SYNOPSIS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Vehicle- and Active-Controlled, Phase 3 Study Evaluating the Efficacy and Safety of Bilastine Ophthalmic Solution 0.6% Compared to Vehicle and Zaditen (Ketotifen Ophthalmic Solution 0.025%) for the Treatment of Allergic Conjunctivitis in the Conjunctival Allergen Challenge (Ora-CAC®) Model
Protocol Number:	17-100-0012/BOFT-0218/AC-CAC
Investigational Product:	Bilastine Ophthalmic Solution 0.6%
Study Phase:	Phase 3
Primary Objective:	To evaluate the efficacy of Bilastine ophthalmic solution 0.6% compared to vehicle and Zaditen (Ketotifen ophthalmic solution 0.025%) for the treatment of the signs and symptoms of allergic conjunctivitis.
Secondary Objectives:	To evaluate the safety and tolerability of Bilastine ophthalmic solution 0.6% compared to vehicle and Zaditen (Ketotifen ophthalmic solution 0.025%)
Overall Study Design:	
Structure:	*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. Subjects will receive a final dose of study medication at Visit 5

	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 15 (±3) to all randomized 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.
Duration:	This study consists of six (6) office visits over a period of approximately five to nine (5-9) weeks.
Controls:	• Vehicle of Bilastine Ophthalmic Solution • Zaditen (Ketotifen ophthalmic solution 0.025%)
Dosage/Instillation:	At Visit 4a, a trained study technician will instill one (1) drop of assigned investigational product into each eye approximately 16 hours (+1 hour) prior to the Visit 4b CAC using the designated bottle . At Visit 5, a trained study technician will instill one (1) drop of assigned investigational product into each eye approximately 15 minutes (+1 minute) prior to the Visit 5 CAC using the designated bottle l. The pre-specified technicians responsible for instilling the investigational product will not be involved with any other clinical study procedures at the site.
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 (16 hours from Visit 4a):** 16 Hour

	Duration of Action CAC **Visit 5 (Day 8 ± 3):** In-Office Instillation / 15-Minute Onset of Action CAC **Day 15 (± 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:	Approximately 225 subjects will be enrolled at up to seven (7) sites.
Condition/Disease:	Allergic Conjunctivitis
Inclusion Criteria:	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 Visit 2 and during the study trial period; 7) (for females capable of becoming pregnant) agree to have urine pregnancy testing performed at screening on Visit 2 and Visit 4a (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. Women considered capable of becoming pregnant include all females who have experienced menarche and have not 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 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:	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;

[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.
[2] not necessarily at the same time point

	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: **<u>7 Days</u>** • 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); **Baby aspirin (81 mg) is allowed as long as a stable dose has been maintained for at least 30 days prior to Visit 1 and will continue to be maintained for the duration of the study.* **<u>14 Days</u>** • inhaled, ocular, topical, or systemic corticosteroids or mast cell stabilizers; **<u>45 Days</u>** • 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, and 5, 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.
Study Formulations and Formulation Numbers:	• Bilastine Ophthalmic Solution 0.6% • Zaditen (Ketotifen ophthalmic solution 0.025%) • Vehicle of Bilastine Ophthalmic Solution
Evaluation Criteria:	
Efficacy Measures and Endpoints:	**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 and 5. **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 and 5: • Conjunctival redness evaluated by the investigator • 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 and 5. • Slit lamp Biomicroscopy conducted at Visit 2, 3, 4a, 4b and 5. • Intraocular Pressure measured at Visit 2 and Visit 5 • Dilated Fundoscopy measured at Visit 2 and Visit 5.
Other:	**<u>Tolerability Measures:</u>** • 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 **Primary Hypothesis:** Statistical hypotheses for the ocular itching endpoint are as follows and will be tested in hierarchical order: H_{10}: There is no difference in ocular itching scores between Bilastine Ophthalmic Solution and vehicle treated subjects for at least 1 of the 3 time points during each	

respective visit (Visits 4b and 5).

