CLOUDBREAK THERAPEUTICS

Protocol-short

A Phase 2a Multicenter, Randomized, Vehicle-Controlled, Dose Escalating Study to Evaluate the Safety, Efficacy and Pharmacokinetics of CBT-001 Ophthalmic Solution in Patients with Primary or Recurrent Pterygium

Protocol Number:	**CBT-CS101**
ClinicalTrials.gov Identifier	**NCT03049852**
Name of Investigational Product:	**CBT-001 Ophthalmic Solution**
Governing IRB/IEC:	**Sterling IRB**
Sponsor:	**Cloudbreak Therapeutics, LLC** **15615 Alton Parkway, Suite 450** **Irvine, CA 92618, USA**
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Date:	**April 12, 2017**

Study Number: CBT-CS101

Name of Sponsor:

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Email: ni_jinsong@cloudbreaktherapeutics.com
Contact Person: Jinsong Ni, Ph.D.

Name of Finished Product: Ophthalmic Solution of CBT-001

Name of Active Ingredient: CBT-001

Title of Study: A Phase 2a multicenter, randomized, vehicle-controlled, dose escalating study to evaluate the safety, efficacy and pharmacokinetics of CBT-001 ophthalmic solution in patients with primary or recurrent pterygium

Study Period:

Study Initiation Date (First Subject Enrolled): May, 2017

Study Completion Date (Last Subject Completed): December, 2017

Phase of Development: Phase 2a Stage 2

Objectives:

To evaluate the safety, tolerability and effect in patients with primary pterygium or pterygium recurrence via unilateral topical ocular dosing of CBT-001 ophthalmic solution for 28 days with 5 months follow-up observation

Methodology:

Strategy:

- Evaluate ocular and systemic safety profile of CBT-001 ophthalmic solution in patients with primary or recurrent pterygium, that are associated with moderate to severe pterygium vascularity;
- Establish whether CBT-001 is efficacious in reducing pterygium vascularity;
- Assess whether CBT-001 is efficacious in inhibiting pterygium lesion growth;

Plan:

A multicenter, double-masked, vehicle-controlled and parallel study is designed with 28 days TID repeat ocular dosing of vehicle and the highest tolerable dose (e.g., 0.2%), followed by 5-month post dose observation. Ophthalmic and physical examinations will be performed at screening, Day 1 and weeks 2, 4, 8, 16, and 24. External photograph of the pterygium eye will be taken using a digital camera and the lesion length, width and area as well as pterygium vascularity will be measured or graded from these images at an independent image reading center.

Number of Subjects: 50 patients with primary or recurrent pterygium.

Diagnosis and Main Criteria for Eligibility:

Major Inclusion Criteria

- Primary pterygium with 0.6-3.5 mm lesion length from the anterior edge of limbus to the central cornea, associated with pterygium vascularity ≥ Grade 3 using the 5-point Pterygium Hyperemia Grading Scale

a. A minimum of Grade 3 (moderate) pterygium vascularity in the study eye at the screening (day -60 to day -7) and baseline (day 1) visits, using the 5-point Pterygium Hyperemia Grading Scale (0 = absent, 1 = trace, 2 = mild, 3 = moderate, 4 = severe);
b. About 0.6-3.5 mm of encroachment of the pterygium onto the cornea of the study eye at the screening (day -60 to day -7) and baseline (day 1) visits as measured by slit lamp examination (investigator assessment). The measurement is as described by Welch et al [Welch et al, 2011]. A standard magnification of 16 is used and the variable aperture is focused on the pterygium from the limbus to the apex. Reading the size on the slit lamp scale, measurements are taken from the limbus to the apex of the lesion on the cornea and recorded to the nearest tenth of a millimeter.
c. T2 (intermediate) or T3 (fleshy) grade in study eye at the screening (day -60 to day -7) and baseline (day 1) visits, using the Pterygium Morphology Grading Scale. Pterygium Morphology Grading Scale is classified as T1 = atrophic, T2 = intermediate, T3 = fleshy based upon the pterygium morphology photographic-based clinical grading system created by Tan and colleagues [Tan et al, 1997].
    i. T1 (Atrophic): Pterygium in which episcleral vessels underlying the body of the pterygium are unobscured and clearly distinguished.
    ii. T2 (Intermediate): Pterygium in which episcleral vessel details are indistinctly seen or partially obscured.
    iii. T3 (Fleshy): Thick pterygium in which episcleral vessels underlying the body of the pterygium are totally obscured. Pterygium vessels are distinguished from episcleral vessels by the straightened radial orientation of the pterygium vessels.

- Pterygium recurrence, defined as the presence of corneal vessels with concomitant conjunctival vascularity of ≥ Grade 3 after excision surgery of primary pterygium.
- All patients of both genders 18 years of age or older

Able to provide written informed consent and comply with study assessments for the full duration of the study.

