SYNOPSIS

Study Title: A Phase 4 Study to Assess the Clinical Efficacy of H.P. Acthar Gel 80 U/ml to Improve the Signs and Symptoms in Subjects with Dry Eye Disease

Objectives: The primary objective of this study is to investigate the safety and efficacy of H.P. Acthar Gel 80 U/ml in subjects with a documented clinical diagnosis of dry eye disease.

Study Population: The study population will consist of subjects diagnosed with dry eye disease.

Number of Subjects: Approximately 12 subjects

Investigational Product: H.P. Acthar Gel 80 U/ml sufficient for the duration of the study will be supplied by Mallinkrodt to the enrolled subjects

Route and Duration of Administration: Product will be injected subcutaneously weekly by subjects for approximately 12 weeks.

Study Design: This is a Phase 4, single center single arm study designed to evaluate the safety and efficacy of H.P. Achthar Gel in subjects with dry eye disease.

Approximately 25 subjects will be screened and 12 subjects enrolled at one center in the United States.

Subjects will be given 80 international units of study medication subcutaneously depending on the severity of the disease as determined by the primary investigator.

The study will include 3 study visits over 12 weeks. At Visit 1 Screening (14 +/- 1 days prior to Day 1), subjects meeting inclusion/exclusion criteria will begin investigational drug use. Subjects will return for evaluations at Visit 2 (Day 42+/-3 days) and Visit 3 (Day 84 +/-5 days). Subjects will be released from the study at the end of Visit 3 (Day 84+/- 5 days.)

Assessments in this study will include:

Subject rated assessment of ocular discomfort at study visits
Best corrected visual acuity
Slit lamp biomicroscopy
Corneal fluorescein staining
Conjunctival lissamine staining
Anesthetized Schirmer Test evaluation
Intraocular Pressure measurement
Dilated Ophthalmoscopy
Medical assessments for tuberculosis, active fungal or viral disease, cirrhosis, hypertension and/or diabetes

Efficacy Endpoints: The trial will have 2 primary endpoints: 1 sign endpoint (conjunctival hyperemia at Visit 4 (Day 84+/-5) and 1 symptom endpoint (ocular discomfort at Visit 4.

Secondary Endpoints corneal and conjunctival staining, intraocular pressure

Safety Endpoints: Assessment of adverse events
Slit lamp biomicroscopy
IOP measurement
BCVA
Dilated Ophthalmoscopy

Inclusion Criteria
At Visit 1 (Screening) individuals of either gender or race will be eligible for study participation if they

1. Provide written informed consent and HIPAA authorization prior to any study related procedures
2. Are 18 years of age or older
3. Are willing and able to follow instructions and can be present for required study visits.
4. Have documented clinical diagnosis of dry eye disease in one or both eyes.
5. Have a score of at least 40mm on the ocular discomfort scale
6. Have at least 5 spk on one or both corneas
7. Have a grade of 1 or greater in the nasal or temporal areas of one or both eyes.
8. Have normal lid anatomy.
9. Are women of child bearing potential who are not pregnant or lactating and who are either abstinent and willing to remain so for the course of the trial or have an IUD in place for at least 3 months prior and through Visit 4, barrier method with spermicide for at least 3 months prior and through Visit 4, stable hormonal contraceptive for at least 3 months prior and through Visit 4 or in a monogamous relationship with a surgically sterilized (vasectomized) partner at least 6 months prior to Visit 1 and through the course of the trial.
10. Are postmenopausal (no menstrual cycle for at least one year prior to Visit 1) or have undergone bilateral tubal ligation, hysterectomy, hysterectomy with uni or bilateral oophorectomy, or bilateral oophorectomy.
11. Have been cleared of active tuberculosis or other fungal or viral disease, cirrhosis and have been found to have stable hypertension and/or diabetes.

