2 SYNOPSIS

Sponsor: FAES FARMA

Name of Finished Product: Bilastine Ophthalmic Solution (0.2%, 0.4%, and 0.6%)

Name of Active Ingredient: Bilastine

Protocol Title: A Single-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2, Dose Ranging Evaluation of the Effectiveness of Bilastine Ophthalmic Solution (0.2%, 0.4%, and 0.6%) Compared to Vehicle for the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge (Ora-CAC®) Model

Protocol Number:17-100-0002

Investigator: Single-Center

Study Phase of Development: Phase 2

Objectives:
To evaluate the efficacy of Bilastine ophthalmic solution (0.2%, 0.4%, and 0.6%) compared to vehicle for the treatment of the signs and symptoms of allergic conjunctivitis.

Structure:
Single-center, double-masked, randomized, vehicle-controlled, Phase 2, dose ranging CAC study.

Duration: This study consists of eight (8) office visits over a period of approximately six to ten (6-10) 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 (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. Subjects will receive a final dose of study medication at Visit 6 approximately 15 minutes prior to CAC.

Follow-Up Period: A documented telephone call will be made by the investigator (or investigator's designee) on Day 29 (±3) to all subjects approximately one week after their last visit to query if there have been any changes in their medical history or medications or if they have had any emergency room visits or hospitalizations since their last study visit. Documentation will be made to record this telephone call follow-up.

Summary of Visit Schedule:

Visit 1 (Day -50 to Day -22):	Screening/ Informed Consent/ Skin Test
Visit 2 (Day -21 ± 3):	Titration CAC
Visit 3 (Day -14 ± 3):	Confirmation CAC
Visit 4a (Day 1):	Enrollment/Randomization/ In-Office Instillation
Visit 4b (Day 1; 16 hours from Visit 4a):	16 Hour Duration of Action CAC

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Visit 5a (Day 15 ± 3):	In-Office Instillation
Visit 5b (Day 15 ± 3; 8 hours from Visit 5a):	8 Hour Duration of Action CAC
Visit 6 (Day 22 ± 3):	In-Office Instillation/ 15-Minute Onset of Action CAC
Day 29 (± 3):	Follow-Up Telephone Call

Measures Taken to Reduce Bias:
Randomization will be used to avoid bias in the assignment of subjects to investigational product, to increase the likelihood that known and unknown subject attributes (e.g. demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Finally, masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

Study Population Characteristics

Number of Subjects:
Up to 240 subjects will be screened in order to enroll approximately 120 subjects at one (1) site. Discontinued subjects will not be replaced (i.e., their subject numbers will not be reassigned/reused).

Diagnosis
Allergic Conjunctivitis

Inclusion Criteria
Each subject must:

1) be at least 18 years of age at Visit 1 of either gender and any race (a government issued ID will be verified at the time ICF is signed);
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 2 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) and exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration and for at least 14 days prior to the instillation of investigational product (Visit 4a). Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined

[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.

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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 visual acuity of [redacted] or better in each eye as measured using an ETDRS chart;
9) have a positive bilateral post-CAC reaction [redacted] within 10 (±2) minutes of instillation of the last titration of allergen at Visit 2;
10) have a positive bilateral post-CAC reaction [redacted] for at least two out of the first three time points[1] 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 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

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

45 Days

[1] not necessarily at the same time point

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- 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 [redacted]

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.

Test Product, Dose and Mode of Administration, Batch Number:

- Bilastine Ophthalmic Solution (0.2%)
- Bilastine Ophthalmic Solution (0.4%)
- Bilastine Ophthalmic Solution (0.6%)

Reference Therapy, Dose and Mode of Administration, Batch Number:

- Vehicle of Bilastine Ophthalmic Solution

Criteria for Evaluation:

Efficacy Measures:

Primary:

- Ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC [redacted] at Visits 4b, 5b, and 6.

Secondary:

The following assessments will occur at 7(±1), 15(±1), and 20(±1) minutes post-CAC [redacted] at Visits 4b, 5b, and 6:

- Conjunctival redness evaluated by the investigator

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- 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

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, and 6.
- Slit lamp Biomicroscopy conducted at Visit 2, 3, 4a, 4b, 5a, 5b, and 6.
- Intraocular Pressure measured at Visit 2 and Visit 6
- Dilated Fundoscopy measured at Visit 2 and Visit 6.

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

Multiplicity Adjustments:

The comparisons of the three active treatment arms to vehicle will each be tested against vehicle independently. [redacted]

[redacted]

[redacted]

Sample Size:

Approximately 120 subjects will be randomized at Visit 4a, or approximately [redacted] per treatment arm. It is expected that approximately [redacted] per treatment arm for the primary analysis at Visit 6.

[redacted]

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[redacted]

Primary Analyses:

[redacted]

Secondary Analyses:

[redacted]

Safety Analyses:

The incidence of subjects with any treatment-emergent adverse events (TEAEs) occurred during the study will be the key safety variable. The percentage of subjects with any TEAE will be summarized for each

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treatment group for ocular and non-ocular TEAEs separately. Incidence will be tabulated by MedDRA (latest available version) system organ class and preferred term within each system organ class. Treatment-emergent adverse events (TEAEs) will also be summarized for related TEAEs (r-TEAEs) and SAEs (related/unrelated), by maximal intensity, and by day of onset relative to the start of treatment.

Other safety variables, including slit lamp biomicroscopy, dilated fundus examination, visual acuity, and IOP, will be summarized descriptively using quantitative and qualitative summary statistics as appropriate. Changes and shifts from baseline will also be summarized where applicable.

Summary of Known and Potential Risks and Benefits to Human Subjects

Refer to Investigator's Brochure (IB)