Marshall B. Ketchum University
2575 Yorba Linda Blvd Fullerton CA 92831

Jerry R. Paugh, OD, PhD *Principal Investigator* Telephone(direct): 714-449-7487 jpaugh@ketchum.edu	Jay Jiang, PhD *Student Investigator* jayjiang.ms24@ketchum.edu	William Ridder III, OD, PhD *Co-Investigator* Telephone (direct): 714-449-7494 wridder@ketchum.edu
Daniel May, MD *Co-investigator* Telephone(direct) 714-872-5690 dmay@ketchum.edu	Rima Khankan, PhD *Co-Investigator* Telephone (direct): 714-992-7831 rkhankan@ketchum.edu	
Day Emergency Number (714) 870-0258	Night Emergency Number (714) 870-0258	

Consent Document

A Randomized Controlled Trial of Topical Androgen Treatment in Dry Eye

Please take as much time as you need to read this information and to ask questions

Key Points to Consider

- Because you are suffering the discomfort of dry eyes we are inviting you to participate in a research study of a drug to treat dry eye. It is called androgen gel.
- The investigators will choose to give you either the androgen gel or placebo gel.
- You will put the gel on your eyelid two times a day for 4 weeks
- You need to attend the clinic six times. We will do dry eye tests on you at each visit and two blood draws before and after 4 weeks of the treatment.

- We will not charge you for the gel or study visits. You will receive $65 per visit to participate for the six study visits to the research laboratory at MBKU.

About This Study

The purpose of this research study is to evaluate the effectiveness and safety of applying androgen sex hormone (i.e., testosterone) gel on the eyelids in the treatment of dry eye patients. Several studies have demonstrated positive treatment effects in dry eye, but few have applied testosterone gels to the eyelids. There is approximately a 50% chance that you will be assigned to receive the placebo. Neither you nor the investigators will know which medication you are given, but in the event of an emergency, access to that information can be obtained.

Up to 40 subjects will be enrolled in this study. We will arbitrarily (randomly) assign one-half of the subjects to use a commercially marketed testosterone gel called Natesto, made by Acerus Pharmaceuticals, that is normally applied as a nasal spray three times a day. The placebo (sham treatment) will be a similar gel formulation, but without the testosterone drug.

This study is sponsored by Marshall B. Ketchum University.

First, we want you to know that taking part in this study is entirely voluntary. You may choose not to take part, or you may withdraw from the study at any time without fear of penalty or loss of eye care.

AM I ELIGIBLE TO PARTICIPATE IN THIS STUDY?

Your examining clinician will determine if you are eligible to participate in this study. Your participation is dependent upon you having signs and symptoms of dry eye disease and meeting the criteria below.

Please note this is not a complete list of eligibility criteria. We have included a few examples of study criteria to help you better understand how your eligibility in the study will be determined; your study team will go through the study eligibility criteria with you to verify whether you qualify for participation in this study.

INCLUSION CRITERIA

You can participate in this study if you:

- Are male or female 18 years and older
- Have signs or symptoms of dry eye (ranging from moderate to severe)
- Are willing to discontinue use of artificial tears on the day of the study visit

- Can provide a negative urine pregnancy test at study start (if female)

EXCLUSION CRITERIA

You cannot participate in this study if you:

- Have known or suspected prostate cancer
- Have known or suspected breast cancer
- Females who are pregnant, nursing or planning a pregnancy during the study period
- Use any topical eye medication other than artificial tears
- Wear contact lenses of any type

Conflicts of Interest

The investigators and Marshall B. Ketchum University have no conflicts of interest in this study.

Procedures: What Will Happen

Location of this study:

This study is carried out at the main campus of Marshall B. Ketchum University in the laboratory of Dr. Jerry R. Paugh.

Duration of patient participation:

There will be total of six visits over a period of 14 weeks (three and half months). Blood samples will be taken at two visits in addition to the 6 testing visits at Dr. Paugh's laboratory to monitor systemic blood levels of testosterone.