Exclusion Criteria
In order for subjects to be eligible for the study

1. Have a known hypersensitivity or contraindication to the investigational product or their components.
2. Have used any of the following medications within 14 days prior to screening
    a. Topical or nasal vasoconstrictors

3. Subjects can be on the following medications if they have been on a stable dose for 12 weeks topical cyclosporine, topical lifitegrast and/or topical loteprednol etabonate. Tetracycline compounds, omega 3s, anticholinergics, anticonvulsants, antidepressants, retinoids, systemic immunosuppressive agents including oral corticosteroids, non-steroidals, antihistamines or mast cell stabilizers, punctal plugs, contact lens wear and glaucoma medications.
4. Subjects must be unwilling to abstain from eyelash growth medications for the duration of the trial.
5. Subjects must not have had penetrating intraocular surgery, refractive surgery or corneal transplantation, eyelid surgery within 12 weeks prior to Visit 1.
6. Subjects with a history of herpetic keratitis.
7. Have serious or severe disease or uncontrolled medical condition that in the judgement of the investigator could confound study assessments or limit compliance.

Table of Contents

10. Direct Access to source data/documents

12. Quality control

13. Ethics

12.1 Institutional Review Board

12. 2 Informed Consent Requirements

13. Data Handling and Recordkeeping

13.1 Data quality control and reporting

13.2 Records retention

ACTH	Adrenocorticopic Hormone
AR	Adverse Reaction
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
CRF	Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IOP	Intraocular Pressure
IPL	Intense Pulsed Light
IRB	Institutional Review Board
IUD	Intrauterine device
KCS	Keratoconjunctivitis sicca
MLT	Micropulsed laser trabeculoplasty
mm	millimeter
mmHg	millimeter of mercury
NSAID	Non steroidal anti-inflammatory drug
OSDI	Ocular
SAE	Serious adverse event
SLT	Selected laser trabeculoplasty
SOP	Standard operating procedure
UPT	Urine pregnancy test

US	United States of America

I. Introduction

Up to 25 million people in the United States experience dry eye symptoms (Beaver Dam Offspring Study 2015). Dry eye disease also known as keratoconjunctivitis sicca (KCS) is characterized by ocular pain, irritation, foreign body sensation, blurred vision, tearing and pain. Patients with dry eye can experience significant discomfort, reduced visual function and even disability resulting in a decreased quality of life or work productivity.

Current treatment of dry eye disease generally begins with artificial tear replacement and progresses to topical anti-inflammatory therapy, punctal plugs, oral fish oil and IPL. Topical cyclosporine (Restasis) and topical lifitegrast (Xiidra) are currently the only FDA approved prescription medications for dry eye disease. In many cases, these treatments are insufficient or only partially effective. Other adverse events can also occur including ocular irritation, dysgeusia and blurred vision for lifitegrast and burning, slow onset of response and limited efficacy efficacy for cyclosporine.

Inflammation plays a prominent role in the development, perpetuation and progression of dry eye disease. Steroids are used to treat an array of ocular conditions that have inflammatory components and are generally indicated for the treatment of steroid responsive inflammatory conditions of the conjunctiva, cornea, and anterior segment.

Mallinkrodt Pharmaceuticals has a unique product, H.P. Acthar contains the hormone ACTH (adrenocorticotropic hormone) that promotes the increased production of the body's own production of anti-inflammatory cortisol as well as binding the specific receptor (melanocortin) to help down-regulate both inflammation and the signals that keep chronic inflammation going once stimulated, acting specifically on T-helper cells, T-regulatory cells, macrophages and dendritic cells.

1.1 Description of Investigational Product

H.P. Acthar gel is a product containing the hormone ACTH. It is supplied in 5 ml with the 80U/ml syringes and is designed to be injected subcutaneously two or three times weekly in a manner similar to insulin administration according to the severity of the disease in the judgement of the investigator.

1.2 Justification for Route of administration and dose selection

H.P. Acthar gel will be injected subcutaneously two or three times weekly. Subjects will self-administer the dose recommended by the treating physician which may range from 80 international units two to three times per week. Nursing support from Mallinkrodt to train study coordinator and study personnel who will train subjects on proper administration techniques will be available at

all time points in the study. Patients will self-inject the study medicine for the length of the study, 12 weeks total.

1.3 GCP Compliance

This clinical trial will be conducted in compliance with the protocol and Good Clinical Practices (GCP) guidelines and other applicable regulartory requirements.

1.3 Population to be studied

Approximately 25 subjects diagnosed with dry eye disease will be screened for the study. Approximately 12 of these subjects will be enrolled to receive H.P. Acthar gel in the study.

