

SYNOPSIS

Protocol Title:	A Proof-of-Concept, Multi-center, Randomized, Double-Masked Study to Evaluate the Clinical Efficacy and Safety of FST-100 (0.1% Dexamethasone and 0.6% PVP-Iodine) Ophthalmic Suspension in the Treatment of Acute Adenoviral Conjunctivitis.
Protocol Number:	FST100-AVC-004
Study Drug:	<ol style="list-style-type: none">1. FST-100 (0.1% dexamethasone and 0.6% PVP-Iodine) Ophthalmic suspension (Foresight Biotherapeutics, Inc. New York, NY)2. 0.6% PVP-Iodine Ophthalmic Solution Alone3. FST-100 Vehicle
Study Phase:	Proof-of-Concept Study
Primary Objective(s):	To evaluate the clinical efficacy and safety of FST-100 in the treatment of acute adenoviral conjunctivitis.
Secondary Objective(s):	Not Applicable
Overall Study Design:	
Structure:	Multi-center, double masked, vehicle-controlled, safety, and efficacy study
Duration:	Up to 13 days
Controls:	Placebo: FST-100 Vehicle
Dosage/Dose Regimen:	<p>Subjects will be randomized evenly into one of the following three study arms:</p> <ol style="list-style-type: none">1. FST-100 (0.1% dexamethasone and 0.6% PVP-Iodine) Ophthalmic suspension (Foresight Biotherapeutics, Inc. New York, NY)2. 0.6% PVP-Iodine Ophthalmic Solution Alone3. FST-100 Vehicle <p>One to two drops of the study medication will be instilled in the affected eye (s) QID on days 1-5.</p>

Summary of Visit Schedule: The study consists of four visits over 12-13 days. Visit 1 will occur on Day 1, Visit 2 will occur on Day 3+1 day window, Visit 3 will occur on Day 6 +1 day window and Visit 4 will occur on Day 12+1.

Measures Taken to Reduce Bias: Subjects will be randomly assigned 1:1:1 to receive one of the three study treatments. The subjects and the study staff will not know which treatment the subjects are assigned to receive.

Study Population Characteristics:

Number of Subjects: Approximately 176 subjects will be enrolled to complete approximately 160 evaluable subjects (~53 per treatment arm).

Condition/Disease: Acute adenoviral conjunctivitis

Inclusion Criteria: Subjects MUST:

1. Be at least 18 years of age at Visit 1 (Day 1, Baseline) of either sex or any race.
2. Be willing and able to provide consent, either written or if the subject is not able to read, provide consent as stipulated by local laws and local Ethics Committee guidelines (i.e finger print and witness signature)
3. Be willing and able to follow all instructions and attend all study visits.
4. Be willing to avoid disallowed medications and treatments (see exclusions 9, 10, 11, and 12) for the duration of the study.
5. Be willing to discontinue contact lens wear for the duration of the study.
6. Agree to submit to a pregnancy test at Visit 1 prior to enrollment and at Visit 4, or not be of childbearing potential.
7. Agree to use an acceptable method of contraception for the duration of the study or not be of childbearing potential. Acceptable methods of birth control include: spermicide with barrier, oral, transdermal, injectable, or implantable contraception, IUD, abstinence, and surgical sterilization of partner. Female subjects are not of childbearing potential if they have had a hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or are post-menopausal by at least 12 months.
8. Have a Best Corrected Visual Acuity (BCVA) of 0.60

logMAR or better in each eye as measured using an EDTRS chart.

9. Have a positive RPS Adeno Detector test at Visit 1.
10. Report presence of signs of adenoviral conjunctivitis for less than or equal to five (5) days prior to Visit 1.
11. Have a clinical diagnosis of suspected acute adenoviral conjunctivitis in at least one eye and the presence of the following minimal clinical signs:
 - Conjunctival hyperemia (a minimum grade of '1' on 0-3 scale)
 - Watery conjunctival discharge (a minimum grade of '1' on a 0-3 scale)

Note: Selection of study eye will be based on whichever eye has the greater cumulative score for hyperemia and discharge at the baseline visit.

Exclusion Criteria:

Subjects MAY NOT:

1. Have known sensitivity or poor tolerance to corticosteroids, to PVP-Iodine, or to any other component of the study medications.
2. Have a history of ocular surgical intervention within six (6) weeks prior to Visit 1 or during the study.
3. Have presence of any active ocular inflammation (e.g., uveitis or iritis), other than acute adenoviral conjunctivitis.
4. Have clinical signs or presence of an ocular infection other than acute adenoviral conjunctivitis (e.g. bacterial, fungal or other ocular viral infection, such as herpes).
5. Be a known intraocular pressure steroid responder, have a known history of glaucoma or have a known history of an elevated intraocular pressure greater than 21 mmHg.
6. Have any clinically significant optic nerve defects visible upon non-dilated fundus examination.
7. Have a history of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome.
8. Have active ulcerative keratitis.
9. Be unable to discontinue contact lens wear for the duration of the study.
10. Have used any topical ocular or systemic anti-virals within 7 days of enrollment.
11. Have used any topical ocular, aerosolized/nebulized, or systemic corticosteroid agents within 14 days of enrollment. Stable (greater than 1 month prior to enrollment) use of inhaled (using mouthpiece) and nasal corticosteroids and topical dermal steroids (except

around the eyes) are allowed. Dose must continue unchanged for the duration of the study.