- Visit 1: screening visit
- Visit 2: baseline exam (pre-treatment phase)
- Visit 3: 2 weeks after starting the treatment
- Visit 4: 4 weeks after starting the treatment
- Visit 5: 4 weeks after stopping the treatment
- Visit 6: 8 weeks after stopping the treatment

Study procedures

<u>Visit 1: the screening visit, approximately 90 minutes; the procedures include:</u>

- Documentation of your medical and eye history
- Evaluation of your meibomian gland condition (you may experience some mild discomfort during exam procedures)
- A urine pregnancy test (if applicable)
- An examination of the front of the eye for dry eye
- Patient questionnaires

If you qualify at the screening visit, you will be able to continue to the next steps. If you are not qualified, you still can be reimbursed $65 for your participation.

Visit 2: the Baseline exam Visit (Day 0), approximately 90 minutes; the procedures will include:

- Evaluation of your meibomian gland condition (you may experience some mild discomfort during exam procedures)
- An examination of the front of the eye for dry eye
- Patient questionnaire(s)
- An evaluation of head and facial hair growth
- Measurement of blood pressure and intraocular pressure
- A blood draw (about 2 tablespoonfuls of blood will be taken from a vein in your arm for evaluation) at a nearby clinical laboratory. Your investigator will receive the results of the blood evaluation. If you would like to know the results of your test, ask the investigator to discuss them with you.
- You will be dispensed study gel and shown how to apply the gel on the surface of upper and lower eyelid in each eye
- You will be instructed to apply of the study medication in each eye twice daily (in the morning after washing your face and at least one-half hour before bedtime). On the days of your study visit, one of the two daily doses of study medication will be given at the doctor's office.

Visit 3 and 4: at Weeks 2 and 4, all visits approximately 90 minutes; the procedures will include:

- Evaluation of your meibomian gland condition (you may experience some mild discomfort during exam procedures)
- An examination of the front of the eye for dry eye
- Patient questionnaire(s)
- Apply study gel
- An evaluation of head and facial hair growth (week 4 only)
- A blood draw of about 2 tablespoonsful of blood will be taken from a vein in your arm for evaluation. (Week 6 only)
- You will be asked to stop using any study gel at week 4.
- You will be instructed to return to the study doctor's office at the fourth visit with all unused units of investigational medication. You should discard the used unit doses after applying gel to the surface of upper and lower eyelid of your eyes.

Visit 5 and 6: at weeks 8 and 12, approximately 90 minutes; the procedures will include:

- Evaluation of your meibomian gland condition (you may experience some mild discomfort during exam procedures)
- An examination of the front of the eye for dry eye
- Patient questionnaire(s)
- An evaluation of head and facial hair growth (week 12 only)
- Measurement of blood pressure and intraocular pressure (week 12 only)

You should return promptly for all study visits. If you cannot make your scheduled appointments, please notify the investigators as soon as possible to reschedule your visit.

Please report any of the following to the investigator:

- changes in your medications (over the counter and prescription)
- missed doses of the study medication. Please use twice per day, once in the morning and once in the evening.
- changes in how you feel
- if you suspect you may be pregnant

Safety, Risks, and Discomforts

Side effects and discomfort associated with study treatment which you may experience include hirsutism (excessive hair growth), scalp hair loss, acne, change in sexual functioning and voice deepening. If these side effects occur, they should go away after the study medication is stopped. Very high doses of testosterone (much higher than used in this study) given by mouth or applied to the skin for a long period of time have been shown to result in changes in liver function, cholesterol, or mood.

Although the risk is low after topical administration of testosterone, subjects with the following conditions will be excluded from the study:

- Current or recent vein blockages (venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). Subjects who have symptoms of pain, edema, warmth and erythema in the lower extremity or acute shortness of breath during the study should report these to the investigators and seek medical care.
- Recent cardiovascular events (e.g., myocardial infarction (heart attack), stroke). Subjects who report signs or symptoms of heart attack or stroke should seek medical care.
- Liver (hepatic) disorders (hepatitis, jaundice, hepatic cancer et al.). Subjects should monitor for signs or symptoms of hepatic dysfunction (e.g., jaundice)

- Subjects who are taking insulin, warfarin, or corticosteroids

Although the risk is low after topical administration of testosterone, subjects who experience the following conditions will be monitored and possibly exited from the study:

- Swelling due to sodium and water retention
- Enlargement of breast tissue
- Sleep apnea or worsening of sleep apnea
- Serum lipid changes

Blood samples will be taken similar to a routine blood panel ordered by your physician at baseline and after four weeks of topical gel application. At baseline we will use the red blood cell count (called "hematocrit") to exclude those with elevated levels. Other monitoring measurements will be for blood lipid levels, blood testosterone levels, and to monitor prostate specific antigen for males. You might feel pain or light-headedness from this. You might get a bruise at the injection site, and there is a small chance you might get an infection.

