VP-VSJ-110-2101

A SINGLE-CENTER, DOUBLE-MASKED, RANDOMIZED, PLACEBO-CONTROLLED, PHASE 2, EVALUATION OF THE SAFETY AND EFFICACY OF VSJ-110 OPHTHALMIC SOLUTION IN THE TREATMENT OF ALLERGIC CONJUNCTIVITIS USING AN ALLERGEN CHALLENGE MODEL

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Sponsor: Vanda Pharmaceuticals Inc.
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Study Product: VSJ-110 0.034% Ophthalmic Solution

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Study Phase: II

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CONFIDENTIAL

SYNOPSIS

Name of Sponsor/Company: Vanda Pharmaceuticals Inc.	
Name of Investigational Product: VSJ-110 0.034%	
Title of Study: A Single-Center, Double-Masked, Randomized, Placebo-Controlled, Phase 2, Evaluation of the Safety and Efficacy of VSJ-110 Ophthalmic Solution in the Treatment of Allergic Conjunctivitis Using an Allergen Challenge Model	
Study Center(s): Single-center in the United States	
Studied Period: Date first patient enrolled: October 2020 Estimated study duration: 3 months	**Phase of Development:** II
Number of Patients (planned): Approximately 40 patients randomized (20 per arm, 1:1 randomization scheme) who have a positive history of ocular allergies. Discontinued subjects will not be replaced (i.e., their subject numbers will not be reassigned/reused).	
Inclusion Criteria *Each subject must:* 1) be at least 18 years of age at Visit 1 of either gender and any race; 2) provide written informed consent and sign the HIPAA form; 3) be willing and able to follow all instructions and attend all study visits; 4) have a positive history of ocular allergies and a positive skin test reaction to a seasonal (grass, ragweed, and/or tree pollen) or perennial allergen (cat dander, dog dander, dust mites, cockroach) as confirmed by an allergic skin test conducted at Visit 1 or within the last 24 months; 5) be able and willing to avoid all disallowed medications for the appropriate washout period and during the study (see exclusion 6); 6) be able and willing to discontinue wearing contact lenses for at least 72 hours prior to and during the study trial period; 7) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at screening (must be negative), prior to dosing with investigational product, and exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. Women considered capable of becoming pregnant include all females who have experienced menarche and have not	

[1]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.

experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);

8) have a calculated best-corrected visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart;
9) have a positive bilateral post-CAC reaction (defined as having scores of ≥2 ocular itching and ≥2 conjunctival redness) within 10 (±2) minutes of instillation of the last titration of allergen at Visit 2;
10) have a positive bilateral post-CAC reaction (defined as having scores of ≥2 ocular itching and ≥2 conjunctival redness) for at least two out of the first three time points[2] following the challenge at Visit 3.

Exclusion Criteria

Each subject must not:

1) have known contraindications or sensitivities to the use of the investigational product or any of its components;
2) have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters (including but not limited to narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium, history of corneal transplantation or a diagnosis of dry eye);
3) have had ocular surgical intervention within three (3) months prior to Visit 1 or during the study and/or a history of refractive surgery within the past six (6) months;
4) have a known history of retinal detachment, diabetic retinopathy, or active retinal disease;
5) have the presence of an active ocular infection (bacterial, viral or fungal) or positive history of an ocular herpetic infection at any visit;
6) use any of the following disallowed medications during the period indicated **prior to Visit 2** and during the study:

7 Days

- systemic or ocular H_1 antihistamine, H_1 antihistamine/mast cell stabilizers, H_1 antihistamine- vasoconstrictor drug combinations;
- decongestants;
- monoamine oxidase inhibitors;
- all other topical ophthalmic preparations (including artificial tears);
- lid scrubs;
- topical prostaglandins or prostaglandin derivatives;
- ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs);

14 Days

[2] not necessarily at the same time point

- inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers;

45 Days

- depo-corticosteroids;

Note: Currently marketed over-the-counter anti-allergy eye drops (i.e. anti-histamine/ vasoconstrictor combination products such as Visine®-A®) may be administered to subjects by trained study personnel at the end of Visits 2, 3, 4b, 5b and 6, after all evaluations are completed.