H_{1a}: There is a difference in ocular itching scores between Bilastine Ophthalmic Solution and vehicle treated subjects for all 3 time points during both respective visits (Visits 4b and 5).

H_{20}: Bilastine Ophthalmic Solution is inferior to Ketotifen Ophthalmic Solution in terms of ocular itching scores for at least 1 of the 3 time points at Visit 5.

H_{2a}: Bilastine Ophthalmic Solution is non-inferior to Ketotifen Ophthalmic Solution in terms of ocular itching scores for all 3 time points at Visit 5

H_{30}: There is no difference in ocular itching scores between Ketotifen Ophthalmic Solution and vehicle treated subjects for at least 1 of the 3 time points at Visit 5.

H_{3a}: There is a difference in ocular itching scores between Ketotifen Ophthalmic Solution and vehicle treated subjects for all 3 time points at Visit 5.

Primary Analyses:

The primary efficacy variable is measured at Visit 4b (16 hours post treatment) and Visit 5 (15 minutes post treatment). The primary efficacy analyses will be conducted on the intent-to-treat (ITT) population with multiple imputation using Markov Chain Monte Carlo (MCMC) for missing data.

Analysis of covariance (ANCOVA) models will be used to estimate least square (LS) means, the corresponding 95% confidence intervals (CI), and the estimated treatment differences for each treatment group. Statistical models will be run at each post-CAC time point at Visits 4b and 5 with the average of the subjects' post-CAC scores at Visit 3 included as a covariate. LS means will be used to make treatment comparisons.

Two-sample t-tests will be used as unadjusted sensitivity analyses at each post-CAC time point, as well as non-parametric Wilcoxon rank sum tests. Sensitivity or supportive analyses will be performed on the ITT population using LOCF to impute missing data, a control-based pattern mixture model to impute missing data, and with observed data only, as well as on the per-protocol population with observed data only.

For the LOCF imputation, only post-challenge observations within the same visit will be carried forward. If a subject does not have a post-challenge assessment at a given visit, the subjects will not be included in the analysis for that visit.

Secondary Analyses:

Conjunctival redness will be analyzed in a manner similar to the primary efficacy analysis, following the same populations and missing data methods. Conjunctival redness will also be analyzed using a non-inferiority test comparing Bilastine and Ketotifen treated subjects in a manner similar to the primary endpoint.

Treatment comparisons between Ketotifen and vehicle treated subjects will also be conducted for conjunctival redness in a manner similar to the primary efficacy analyses.

Other secondary endpoints, including episcleral, and ciliary redness; chemosis; eyelid swelling; tearing/watery eyes; rhinorrhea; nasal pruritus; ear or palate pruritus; and nasal congestion will be analyzed as quantitative or qualitative measures as appropriate. For quantitative measures, ANCOVA models will be used to estimate LS means, the corresponding 95% CIs and the estimated treatment differences for each treatment group (similar to the ANCOVA model used for the primary analysis). LS means will be used to make treatment comparisons. Qualitative measures will be analyzed using a Fisher's exact test or Chi-Square test as appropriate. These analyses will be conducted for the ITT population with observed data only and for the PP population with observed data only.

Sample Size:

Approximately 225 subjects will be randomized at Visit 4a in a 2:2:1 ratio across the three treatment arms (90 Bilastine; 90 Ketotifen; 45 Vehicle). It is expected that approximately 5% of subjects will discontinue from the trial prior to completing Visit 5.