There may be risks associated with stopping the ophthalmic medication you are currently taking, such as changes in your symptoms of dry eye. These may include stinging/burning, tearing, discharge, itching, sandiness/grittiness, blurred vision, dryness of the eye, light sensitivity, or pain.

The investigational gel must be used only by the person for whom it has been prescribed, and must be kept out of the reach of children and persons of limited capacity to read or understand. In order to avoid inadvertent administration of the testosterone, subjects should be warned to keep their eyelids away from children, adults, and pets (hugging or kissing) for several hours after administration of the treatment gel. It is highly recommended to use disposable towels and cleaning hands after administration rather than regular bathroom linens.

If you experience any illness or discomfort during the study, you should notify any of the study doctors. One of the study doctors will then evaluate you to determine if you should continue in the study. If necessary, your study medication may be stopped, and appropriate therapy may be started.

There may be side effects or discomforts from the study treatment, which are not yet known. You could have an allergic reaction to the study medication. A severe allergic reaction could be life-threatening. **In addition, if you are pregnant or become pregnant, there may be a risk to the fetus.**

Risks for women who could become pregnant

The risks to an unborn baby or a nursing child from the study drug are not known. There may be possible masculinization of a female fetus. If you are pregnant or become

pregnant, the study drug may cause problems to your unborn baby. Birth defects and other problems including premature birth are known risks of some drugs. Women who are pregnant or nursing a child may not participate in this study. You must confirm that, to the best of your knowledge, you are not pregnant now, and you do not plan to become pregnant during the study. You may be required to have more pregnancy tests than are currently scheduled during the study. A pregnancy test does not stop you from becoming pregnant. If you are of childbearing potential, the study doctor will discuss appropriate birth control options with you. If you think that you have become pregnant during the study, you must tell any of the study doctors immediately.

Childbearing female subjects would be safe to pursue a pregnancy after the testosterone level has returned to pre-study levels. It can be confirmed at weeks 8 after discontinuation of treatment and can be rechecked 4 weeks later if the testosterone level is still above pre-study level.

Benefits

You may not receive any direct medical benefit from participating in this study. However, the possible benefits to other people with this condition include more information about dry eye and the development of future treatments. If the treatment is found to be effective, it will not be offered to those subjects who were in the placebo group as this is a proof of principle study only.

Costs and Payments

You will not be charged to take part in this study. You will be reimbursed upon completion of the study for your time and inconvenience for each of the visits that you complete according to the following visit schedule:

Screening visit	$65
Week 0(Day 0)	$65
Week 2	$65
Week 4.	$65
Week 8	$65
Week 12	$65

$390 total for completing all visits

In the event that you do not complete the full visit at screening, you will receive a prorated amount based on the procedures performed to determine your eligibility. If you withdraw for unforeseen personal reasons or circumstances preventing further participation, you will receive a prorated amount for each scheduled visit you completed.

Other Health Care Options

Alternative treatments that are available to treat your dry eye and meibomian gland dysfunction include artificial tears (eye drops, ointments, or gels), lids scrubs, lid massages, warm compresses and medications prescribed by your investigator. The investigator will discuss with you the advantages and disadvantages of alternative treatments. Please consider asking your doctor about these options before you decide whether to take part in this study.

There may be risks associated with stopping the ophthalmic medication you are currently taking, such as changes in your symptoms of dry eye. These may include stinging/burning, tearing, discharge, itching, sandiness/grittiness, blurred vision, dryness of the eye, light sensitivity, or pain.