2. Trial Objectives and Purpose

2.1 Objective

The primary objective of the study is to investigate the safety and efficacy of H.P. Acthar gel injections in subjects who have a documented clinical diagnosis of dry eye disease.

3. Trial Design

3.1 Primary Efficacy Endpoints

1. Improvement of Patient Comfort over the length of the study according to a validated dry eye comfort questionnaire, OSDI.
2. Improvement of number of spk in cornea over study treatment period

3.2 Secondary Efficacy Endpoint

1. Conjunctival staining with lissamine green

3.3 Safety Endpoints

1. intraocular pressure
2. Assessment of AEs
3. Slit lamp biomicroscopy
4. BCVA
5. Dilated Ophthalmoscopy
6. Medical assessments of active fungal or viral disease, active tuberculosis, cirrhosis and stability of hypertension and/or diabetes.

3.4 Description of Trial Design

This is a Phase 4, single center prospective pilot study designed to evaluate the safety and efficacy of H.P. Acthar gel in treating the signs and symptoms of dry eye disease over a 3 month period.

The study will include up to 4 clinic visits.

Approximately 12 subjects of 25 screened will be eligible and enrolled into the study.

Assessments included in the study include:
Subject rated assessment of eye dryness
Anesthetized Schirmer test
BCVA
Slit lamp biomicroscopy
Corneal fluorescein staining
Conjunctival lissamine green staining
IOP measurement
Dilated ophthalmoscopy
Pregnancy testing for those of childbearing potential
Concomitant medication use assessment
Assessment of AEs
Medical examinations to screen for tuberculosis, active fungal and/or viral disease, cirrhosis of the liver, and/or unstable hypertension or diabetes.

Composition of Study Drug: HP Acthar Gel is supplied a 5 ml multi-dose vial containing 80 USP units per mL.

At Visit 1, eligible subjects will receive a 6 week supply of study drug and training on injection. Additional vials may be made available for subjects in need.

Investigational product will be stored in a secure area with limited access at 2-8 degrees Celsius/36-46 Fahrenheit (refrigerated) with upper limit excursions to 46 degrees Fahrenheit allowed. Subjects will be asked to complete injections at approximately the same time of day.

4. Selection of Subjects
    4.1 Subject Inclusion and Exclusion Criteria
        4.1.1 Inclusion Criteria

Inclusion Criteria

At Visit 1 (Screening) individuals of either gender or race will be eligible for study participation if they

1. Provide written informed consent and HIPAA authorization prior to any study related procedures
2. Are 18 years of age or older
3. Are willing and able to follow instructions and can be present for required study visits.
4. Have documented clinical diagnosis of dry eye disease in one or both eyes.
5. Have a score of at least 40mm on the ocular discomfort scale
6. Have at least 5 spk on one or both corneas
7. Have a grade of 1 or greater in the nasal or temporal areas of one or both eyes.
8. Have normal lid anatomy.
9. Are women of child bearing potential who are not pregnant or lactating and who are either abstinent and willing to remain so for the course of the trial or have an IUD in place for at least 3 months prior and through Visit 4, barrier method with spermicide for at least 3 months prior and through Visit 4, stable hormonal contraceptive for at least 3 months prior and through Visit 4 or in a monogamous relationship with a surgically sterilized (vasectomized) partner at least 6 months prior to Visit 1 and through the course of the trial.
10. Are postmenopausal (no menstrual cycle for at least one year prior to Visit 1) or have undergone bilateral tubal ligation, hysterectomy, hysterectomy with uni or bilateral oophorectomy, or bilateral oophorectomy.

4.1.1 Exclusion Criteria

In order for subjects to be eligible for the study

1. Have a known hypersensitivity or contraindication to the investigational product or their components.
2. Have used any of the following medications within 14 days prior to screening
    a. Topical or nasal vasoconstrictors
3. Subjects can be on the following medications if they have been on a stable dose for 12 weeks topical cyclosporine, topical lifitegrast and/or topical loteprednol etabonate. Tetracycline compounds, omega 3s, anticholinergics, anticonvulsants, antidepressants, retinoids, systemic immunosuppressive agents including oral corticosteroids, non-steroidals, antihistamines or mast cell stabilizers, punctal plugs, contact lens wear and glaucoma medications.
4. Subjects must be unwilling to abstain from eyelash growth medications for the duration of the trial.
5. Subjects must not have had penetrating intraocular surgery, refractive surgery or corneal transplantation, eyelid surgery within 12 weeks prior to Visit 1.
6. Subjects with a history of herpetic keratitis.

