: Study Initiation Date (First Subject Enrolled): 04 March 2022 Study Completion Date (Last Subject Completed): 07 September 2022
Phase of Development: Phase 2
Objectives: The study objective for Stage 1 was to evaluate the safety and efficacy of CBT-008 topical ophthalmic solution for treating meibomian gland dysfunction−associated dry eye disease (MGD-DED). The study objective for Stage 2 was to determine the pharmacokinetics (PK) profile of CBT-008 topical ophthalmic solution after a single topical ocular dose in meibomian gland dysfunction (MGD) or healthy patients.
Methodology: This was a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study with a 4-week treatment period (Stage 1). The co-primary endpoints were measured at Week 4. Stage 2 used a 2-day, single-center, randomized, open-label design to assess PK. Patients from a single center who completed Stage 1 participated in Stage 2 (unless more patients were needed, in which case healthy

volunteers could be enrolled).

Stage 1: Randomized comparison of CBT-008 (2 concentrations) vs CBT-008 vehicle
In Stage 1, patients were randomized in a 1:1:1 treatment allocation to receive CBT-008 2.5%, CBT-008 10%, or CBT-008 vehicle, with no stratification by site or by baseline signs and/orsymptoms. One drop of study drug was self-administered in both eyes (OU) 3 times daily (TID) for 1 month, starting at the Day 1 Visit, with additional visits at Weeks 1, 2, and 4. Efficacy was assessedby co-primary endpoints – change from baseline at Week 4 in ocular discomfort score (ODS) and in cornea staining grade using the National Eye Institute (NEI) scale of 0 to 3. Additional efficacy variables were change in ocular discomfort as assessed with a visual analog scale (VAS), change in BLepharitIS Symptom (BLISS) score, change in meibum quality score (MQS), change in eyelid margin vascularity grade (EMVG), change in tear break-up time (TBUT), and change in Schirmer I Test score. Safety was assessed by adverse events (AEs), best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit lamp biomicroscopy, dilated ophthalmoscopy, vital signs, urine pregnancy test (for women of childbearing potential), and laboratory assessments.

Stage 2: Pharmacokinetic analysis of CBT-008
Following at least a 1-month waiting period after completion of Stage 1, patients from a single site enrolled in an optional PK substudy (healthy volunteers could have been used if not enough patients were enrolled). Patients were dosed by site staff to receive 1 drop of CBT-008 2.5% or CBT-008 10% in the study eye only. Blood was collected from these patients at pre-dose and at the following postdose time points: 15 ± 3 min, 30 ± 5 min, 1 hr ± 10 min, 2 hr ± 10 min, 4 hr ± 15 min, and 8 hr ± 30 min.

Number of Subjects:

Stage 1

Planned: Approximately 90 patients

Analyzed: 95 patients

Stage 2

Planned: Sixteen patients

Analyzed: 19 patients

Diagnosis and Main Criteria for Eligibility:

Major Inclusion Criteria

Stage 1 inclusion criteria

- Diagnosed with MGD in both eyes and meet the following:
    a. ODS ≥ 2
    b. VAS score between 35-90% for at least 1 of the 7 categories
    c. Total Cornea staining grade ≥ 3
    d. Total meibum quality score (MQS) between 6-17 from the sum of the 6 lower eyelid central glands in at least one lower eyelid
    e. FTBUT ≤ 5 s
    f. Schirmer I Test (anaesthetized) ≥ 5 mm after 5 minutes in study eye

g. BCVA LogMAR ≥ +0.7 in each eye.

- Subject continues to qualify at visit 2 despite the ability and willingness to apply eyelid hygiene as instructed. Willing to withhold the use of artificial tears and eye lubricants during the treatment phase.
- ≥ 18 years old
- Able to provide written informed consent and comply with study assessments for the full duration of the study.

Stage 2 inclusion criteria

1. Patients who completed the Stage 1 Exit Visit for at least 1 month or healthy volunteers

2. At least 18 years of age at time of consent and able to provide written informed consent

Major Exclusion Criteria

Stage 1 exclusion criteria

- Uncontrolled systemic disease in the opinion of the Investigator
- Active allergy, infection, or ocular surface inflammatory disease unrelated to MGD
- History of ocular herpes disease in either eye
- Ocular surgery history within 6 months
- Patients taking eye lubricants must stop after Day 1 visit
- Use of topical treatment of the eye/eyelid with antibiotics, NSAIDS, or vasoconstrictors to treat MGD or DED within 14 days of screening; steroids, cyclosporin A or lifitegrast within 28 days of screening
- Current or anticipated use of other topical ophthalmic medications. Patients must have discontinued use of ophthalmic medications for at least 2 weeks prior to the screening visit, the use of artificial tears is allowed.
- Anticipated wearing of contact lenses during any portion of the study. Patients, who wear soft contact lenses should discontinue wearing them at least 3 days prior to screening visit. Patients wearing rigid gas permeable or hard contact lenses should discontinue wearing them at least 3 weeks prior to screening visit
- Active rosacea involving the eyelids within 60 days of Screening
- Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to entry into this study
- Any condition or situation which may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study
- Female who are pregnant or nursing or planning a pregnancy during the study