Power to Test H_{01}

90 subjects in the Bilastine treatment arm and 45 subjects in the vehicle treatment arm will provide >99.9% power to demonstrate a statistically significant difference in ocular itching between Bilastine Ophthalmic Solution and vehicle treated subjects at each primary post-CAC time point (3[±1], 5[±1], and 7[±1] minutes) at Visit 4b and 5, assuming a treatment difference of 1.25 units, a standard deviation of 0.90 units, and a two-sided Type I error of 0.05. Additionally, this sample size will have at least 99.4% power to demonstrate a statistically significant difference at all primary post-CAC time points at Visit 4b and 5 for ocular itching between Bilastine Ophthalmic Solution and vehicle treated subjects, assuming independence among time points.

Additionally, 90 subjects in the Bilastine treatment group and 45 subjects in the vehicle treatment group yields 97.65% probability of showing a point estimate difference for itching between Bilastine Ophthalmic Solution and vehicle treated subjects of at least 1.0 unit for a majority of the post-CAC time points and 0.5 units for all of the post-CAC time points at Visit 4b and 5 assuming a common standard deviation (SD) of 0.90 units, a treatment difference of 1.25 units, and independence between time points.

Power to Test H_{02}

90 subjects in the Bilastine treatment group and 90 subjects in the Ketotifen treatment group produces 96% power to reject the null hypotheses corresponding to the non-inferiority test for ocular itching (H_{20}) for a single time point. This calculation assumes a non-inferiority margin of Δ=0.40, a one-sided significance level of 0.025, an actual treatment difference of 0.10 in favor of Bilastine, and a standard deviation of 0.90 units. Additionally, the same sample size and assumptions produce 88.5% power to show the

Bilastine Ophthalmic Solution is non-inferior to Ketotifen Ophthalmic Solution in terms of ocular itching scores for all 3 time points at Visit 5.

Power to Test H_{03}

90 subjects in the Ketotifen treatment group and 45 subjects in the vehicle treatment group produces >99.9% power to reject H_{30} (no difference in ocular itching between Ketotifen and vehicle treated subjects) for a single time point. This calculation assumes a two-sided significance level of 0.05, a treatment difference of 1.1 units and a standard deviation of 0.90 units. Additionally, this sample size will have 99.4% power to demonstrate a statistically significant difference at all primary post-CAC time points at Visit 5 for ocular itching between Ketotifen and vehicle treated subjects, assuming independence among time points. The same sample size and assumptions produce 81.88% probability of showing a point estimate difference for itching between Ketotifen Ophthalmic Solution and vehicle treated subjects of at least 1.0 unit for a majority of the post-CAC time points and 0.5 units for all of the post-CAC time points at Visit 5.

Multiplicity Adjustments:

A hierarchical testing procedure will be used to maintain an overall Type I error rate of 0.05 for testing the primary hypotheses for ocular itching.

Safety Analyses:

The incidence of subjects with any treatment-emergent adverse events (TEAEs) during the study will be the key safety variable. The percentage of subjects with any TEAE will be summarized for each treatment group for ocular and non-ocular TEAEs separately. Incidence will be tabulated by MedDRA system organ class and preferred term within each system organ class. TEAEs will also be summarized for related treatment-emergent adverse events (rTEAEs) and SAEs, and by maximal intensity. All n-TEAEs and TEAEs (hereinafter referred as AEs) will be coded using latest available MedDRA version.

All AEs will be listed by subject. TEAEs listing will include the TEAE, treatment group, onset and stop date, intensity, relationship to study medication, and seriousness. Separate listings will be prepared, if applicable, for subjects who experience a SAE and for subjects who discontinue because of an TEAE.

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

Bilastine was demonstrated to be safe and efficacious in treating ocular itching associated with allergic conjunctivitis in the Phase 2 topical ocular clinical study. In this study, 19 TEAEs were reported by 18 of the 121 subjects. Seven of these AEs were

reported in the vehicle group. Eight of the 19 TEAEs were ocular TEAEs, and 11 were non-ocular TEAEs. Most (13) subjects who reported TEAEs identified them as mild in severity, while 5 subjects reported TEAEs of moderate severity. The Bilastine 0.6% group had one non-ocular TEAE (hypoasethesia) that was mild in severity and considered not related to treatment; the investigator decided to withdraw treatment for this subject. One subject in the Bilastine 0.4% group had a TEAE (mild headache) that was considered to be related (definite/certain) to treatment. Visual acuity reduced was reported by two subjects in the Bilastine 0.2% group and were not reported in any of the other treatment groups; these TEAEs were mild in severity and were considered not related to treatment.