7. Have serious or severe disease or uncontrolled medical condition that in the judgement of the investigator could confound study assessments or limit compliance.

11. Procedures

Written informed consent and HIPAA authorization will be obtained from all subjects prior to any study procedures being performed.

a. Visit Description

i. Visit 1 +/-1 day

After obtaining written informed consent and HIPAA authorization as well as medical clearance for the study, site staff will perform/assess the following in the order below. Each subject will be identified by last name, first initial for the duration of the study.

Subject rated assessment of ocular discomfort by visual analog scale.
Significant non-ocular and significant ocular medical history
Concomitant medication usage and significant medications taken 6 months prior to screening
Inclusion/exclusion criteria
Urine pregnancy test if required.
BCVA
Slit lamp biomicroscopy
Corneal fluorescein staining
Conjunctival lissamine staining
Anesthetized Schirmer test
IOP
Dilated ophthalmoscopy
Training on study medication dosage
Dispense study medications

ii. Visit 2: Day 14

This visit will occur on Day 14+/-2 calculated from Visit 1 and the following evaluations will be performed
BCVA
IOP
Slit lamp biomicroscopy

5.1.3 Visit 3: Day 42+/3

This visit will occur on Day 42+/- 3 as calculated from Visit 1 and the following evaluations will be performed
Subject rated assessment of eye dryness
Use of any concomitant medications since the last visit
Occurrence of any AEs since the last visit
BCVA
Slit lamp biomicroscopy
Corneal fluorescein staining
Conjunctival lissamine staining
Anesthetized Schirmer test

IOP
5.1.4 Visit 4: Day 84+/-5
This visit will occur on Day 84+/- 5 as calculated from Visit 1 and the following evaluations will be performed
Subject rated assessment of ocular discomfort by visual analog scale.
Concomitant medication usage since Visit 2
Inclusion/exclusion criteria
BCVA
Slit lamp biomicroscopy
Corneal fluorescein staining
Conjunctival lissamine staining
Anesthetized Schirmer test
IOP
Dilated ophthalmoscopy
Urine pregnancy test for women of childbearing potential
Final medical screening for tuberculosis, active fungal or viral infection, liver cirrhosis, unstable hypertension or diabetes or other steroidogenic side effects as determined by the screening physician

Release of subject from the study

5.1.5 Unscheduled visit
Any visit or procedures performed beyond those specified within the protocol must be documented in the Unscheduled visit page of the CRF. Unscheduled visits may include but are not limited to reporting adverse events, changes in concomitant medications or ophthalmic assessments deemed appropriate by an appropriately qualified eye care professional. If the subject is discontinuing study participation at the unscheduled visit, the CRF for Visit 3 should be completed rather than the CRF for Unscheduled Visit.

5.1.6 Early Termination Visit
In the event of termination prior to Visit 3, every attempt will be made to ensure that all Visit 3 assessments are performed. If this is not feasible, at least the following should be performed:
Subject rated assessment of eye dryness
Use of concomitant medications since last visit
Occurrence of any AEs since the last visit
Unused investigational product should be collected
BCVA
Slit lamp biomicroscopy
IOP
Pregnancy test for women of childbearing potential

Final medical screening for tuberculosis, active fungal or viral infection, liver cirrhosis, unstable hypertension or diabetes or other steroidogenic side effects as determined by the screening physician

b. Rescue Medication Use

Any subjects not responding adequately to the study medication may be rescued and placed on alternate therapy at the investigator's discretion at any time. The choice of rescue medications will be at the investigator's discretion. Any subject placed on rescue therapy will discontinue use of study drug and continue study participation through Visit 3.