Stage 2 exclusion criteria

1. Females who were pregnant or nursing

2. Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to entry into this study

3. Previously randomized in the CBT-CS102 clinical trial and dosed with CBT-006

Test Product, Dose and Mode of Administration, Batch Number:
Stage 1: CBT-008 ophthalmic solution (2.5% or 10%) was administered as 1 drop OU TID
Stage 2: CBT-008 ophthalmic solution (2.5% or 10%) was administered as 1 drop in the study eye

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.

Duration of Treatment:
Stage 1: 1 month
Stage 2: 1 day (1 dose)

Study Measurements:

Stage 1 efficacy:

• ODS (co-primary endpoint at Week 4)

• Cornea staining grade (co-primary endpoint at Week 4)

• Ocular discomfort using the VAS

• BLISS

• MQS

• EMVG

• TBUT

• Schirmer I Test score

Stage 1 safety:

• BCVA

• IOP

• Slit lamp biomicroscopy

• Dilated ophthalmoscopy

• Vital signs

• Urine pregnancy test

• Urinalysis

• Hematology and blood chemistry

• AEs

Stage 2 pharmacokinetics:

• Peak concentration at Tmax (Cmax), time of peak concentration (Tmax), and, if applicable, area under the curve from time 0 to 8 hours post-dose (AUC0-8hr) and terminal half-life (t1/2)

Statistical Methods:

Stage 1 statistical methods:
Continuous (quantitative) variable summaries included the number of patients (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Categorical (qualitative)

variable summaries included the frequency and percentage of patients who were in the particular category of each possible value.
Unless otherwise indicated, all statistical tests were conducted at the 0.05 significance level using 2-tailed tests, and P values were reported. Corresponding 95% confidence intervals were presented for statistical tests, if applicable.
The analyses and documentation described in this Statistical Analysis Plan (SAP) were for the final analysis of the study. All statistical analyses were programmed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA).
Due to the exploratory nature of this study, the planned sample size was determined empirically. To account for premature discontinuation, 90 patients were planned to be enrolled, with the expectation that at least 75 patients (25 per treatment group) would complete the study. It was anticipated that this sample size would be adequate to identify trends in the data.
Stage 2 statistical methods:
Prior to database lock, a detailed SAP was approved. Descriptive statistics (mean, SD, etc.) were calculated for plasma CBT-008 concentrations for each treatment group. If applicable, plasma PK parameters were calculated. Parameters included Cmax, Tmax, and, if applicable, AUC0-8hr and t1/2.

Duration of Study Follow-Up: None

Stage 1 Schedule of Events

Study Procedures	Visit 1 Screening	Visit 2 Day 1[a]	Visit 3 Week 2	Visit 4 Week 4
Informed Consent/Authorization	X			
Subject ID Assignment	X			
Demographics	X			
Medical / Ocular History	X			
Concomitant Medications/Concurrent Procedures	X	X	X	X
Vital Sign measurements (blood pressure, heart rate, body temperature)	X	X	X	X
Pregnancy test, if applicable	X	X	X	X
Blood chemistry & hematology	X			X
[redacted]				
Ophthalmoscopy (dilated)	X			X
Query for Serious Medical Events/Adverse Events	X	X	X	X
Randomization		X		
Inclusion/Exclusion Criteria	X	X		
Study Medication		Dispense	Dispense+ Collect	Collect
Exit				X

a All measurements at baseline Day 1 are prior to the instillation of first dose.

Stage 2 Schedule of Events

Study Period	**Visit 1 – Screening (Day -7 ± 4)**	**Visit 2 – Day 1 (time after dosing in hour)**							
Time Points	Anytime	Pre-dose	H: 0	H: 0.25	H: 0.5	H: 1.0	H: 2.0	H: 4.0	H: 8.0
Inform Consent Form	X								
Medical History	X	X							
Demographics	X								
Pregnancy Test	X								
Serious Medical Events	X	X							
Dosing			X						
Blood PK Sampling		X		X	X	X	X	X	X
Exit									X