7) have any significant illness (e.g. any autoimmune disease requiring therapy, severe cardiovascular disease [including arrhythmias] the investigator feels could be expected to interfere with the subject's health or with the study parameters and/or put the subject at any unnecessary risk (includes but is not limited to: poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, organ transplants, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens;
8) have received allergy immunotherapy within the last 2 years;
9) manifest signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 2, 3 or 4a (defined as the presence of any itching or >1 [greater than 1] redness in any vessel bed);
10) have a history of glaucoma or ocular hypertension;
11) have planned surgery (ocular or systemic) during the trial period or within 30 days after;
12) have used an investigational drug or medical device within 30 days of the study or be concurrently enrolled in another investigational product trial;
13) be a female who is currently pregnant, planning a pregnancy, or lactating;
14) have symptoms that, in the opinion of the investigator, may be associated with COVID-19 or in the last 14 days came into contact with someone diagnosed with COVID-19.

Investigational Product, Dosage, and Mode of Administration:

Topical ocular VSJ-110 0.034% will be administered bilaterally into the eye.

Duration of Treatment (Randomization Phase):
This study consists of seven (7) office visits over a period of up to eleven (11) weeks.

Reference Therapy, Dosage, and Mode of Administration:

Topical ocular Vehicle of VSJ-110 will be administered bilaterally into the eye.

Objectives:

Primary Objective:

- To evaluate the efficacy of VSJ-110 0.034% compared to vehicle for the treatment of the signs and symptoms of allergic conjunctivitis.

Pharmacogenomic Sub-Study:

- To identify genetic markers associated with allergic conjunctivitis and/or response to VSJ-110

Overall Design:

Duration: This study consists of seven (7) office visits over a period of up to eleven (11) weeks.

Screening Period: At Visit 1, subjects will sign the informed consent and an allergic skin test will be performed, if required. At Visit 2, each qualifying subject will undergo a bilateral conjunctival allergen challenge (Ora-CAC®) titration using an allergen they had a positive reaction to on their skin test. Subjects who elicit a positive reaction post-CAC will undergo the confirmation CAC at Visit 3 using the same allergen they qualified with at Visit 2.

Treatment Period: Treatment will begin at Visit 4a after subjects are randomized. At this visit, subjects will receive an in-office dose of the treatment they were randomized to receive. Approximately 16 hours post-instillation of study medication, subjects will undergo CAC at Visit 4b. At Visit 5a, subjects will receive an in-office dose of the same study medication. Approximately 8 hours post-instillation of study medication, subjects will undergo CAC at Visit 5b. At Visit 6, subjects will receive an in-office dose of the same study medication approximately 15 minutes prior to CAC. Subjects will receive a final in-office dose of the same study medication at Visit 7 prior to Schirmer's Test and Optical Coherence Tomography (OCT).

Criteria for Evaluation:

Efficacy Measures:

Primary:

- Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC (0-4 scale, allowing half unit increments) at Visits 4b, 5b, and 6.
- Conjunctival redness evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0 to 4 scale) at Visits 4b, 5b, and 6.

Secondary:

The following assessments will occur at 7(±1), 15(±1), and 20(±1) minutes post-CAC (all use a 0 to 4 scale, except eyelid swelling, 0 to 3) at Visits 4b, 5b, and 6:

- Ciliary redness evaluated by the investigator
- Episcleral redness evaluated by the investigator
- Chemosis evaluated by the investigator
- Eyelid swelling evaluated by the subject
- Tearing evaluated by the subject
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject

Exploratory:

- Digital Photographs may be taken of all subjects within 10 minutes of the last post-CAC assessment at Visits 3, 4b, 5b, 6.
- Tear meniscus quantitation & replenishment dynamics: Schirmer's Test and OCT at Visit 7.
- Buccal cell samples will be collected at Visit 1 for pharmacogenetic assessments.
- Pharmacokinetic Measures at pre-dose and 5 minutes(±2), 15 minutes(±2), and 30 minutes(±2) post dose at Visit 4a.

Safety Measures:

- Adverse Events assessed at all office visits
- Visual Acuity at Distance Utilizing an ETDRS chart conducted at Visit 2, 3, 4a, 4b, 5a, 5b, 6, and 7.
- Slit lamp Biomicroscopy conducted at Visit 2, 3, 4a, 4b, 5a, 5b, 6, and 7.
- Intraocular Pressure measured at Visit 1 and Visit 7
- Dilated Fundoscopy measured at Visit 1 and Visit 7

Tolerability Measures:

- Drop comfort assessment (assessed by subjects upon instillation, at 1, and 2 minutes post-instillation) at Visit 4a.Drop descriptor query (assessed at 3 minutes post-instillation) at Visit 4a.