The most frequently reported ocular TEAE in the Phase 2 study was visual acuity reduced. Other ocular TEAEs reported (one TEAE each) included blepharitis, macular fibrosis, hordeolum, and keratitis in the bilastine groups, and corneal deposits and eye discharge in the vehicle group. The most frequently reported non-ocular TEAE was viral upper respiratory tract infection. Other non-ocular TEAEs reported (one each) included pyrexia, nephrolithiasis, headache, and hypoasethesia in the bilastine groups and gastroenteritis viral and arthralgia in the vehicle group. Subjects assessed tolerability (drop comfort) as comfortable in all treatment groups. Bilastine 0.6% showed strong efficacy for onset of action at 15 minutes and at 16 hours, indicating that it could be used for once daily treatment of allergic conjunctivitis.

Several bilastine clinical studies via oral administration have shown efficacy and safety for the treatment of nasal as well as non-nasal (i.e., ocular) symptoms of rhinoconjuncitivitis. The incidence of somnolence and fatigue as adverse events in 10 Phase II and III studies in patients treated with oral bilastine was comparable to placebo and significantly lower than in patients receiving active comparators, including cetirizine. Preclinical studies in several species with oral bilastine and subsequent toxicokinetic (TK) modeling for ocular administration demonstrated that bilastine showed systemic toxicity only at concentrations significantly higher than the proposed topical ocular dosing. Bilastine 20 mg tablets are authorized in the European Economic Area (29 countries) and in over 86 other countries worldwide for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and adolescents older than 12 years. Post-marketing experience in the EEA and other countries has included cumulative human exposure of approximately 71,769,892 therapeutic cycles or 4,129,226 patient-years to oral bilastine 20 mg tablets, with no new safety findings. The most frequently reported treatment-related TEAEs across 10 Phase II and Phase III bilastine oral administration clinical studies were headache, somnolence, fatigue, dizziness, and upper abdominal pain, with similar percentages of patients reporting related TEAEs in the bilastine and placebo groups. Other possible, uncommon adverse reactions include abnormal ECG and liver changes indicated by blood tests. The safety profile of oral bilastine in adolescent patients, in children from 2 to 11 years, and in elderly patients has been similar to that in adults.

Zaditen has been associated with the following side effects:

After drug instillation, transient blurred vision or somnolence may occur, which can affect driving or the capacity to operate machines.

Immune system disorders
Uncommon: Hypersensitivity

Nervous system disorders
Uncommon: Headache

Eye disorders
Common: Eye irritation, eye pain, punctate keratitis, punctate corneal epithelial erosion.
Uncommon: Vision blurred (during instillation), dry eye, eyelid disorder, conjunctivitis, photophobia, conjunctival haemorrhage.

Gastrointestinal disorders
Uncommon: Dry mouth

Skin and subcutaneous tissue disorders
Uncommon: Rash, eczema, urticaria

General disorders and administration site conditions
Uncommon: Somnolence

Adverse drug reactions from post-marketing experience (Frequency not known):
Hypersensitivity reactions including local allergic reaction (mostly contact dermatitis, eye swelling, eyelid pruritis and oedema), systemic allergic reactions including facial swelling/oedema (in some cases associated with contact dermatitis) and exacerbation of pre-existing allergic conditions such as asthma and eczema.

The use of oral dosage forms of ketotifen may potentiate the effect of CNS depressants, antihistamines and alcohol. Although this has not been observed with Zaditen eye drops, the possibility of such effects cannot be excluded.