Major Exclusion Criteria

- Uncontrolled systemic disease
- Active ocular disease, corneal abnormalities other than pterygium, active ocular infection, or any ocular pathology unrelated to pterygium in either eye that could affect the assessment of the pterygium
- History of ocular herpes disease in either eye
- Any retina disease that could affect visual acuity (e.g., age-related macular degeneration)
- Any ocular surgical procedure within the last 3 months
- 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 Day 1 visit. Patients wearing rigid gas permeable or hard contact lenses should discontinue wearing them at least 3 weeks prior to Day 1 visit
- Female patients who are pregnant, nursing, or planning a pregnancy during the study
- Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to entry into this study
- History of myocardial infarction or stroke
- Any condition or situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study
- Known allergy or sensitivity to the study medication(s) or its components

- Double pterygium (i.e., eye with nasal and temporal pterygia)
- Pterygium that would require surgery
- Pingueculae, pseudo-pterygia (e.g., chemical or thermal burn, trauma, marginal corneal disease); neoplasia (e.g., carcinoma in situ, squamous cell carcinoma, other neoplastic diseases)
- Current or anticipated use of topical ophthalmic medications in the study eye. Patients must have discontinued use of ophthalmic medications in the study eye for at least 2 weeks prior to Day 1 visit.
- **Eye:** an eye does not qualify for the study if any of these criteria are present. However, if none of these criteria are present in the other eye, the patient may still qualify for enrollment based on that eye provided the patient/eye meets all the inclusion and none of the exclusion criteria.

Test Product, Dose and Mode of Administration, Batch Number: CBT-001 ophthalmic solution of vehicle or the highest tolerable dose (e.g., 0.2%), unilateral topical ocular dosing

Duration of Treatment: 28 days of continuous unilateral ocular dosing with follow-up period of 1, 3, and 5-month post dose

Study Measurements:

Safety:

- Ocular: visual acuity, intraocular pressure, biomicroscopy, ophthalmoscopy
  Systemic: vital signs, clinical laboratory (Chem-panel), hematology

Adverse event reporting

Efficacy:

Primary Efficacy Endpoint:

Comparison between drug-treated and vehicle-treated groups on changes of the severity grade of pterygium vascularity from baseline (Day 1) at Week 4;

Secondary Efficacy Endpoints:

Comparison between drug-treated and vehicle-treated groups on change from baseline (Day 1) at Weeks 2, 4, 8, 16 and 24 in:

- Corneal lesion length, defined from the anterior edge of the limbus onto the central cornea
- Corneal lesion area;
- Corneal lesion width;

Comparison between drug-treated and vehicle-treated groups on changes of the severity grade of pterygium vascularity from baseline (Day 1) at Weeks 2, 8, 16 and 24;

Changes from baseline (Day 1) at Weeks 2, 4, 8, 16, and 24 in:

- Corneal lesion length
- Corneal lesion area
- Corneal lesion width

Change in severity grade of pterygium vascularity from baseline (Day 1) at Weeks 2, 4, 8, 16, and 24

Comparison between drug-treated and vehicle-treated groups on change from baseline (Day 1) at Weeks 2, 4, 8, 16 and 24 in:

- Topographic astigmatism in diopters

Comparison between drug-treated and vehicle-treated groups on change from baseline (Day 1) at Weeks 2, 4, 8, 16 and 24 in:

Scores of Pterygium Symptom and Life Quality (PSLQ) questionnaire

Statistical Methods: Two database locks are planned for the study, interim and final. The interim analysis will be performed after at least 80% of patients have completed their week 4 visit or discontinued prematurely. The final analysis will be performed after study completion.

The O'Brien-Fleming group-sequential method will be used for a multiple-comparison adjustment of p-values for efficacy due to analyzing the data for both interim and final analyses. For the final analysis, a 2-sided test with p-value ≤ 0.048 will be considered statistically significant for all between and within treatment comparisons.

- In general, continuous data will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum and maximum) and will be analyzed using analysis of variance (ANOVA) techniques or 2-sample t-tests for between-group comparisons, and paired t-tests for within-group analyses. Categorical variables will be summarized by sample size (N), frequency count and percent, and analyzed using Pearson's chi-square test or Fisher's exact test. Ordinal variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) or the Wilcoxon rank-sum test for between-treatment comparisons and the sign-rank test for within-treatment comparisons. No imputation for missing data will be performed.

Duration of Study Follow-Up: 1, 3, and 5 months after the completion of 28 days of continuous ocular dosing.

ATTACHMENT: SCHEDULE OF EVENTS

Study Procedures	Screening Days -60 to -7	Day 1[a]	Week 2 (± 5 days)	Week 4 (± 5 days)	Week 8 (± 7 days)	Week 16 (± 7 days)	Week 24 (± 7 days)
Informed Consent/Authorization	X						
Inclusion/Exclusion Criteria	X	X					
Demographics	X						
Medical / Ocular History	X						
Pregnancy Test	X	X	X				
Serious Medical Events (SME)	X	X					
Subject ID Assignment	X						
Concomitant Medications/Concurrent Procedures	X	X	X	X	X	X	X
Pterygium Symptom and Life Quality (PSLQ) questionnaire	X	X	X	X	X	X	X
Vital Sign measurements (blood pressure, heart rate, body temperature)	X	X	X	X	X	X	X
Hematology & Blood Chemistry	X			X			X
Pterygium Photography[b]		X	X	X	X	X	X
Pterygium Vascularity Assessment	X	X					
Pterygium Morphology Assessment	X	X					
Pterygium Size Assessment	X	X					
Biomicroscopy	X	X	X	X	X	X	X
Topographic Astigmatism	X	X	X	X	X	X	X
Best-Corrected Visual Acuity	X	X	X	X	X	X	X
Intraocular Pressure	X	X	X	X	X	X	X
Ophthalmoscopy (dilated)	X	X		X			X
Adverse Events		X	X	X	X	X	X
Randomization		X					
Study Medication		Dispense	Collect	Collect	Collect		
Exit							X

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

[b] Efficacy endpoints will be assessed using pterygium photography at an independent image reading center