Appendix 1 – Informed Consent Document

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Systemic and Topical Antiviral Control of CMV Anterior uveitis: Treatment Outcomes (STACCATO)

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This is a clinical research study. Your study doctor, John Gonzales, M.D., from the UCSF Proctor Foundation, will explain the study to you.

Research studies include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you are suspected to have anterior uveitis (inflammation of the front portion of the eye) caused by the virus, cytomegalovirus (CMV).

Why is this study being done?

CMV anterior uveitis can cause increased pressure inside the eye, pain, cataract formation, and loss of vision. There are many treatment options, however we currently don't know which one is superior and there is no defined standard of care. The purpose of this study is to compare the most commonly used treatment options used in the management of your condition. After confirming the diagnosis, we will assign you to one of three treatment groups and compare the difference in outcomes between each group.

In addition, prior to this visit, the physician who referred you to our clinic may or may not have started you on steroid eye drops to control your inflammation. For our study we intend on giving all participants the same amount of steroid drops for the 28 day duration. We intend on investigating whether the amount of steroid given prior to you starting in this study affects the amount of virus found in the fluid from the eye.

How many people will take part in this study?

Overall, about 99 people will take part in this study. Approximately 33 people will be in each of the 3 treatment groups. The treatment options will be 28 days of oral antiviral therapy, 28 days of 2% antiviral eye drops, or 28 days of inactive therapy.

We expect that up to 70 people will be enrolled into this study here at UCSF. You will be randomly placed into a treatment group, and neither you nor your study doctor will know which treatment you are receiving.

What will happen if I take part in this research study?

Before you can start the study:

Pre-study visit: You will need to have the following exams, tests, and procedures to find out if you can be enrolled in the study. These exams, tests, and procedures are part of regular care for patients with suspected CMV anterior uveitis, and are routinely done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Initial removal of fluid from the front part of your eye (anterior chamber paracentesis): In our clinic we will anesthetise (or numb) your cornea with eye drops and carefully remove a small amount of fluid from inside the front portion of your eye using a small needle. The fluid will then be sent for laboratory testing to determine whether CMV is present in the fluid.
- Initial laboratory testing: we will order blood tests to look at your kidney function, red blood cell count, white blood cell count, and platelet count. Abnormal results will exclude you from participating in this study.
- Women of child-bearing age will undergo a blood pregnancy test, as some study medications can result in birth defects

During the main part of the study:

Exam #1: Approximately 7 days after completing the exams, tests, and procedures above, you will return for follow-up examination, and review of testing to determine if you can participate in this study. If eligible you will complete this form to give your consent to participate in this study. After completion, you will then be enrolled, and then "randomised" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group. All groups will receive their assigned treatment for 28 days. You will receive both oral tablets and topical eye drops. You will not know which ones are active or inactive. You will be instructed to take 4 pills per day, 2 every morning and 2 every evening. You will also be instructed to apply 1 drop of eye solution every 2 hours while awake. You will repeat this regimen every day for all 28 days of treatment. Participants in all groups will be receiving a steroid eye drop regimen of prednisolone acetate 1% three times per day in the affected eye. It is important to note that all three treatment groups are used by practicing ophthalmologists to manage

your condition. A current standard of care has not been defined, which is the question this study hopes to answer.

- **If you are in group 1** you will receive valganciclovir pills and inactive eye drops.
- **If you are in group 2** you will receive inactive pills and topical ganciclovir 2% eye drops.
- **If you are in group 3** you will receive inactive pills and inactive eye drops.

You will also need follow-up exams and tests that are part of regular CMV anterior uveitis care:

- Two follow-up clinic visits will be scheduled at day 7 (Exam #2) and day 28 (Exam #3) of treatment. At each of these visits you will be seen by an ophthalmologist. On study day 7 (Exam #2) we will again remove fluid from your eye (a second anterior chamber paracentesis), to see if the amount of virus in the eye has decreased.
- At day 7 and day 28 blood tests will be repeated. These will be compared with baseline kidney function and blood counts. Any abnormal findings will require removal from the study.

When you are finished with 28 days of treatment:

Once you have finished 28 days of treatment, including your final clinic visit and evaluation, you will have completed the study. Your treating ophthalmologist will determine whether any continued treatment is necessary.

Study location?

All study procedures will be done at the UCSF Proctor Clinic.

Study Chart

Visits	What happens
Pre-study visit	• Baseline fluid removal from the front of the eye using a needle • Baseline blood tests • Pregnancy testing for women of child-bearing age • Baseline clinical exam
Enrollment/ Randomization (Day 1)	• Follow-up clinical examination • Consent, Enrollment and randomization to treatment • Begin treatment: 2 pills twice daily, 6 drops per day • Corneal endothelial confocal microscopy
Exam #2	• Follow-up clinical exam

(Day 7)	• Repeat removal of fluid from the eye using a needle (anterior chamber paracentesis #2) • Repeat blood tests
Exam #3 (Day 28)	• Follow-up clinical exam • Repeat blood tests #2 • Corneal endothelial confocal microscopy

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks of the infection or stopping treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while in the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking these antiviral medications. In some cases, side effects can be serious, long lasting, or may never go away. In very rare cases, side effects may include death.

You should talk to your study doctor about any side effects you experience while taking part in the study.