General Statistical Methods and Types of Analyses

For all the analyses, treatment group differences will be tested at a 2-sided significance level of 0.05. The primary statistical analysis will be based on ANOVA model. Categorical variables such as response will be evaluated using Cochran-Mantel-Haenszel (CMH) method or Fisher's exact test. The details of analysis methods will be specified in the SAP.

Summary of Known and Potential Risks and Benefits to Human Subjects

Refer to Investigator's Brochure (IB)

20. STATISTICS

20.1. Number of Subjects (approximate)

Approximately 80 subjects will be screened in order to enroll approximately 40 subjects at one (1) site. Discontinued subjects will not be replaced (i.e., their subject numbers will not be reassigned/reused).

The sample size chosen for this study is not based solely on statistical considerations, but was chosen after taking into consideration existing data for approved treatments for AC and the preclinical profile of the drug candidate VSJ-110.

20.2. Study Population Characteristics

Subjects at least 18 years of age, of either gender or any race, who have a positive history of allergic conjunctivitis, and who meet all of the inclusion criteria and none of the exclusion criteria.

20.3. Statistical Methods and Analysis Plan

This section describes the planned statistical analyses in general terms. A complete description of the methodology will be specified in a statistical analysis plan (SAP). Any changes in the statistical methods described in this protocol that occur prior to database lock will be documented in the SAP and will not require a protocol amendment.

20.4. Statistical Hypotheses and Methods of Analysis

Prior to Database lock a Statistical Analysis Plan will be finalized detailing the Efficacy, Safety, and Tolerability analyses that will be performed.

20.4.1. Patient Populations for Analysis

The following analysis populations will be defined for this study:

Intent-to-Treat: will include any subject randomized into the study that receives a dose of study drug and that has completed at least one post-baseline efficacy measurement while on study medication;

Safety: Any subject randomized into the study that receives a dose of study drug;

Per-Protocol: Any subject who is randomized and receives the protocol required study drug exposure and required protocol processing.

Efficacy analyses will be performed on the Intent-to-Treat population and the Per-Protocol population. Safety summaries will be based on Safety set. Subject characteristics will be presented for all subjects randomized.

20.4.2. Patient Disposition

20.4.2.1. Completed Subjects

A completed subject is one who has not been discontinued from the study.

20.4.2.2. Discontinued Subjects

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

- AEs
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- manifest clinically active signs of symptoms of allergic conjunctivitis during the ocular and nasal allergic signs and symptoms assessment at Visits 4a, 5a, or 6.
- sponsor termination of study
- COVID-19
- other

Note: In addition, any subject may be discontinued for any sound medical reason.

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora and/or study sponsor and will be clearly documented on the eCRF. Subjects who are discontinued from the study will not be replaced.

20.4.3. Demography and Other Baseline Data

Demographic data and subject characteristics at screening/baseline will be listed and summarized by treatment group for all randomized subjects using descriptive statistics.

Past and current medical history will be summarized by treatment group using the system organ class (SOC) as coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Past medical conditions will be defined as an onset date prior to randomization and resolved (not on-going). Current medical conditions, defined as an onset date on or after the date of randomization or an onset date prior to randomization and unresolved (on-going), will be reported separately, but similarly to the past medical conditions. If both a past and a current (on-going) medical condition record are indicated for a condition, the condition will be presented under current medical conditions only.

20.5. Efficacy Data Analysis

20.5.1. Primary Efficacy Variables

The primary efficacy variable is:

- Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 4b (16 hour duration of action), 5b (8 hour duration of action), and 6 (15 minute onset of action).
- Conjunctival redness evaluated by the investigator at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0 to 4 scale with whole number responses) at Visits 4b (16 hour duration of action), 5b (8 hour duration of action), and 6 (15 minute onset of action).

20.5.2. Secondary Efficacy Variables

Secondary efficacy variables include assessments made on Visits 4b, 5b, and 6, at 7(±1), 15(±1), and 20(±1) minutes post-CAC. All measures use a 0 to 4 scale with whole number responses, except eyelid swelling (0 to 3 scale):

- Ciliary redness evaluated by the investigator
- Episcleral redness evaluated by the investigator
- Chemosis evaluated by the investigator
- Eyelid swelling evaluated by the subject
- Tearing/watery eyes evaluated by the subject
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject

20.6. Subgroup Analysis

The subgroup analysis (such as, gender, age, baseline illness severity etc.) for efficacy variables and safety variables may be conducted as described in the SAP.

20.7. Interim Analysis

No interim analyses are planned.

20.8. Deviations in Analysis from Statistical Plan and Other Issues

During the analysis and reporting process, any deviations from the statistical plan designed for this protocol will be described and justified in the final report.