The need for rescue therapy wil not be considered an AE. Rescued subject experiencing an AE at the time of rescue will be followed through stabilization or resolution of the AE or the end of the study (whichever comes last).

c. Subject Withdrawal and/or Discontinuation

Any subject who wishes to withdraw from the investigational product and the study by his or her own accord for any reason and is entitled to do so without obligation. The investigator may also withdraw any subject form the investigational product use or from study participation if deemed necessary.

Investigational product use may be discontinued and any subject for any reason including but not limited to

1. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk or does not allow the subject to adhere to the protocol
2. Any SAE
3. Subject's decision to withdraw
4. Any woman who becomes pregnant while participating in the study. Information on the pregnancy and outcome will be requested.
5. Subjects fairlure to comply with protocol requirments or study procedures.
6. Termination of the study by the Sponsor, FDA or other regulatory authority.

In the event of withdrawal, the investigator will make every attempt to complete Visit 3 assessments if possible. AEs and SAEs will be followed to resolution or stabilization or until the subject is lost to follow up. Reasons for premature discontinuation will be listed on CRFs.

d. Collection of Data

Source documentation for data collected will be maintained at the investigative site.

12. Treatment of subjects
    a. investigational products to be administered

        All subjects meeting eligibility criteria at Visit ! will receive 6 weeks of study drug.. Subjects will be asked to self administer study drug once or twice weekly.

    b. Concomitant Medications

        All medications that the subject has taken 6 months prior to Visit 1 and through Visit 3 or discontinuation from the study will be recorded on CRFs. The generic name of the drug, route of administration, duration and treatment including start and stop dates, frequency, indication and whether the medication was taken due to an AE or as rescue medication will be recorded for each medication.

        i. Permitted Medications

        Medications not specifically excluded may be taken as necessary.

        ii. Medications Not Permitted

        Topical or nasal vasoconstrictors within 14 days of enrollment
        Subjects can be on the following medications if they have been on a Unstable doses in the prior 12 weeks for the following: topical cyclosporine, topical lifitegrast and/or topical loteprednol etabonate. Tetracycline compounds, omega 3s, anticholinergics, anticonvulsants, antidepressants, retinoids, systemic immunosuppressive agents including oral corticosteroids, non-steroidals, antihistamines or mast cell stabilizers, punctal plugs, contact lens wear and glaucoma medications. eyelash growth medications for the duration of the trial

    c. Investigational product use compliance

        i. Subjects will be expected to remain compliant with dosing recommendations throughout the trial. If subjects miss doses, this information will be recorded in the CRF along with the reason for missed dosing.

            6.4 investigational product accountability

            Study coordinator and/or designated Toyos Clinic personnel will be accountable for investigational product. Clinical trial materials will be shipped to the investigational site under sealed conditions. Study product will be verified by comparing shipment inventory to actual quantity of investigational product received. Accurate records will be maintained. Investigational product will be stored in a secure location with limited access with controlled temperatures. All unused study product will be returned to the Sponsor at the conclusion of the trial.

13. Assessment of Efficacy

Efficacy assessments include the following

Subject rated assessment of eye dryness

SPK on cornea visible with fluoresceing staining

SPK on conjunctiva visible with lissamine green staining

8 Assessment of Safety

8.1 Safety parameters

Safety parameters include

- AE assessments
- BCVA
- Slit lamp biomicroscopy
- Dilated ophthalmoscopy
- IOP measurement
- Medical examination for active tuberculosis, fungal or viral infections, liver cirrhosis, unstable hypertension or unstable diabetes

8.2 Adverse Event definitions

Adverse Event (AE) any untoward medical occurrence associated with the use of an investigational product in humans, whether or not it is deemed drug related.

Serious Adverse Event SAE is any AE occurring that is life threatening, results in death, requires hospitalization, results in birth defect or requires significant medical intervention.

Each AE will be classified as SERIOUS or NON-SERIOUS. The SEVERITY will be classified as MILD, MODERATE, or SEVERE.

The investigator will review each event and assess relationship to study drug: unrelated, unlikely, possibly, probably or definitely.

8.4 SAE Reporting

It is the responsibility of the investigators or their designees to report any event of this nature to the sponsor and the IRB within 24 hours of the event being brought to the investigators or their staff's attention. The investigator will make every effort to follow the event to resolution.