12. Have used any topical ophthalmic solutions, including tear substitutes and diagnostics, within 2 hours of Visit 1 and be unable to discontinue of all topical ophthalmic solutions (including diagnostics) for the duration of the study.
13. Be currently pregnant, nursing, or planning a pregnancy; or be a woman that has a positive pregnancy test.
14. Have any uncontrolled systemic disease or debilitating disease (e.g., cardiovascular disease, hypertension, diabetes, or cystic fibrosis).
15. Have any autoimmune disease.
16. Have prior (within 30 days of beginning study treatment) or anticipated concurrent use of an investigational drug or device.
17. Have a condition or a situation which, in the Investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation.

Study Formulations and Formulation Numbers:

See **Appendix 3**

Evaluation Criteria:

Efficacy Measures:

- The primary efficacy variable is a composite endpoint of adenoviral eradication, as assessed by CC-IFA, and clinical resolution of acute adenoviral conjunctivitis in the study eye at Visit 3. Clinical resolution is defined as the absence (score=0) of the following two clinical signs: watery conjunctival discharge and bulbar conjunctival injection.
- The secondary efficacy variable is decrease in viral load as determined by polymerase chain reaction (PCR) at Visit 3.

Safety Measures:

- Slit Lamp Biomicroscopy
- Best Corrected Visual Acuity
- Urine Pregnancy Testing
- Adverse Events

Other:

No other assessments will be measured

General Statistical Methods and Types of Analyses

Primary Efficacy Analysis

The primary efficacy variable is the composite endpoint adenoviral eradication and clinical resolution of acute adenoviral conjunctivitis in the study eye at Visit 3.

The primary population for the efficacy analysis will be based on the intent to treat (ITT) sample, comprising all subjects who entered the study and received at least one dose of the study medication. Adenoviral eradication is assessed by CC-IFA. Clinical resolution is defined as the absence (score = 0) of the following two clinical signs: watery conjunctival discharge and bulbar conjunctival injection. The primary objective of this study is to determine if FST-100 effectively treats acute adenoviral conjunctivitis. The null hypothesis is that subjects treated with FST-100 and those treated with dexamethasone alone, PVP-iodine alone or Vehicle groups will have the same proportion of subjects with clinical resolution and adenoviral eradication. The alternative hypothesis is that this proportion differs between the dexamethasone alone, PVP-iodine alone or Vehicle groups and FST-100 group with $\alpha = 0.05$ (two-tailed). A chi-square or Fisher's exact test (in the case of expected counts less than 5) will be used to compare FST-100 and vehicle groups with respect to the proportion of subjects with clinical resolution at Visit 3. Because this is a proof-of-concept study, no sample size calculations have been made.

Safety

The safety of FST-100 will be assessed using data listings and statistical summaries for each treatment group at each time point. Safety will be evaluated by the incidence of adverse events, changes in visual acuity, and the slit lamp biomicroscopy exam. All subjects enrolled in the study who received at least one dose of the study medication will be evaluated for safety. All data will be summarized for safety and identified as data from treated or untreated eyes. Adverse experience data will be listed and summarized by treatment group, body system, MedDRA® terms, investigator opinion concerning the relationship of the adverse event to the drug (suspected/unsuspected) and severity (1=mild, 2=moderate, 3=severe). Visual acuity changes will be listed for each eye, and the number of subjects with a clinically significant worsening (> 0.2 LogMAR) in one or both eyes will be tabulated for each dose group. Biomicroscopy changes will be tabulated by treatment group, eye (treated and untreated), and visit. Data from subjects with slit lamp findings at baseline as well as those with treatment emergent findings (findings that were not present prior to treatment or a worsening relative to the pretreatment baseline) will be listed. Summary statistics for continuous data will include computations of the mean, standard deviation, minimum and maximum. Frequency distributions will be provided for discrete variables.

The demographic characteristics (ie, age, sex, and race and iris color), medical history, and ocular history data will be summarized by treatment group for the total study sample. These data will be listed by treatment group for the completed, terminated, and discontinued subjects.

Summary of Known and Potential Risks and Benefits to Human Subjects

Dexamethasone has been available at 0.1% concentration for over four decades in commercial ophthalmic products such as Maxitrol (dexamethasone 0.1%; neomycin sulfate (EQ 3.5mg base/mL; polymyxin B sulfate 10,000 units/mL), Maxidex (0.1% dexamethasone ophthalmic suspension; Alcon Laboratories, Inc), and Tobradex (tobramycin 0.3%/dexamethasone 0.1%). Given this long history, there is extensive safety data available for ophthalmic applications of dexamethasone.

Risks involved with the use of 0.1% dexamethasone include glaucoma with optic nerve damage,

visual acuity and field defects; cataract formation; secondary ocular infection following suppression of host response; and perforation of the globe.

PVP-Iodine is a broad spectrum antiseptic with no known microbial resistance. It kills infectious organisms by iodination of lipids, oxidation of cytoplasmic and membrane compounds, and provides significant antimicrobial activity. Based upon its mechanism of action, the antiviral activity of PVP-Iodine should be retained regardless of viral serotype. Iodine and iodine derivatives have a history of being used to treat ophthalmic, otic, oral, dermal, and other infections. They possess potent broad-spectrum antimicrobial activity and the local delivery of these agents to the site of infection is known to effectively treat, eliminate, and/or prevent the growth of microorganisms. An ophthalmic preparation of 5% PVP-Iodine (Betadine[®]) is available for preparation of the periocular region and irrigation of the ocular surface. Approximately 25 years of safety data is available for ophthalmic applications of PVP-Iodine. However, local sensitivity has been exhibited by some individuals to 5% povidone-iodine ophthalmic solution. The study drug, FST-100 for the ophthalmic indication, acute adenoviral conjunctivitis has a concentration of PVP-Iodine of 0.6%, which is significantly lower than that found in the commercial preparation.