Procedural risks:

The procedure to remove fluid from the eye (anterior chamber paracentesis) carries some risk whether they are performed in the study or as part of your routine care outside the study. The second anterior chamber paracentesis is being conducted as part of routine clinical care. It is a typically safe procedure, although some may experience pain or discomfort. To reduce discomfort, eye numbing drops will be given before the procedure is performed. A severe but extremely rare complication of this procedure includes blood accumulation in the eye (hyphema), persistent leakage of fluid from the eye (leakage of aqueous humour), infection inside the eye (endophthalmitis),

and traumatic cataract, which can affect vision. In extremely rare cases, endophthalmitis may require removal of the eye.

Medication risks:

	Valganciclovir	Topical Ganciclovir
Rare but Serious Side Effects	- Low red blood cell count causing anemia and fatigue - Low white blood cell count increasing risk of infection - Low platelet count leading to risk of bleeding - Kidney failure - Infertility - Birth defects (in pregnant women) - Cancer	- Allergic reaction
More Common but Less Serious Side Effects	- Diarrhea - Nausea - Vomiting - Stomach pain	- Burning sensation in eye - Temporary blurred vision
Less common and Less Serious Side Effects	- Fever - Headache - Sleep disturbances	- Eye redness - Eye irritation

Randomization risks:
You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatments or other available treatments.

Placebo (inactive) risks:
If you are in the group that receives placebo, your condition will go without the active (antiviral) treatment for 28 days. Some uveitis specialists will observe their patients with CMV anterior uveitis to see if the inflammation will resolve on its own or with just steroid eye drops. In such cases, starting oral or topical antivirals is reserved for when the inflammation does not become subside after 4 weeks. The risks of delaying treatment include damage to the cornea with a decrease in vision or the development of glaucoma, which can result in vision loss. However, many uveitis specialists feel that a reasonable and safe option in CMV anterior uveitis is to monitor initially without starting oral or topical antiviral medication.

Blood drawing (venipuncture) risks:

Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.

Reproductive risks:
You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while in this study. Acceptable forms of birth control include intra-uterine (placed inside the uterus), oral (birth control pills), birth control patch placed on your skin, or barrier (i.e. condoms). Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Unknown Risks:
The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

It is possible that one of the treatment options proves to treat CMV anterior uveitis better than the others, in which case your infection will be treated more effectively. It is also possible that one of the treatment options will prove to have fewer side effects or complications, in which case you will be subjected to fewer side effects.

Additionally, we hope this study will help doctors learn more about CMV anterior uveitis, and that this information will help in the treatment of future patients with conditions like yours.

What other choices do I have if I do not take part in this study?

If you choose not to take part in this study, your quality of care will remain the same. The fluid in your eye will still be sampled at the first visit in order to diagnose your infection. Your treatment regimen will be chosen and initiated at your treating ophthalmologist's discretion. At UCSF the standard of care includes oral valganciclovir 900 mg given twice daily or topical ganciclovir 2% provided by a compounding pharmacy for a period of 28 days, with routine follow-up and blood tests. Occasionally, some patients are monitored with just steroid eye drops and are not started on antivirals if the inflammation does not become quiet after approximately 28 days. Additionally, patients treated outside of the study may have a repeat (or second anterior chamber paracentesis) to demonstrate that the amount of virus in their ocular fluid is decreasing. Therefore, this trial is very similar to what happens in "real life".

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Authorised representatives from the following organizations may review your research data for the purpose of monitoring or managing the conduct of this study:

- Representatives of UCSF Proctor Foundation
- Representatives of the University of California
- Representatives of the Food and Drug Administration (FDA)

Are there any costs to me for taking part in this study?

Two types of procedures will be done during this study. Some are part of your standard medical care, such as the first eye fluid analysis, and others are primarily for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer. Although the second eye fluid removal is considered part of routine clinical care, the procedure and testing of fluid will be paid for at no cost to the participant.

All antiviral and inactive (placebo) therapy will be provided for you at no cost.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. John Gonzales, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him at 415-502-2664.

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical

treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Institutional Review Board at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who pays for this study?

Proctor Foundation/UCSF.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor John Gonzales, M.D., at 415-502-2664.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the office of the Institutional Review Board at 415-476-1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site 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.

CONSENT

Please read each sentence below and think about your choice. After reading each sentence, put your initials in the "Yes" or "No" box. If you have any questions about this study, please talk to the study doctor or nurse.

No matter what you decide to do, it will not affect your care.

1. My specimens and associated data may be kept for use in research to determine the amount of virus in my sample.

YES	*NO*

2. Someone may contact me in the future to ask me to take part in more research.

YES	*NO*

3. Any leftover fluid from your anterior chamber paracentesis samples will be collected at stored at UCSF/Proctor Foundation laboratory. In the future the following tests may be performed on any leftover fluid:

- Genetic sequencing of the DNA of CMV, which means identifying the strain of virus you may have based on its genetic signature.
- The duration of specimen retention will be until the specimen is used up.
- Your name and any identifying information will not be included in this stored sample (will become an anonymous sample) to protect your confidentiality/privacy
- Only UCSF researchers will have access to the specimens and the data.
- Your specimen will not be used for commercial value or gain, and subjects will not be paid for their sample
- Should you decide to request destruction of your sample, this will not be possible as your specimen will have been made anonymous and cannot be traced back to you.
- There will be no genetic testing on your own, human DNA, only on the virus (CMV).

YES	*NO*

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
Date	Person Obtaining Consent

Takhar JS, *et al. BMJ Open* 2019; 9:e033175. doi: 10.1136/bmjopen-2019-033175