8. Statistics

9.1 Continuous measures will be summarized descriptively by the mean, standard deviation, median, minimum and maximum values. This is a pilot study with no control and not intended to provide power.

9.1.2 Analysis of Safety

Analysis of safety data will be presented for all subjects. Ophthalmoscopy will be summarized descriptively. IOP, BCVA and biomicroscopy will be summarized as safety outcomes.

9. Direct Access to Source Data/Documents

The investigator and site will permit audits, IRB Review and regulatory inspections by providing direct access to source data and documents.

10. Quality Control

The progress of the study will be monitored by written, email and telephone communications between personnel at the study site and Sponsor. Onsite visits by Sponsor are also acceptable.

11. Ethics

11.1 Institutional Review Board

This protocol and the informed consent must be approved by appropriately constituted and qualified IRB prior to enrollment into the study.

Investigators or their designees will report all SAEs to the their IRB as well as the Sponsor.

11.2 Informed Consent

Written informed consent will be obtained from each participant prior to any study-related procedures being performed. A copy of the signed and dated informed consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the investigative site and be available for review.

Each informed consent will contain Investigator contact information with a telephone number the subject can call 24 hours a day if needed for medical concerns.

12. Data Handling and Recordkeeping

All procedures for handling and analysis of data will be conducted using GCP and FDA regulations for the handling and analysis of data for clinical trials.

12.1 Records Retention

The study site will retain all records related to the study in accordance with GCP guidelines.

Appendex 1: Subject Rated Assessment of eye dryness

Subjects will be asked to subjectively rate their eye dryness at Visit 1,2 and 3. Subjects will be instructed to rate eye dryness using the scale below. The total length of the line from “no dryness” to “maximal dryness” is 100 mm. The length of the line between the “no dryness” starting point and the first point at which the subject mark crosses the line will be measured in mm. This assessment is a general assessment of both eyes.

Instantaneous Evaluation of Eye Dryness

Please place a single line across the line below to indicate the severity of your eye dryness at the present time:

No dryness_____maximal dryness

Appendex 2: Anesthetized Schirmers

Fold the rounded end of the test strip at the notched area.

Instill 1-2 drops of properacaine or tetracaine and wait 5 minutes.

Ask the subject to look up and away from the strip

Place the rounded end of the strip towards the temporal one third of the lower lid.

Repeat procedure on contralateral eye

Instruct the subject to relax and gently close their eyes.

Remove strips after 5 mins and mark with ink the leading and lowest edges of moisture

Measure halfway between the 2 lines and record and the amount of wetting.

Appendix 3 Best Corrected Visual Acuity

Will be assessed at all visits and before any assessment requiring contact with the eye or instillation of drops. LogMAR will be assessed with ETDRS or modified ETDRS charts and will be performed with subjects own corrective lenses or BCVA measured in office, whichever is better.

Scores are recorded according to ETDRS protocol and right eyes are tested first.

Appendix 4 Slit Lamp Biomicroscopy

Will be performed at all study visits. It will be performed with the slit lamp using a beam of width and intensity to provide optimal evaluation of the anterior segment. Abnormal findings will be followed by explanation of pathology.

Lids and Lashes will be recorded as normal or abnormal

Conjunctiva normal or abnormal

Cornea normal or abnormal

Anterior chamber normal or abnormal

Lens normal or abnormal. Age appropriate cataract findings will not be abnormal but will be noted

Iris normal or abnormal

Appendix 5 Corneal fluorescein staining

Will be performed at each visit using methods developed by the NEI Dry Eye Workshop

Evaluation Technique

Liquid fluorescein will be used one drop in each eye. Examinaton will occur after 2 minutes using cobalt filter. Discrete spk will be counted and macropunctate staining will be noted.

Appendex 6 IOP measurements

IOP measurements will be performed using Goldmann applanation tonometry according to the investigators standard protocol. All pressures will be recorded in mm HG. IOP will be measured at each time point and at the investigator's discretion.

Appendix 7 Dilated Ophthalmoscopy

Dilated ophthalmoscopy will occur at the first and last study visit and include assessment of the optic nerve head for pallor and cupping.