Care if You are Injured

The risk of injury in this study is minimal. If you experience an adverse reaction as a direct result of the drug(s) being administered in this study, you should consult your own doctor for emergency care if you are injured in this study. You or your insurance company will need to pay for any healthcare you require. The Marshall B. Ketchum University is not required to pay your medical costs if you become sick or are injured.

Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country, where testosterone cream may ultimately be marketed, but your name will not be disclosed in these documents. Your name may be disclosed to the governing health authorities, the FDA (The U.S. Food and Drug Administration), or the MBKU Institutional Review Board (IRB) if they inspect your medical records.

Appropriate precautions will be taken to maintain confidentiality of medical records and personal information. All data from the study will be maintained confidentially in a separate record of your visits where each patient is identified by number identification only. Any electronic files created that include any patient information or medical data obtained during the study will be kept in password and encryption secured computers of the research staff and Investigators (Drs. Jiang, Paugh, Khankan, Ridder) at the MBKU main campus. These files will not be accessible outside of their respective offices.

However, complete confidentiality cannot be assured, as research records are not exempt from subpoena. Only Center for Vision Research (CVR) personnel (principal investigators, study coordinator, and MBKU IRB) will have access to your study records. Study records will be kept in a secured, separate file within the offices of the Paugh Laboratory at MBKU, and not in the main records area.

A description of this clinical trial will be available on http://www.clinicaltrials.gov as required by U.S. law. This website will not include information that can identify you. At most the web site will include a summary of the results. You can search this web site at any time.

Possible Future Research on Your Data

We may remove all personal identifiers from your data, and then store them for possible future research studies. This research may include other sites outside Marshall B. Ketchum University. The biospecimens (blood draw) will destroyed after the lab tests.

Future Contacts

We will send you a disposition of your dry eye when the study is complete., but not summaries of the study findings.

Termination of Participation

Your participation in this study is entirely voluntary. You may choose to stop taking part at any time. There are no penalties. You will not lose benefits or services that the University owes you.

If you decide to stop taking part in this study, we will respect your decision. However, we request your permission to contact you and follow up on your health status, if necessary.

Studies show that the effects of the drug wear off after 90 days of discontinuation when applied systemically. Topical application on the eyelids will last for even shorter time.

Where to Find More Information

If you have questions about the study procedures, please contact the Principal Investigator. Dr. Jerry R. Paugh. Dr. Paugh's contact details are listed on the front page.

If you have questions about your rights as a research subject, or you were injured in this study, or wish to complain about this study, please contact:

Lawrence R. Stark, Chairperson
Institutional Review Board
Marshall B. Ketchum University
2575 Yorba Linda Blvd Fullerton CA 92831
e-mail: irb@mbku.edu

In addition, we will inform you of anything we learn that could influence your willingness to continue in this study.

Experimental Subject's Bill of Rights

Under the California *Protection of Human Subjects in Medical Experimentation Act*, a subject or subject's conservator or guardian, or other representative, has the right to:

(a) Be informed of the nature and purpose of the experiment;
(b) Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;

(c) Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment;
(d) Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable;
(e) Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits;
(f) Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise;
(g) Be given an opportunity to ask any questions concerning the experiment or the procedures involved;
(h) Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice;
(i) Be given a copy of the signed and dated written consent form;
(j) Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

Subject Statement

- I have read this consent form
- I have been given a copy of this Experimental Subject's Bill of Rights
- I have been told that I will be given a copy of this form
- I have been given the opportunity to ask questions concerning this study and my participation in this study
- I feel that I am sufficiently informed about this study
- I choose voluntarily to take part in this study
- I have been told that refusal to participate will involve no penalties
- I have been told that I may choose to stop taking part at any time without penalty
- I continue to hold my legal rights should someone in this study be negligent or act illegally
- I understand that this document does not replace any Federal, state, or local law

Subject's name

Subject's signature | Date | Time

Investigator Statement *(The subject must not sign in this gray area)*

I verify that I have discussed this research study, its objectives, methods, associated risks, and benefits with the subject and have fully answered all questions to their satisfaction. I have assessed the subject's comprehension of this information.

Investigator's name			
Investigator's signature		Date	Time
			

RECEIVED 28 JUNE 2022