Baricitinib for the Treatment of Ocular Mucous Membrane Pemphigoid

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A Introduction

A1 Study Abstract

Ocular mucous membrane pemphigoid (MMP) is an autoimmune, scarring conjunctivitis that can lead to vision loss and permanent disability. It is a rare disorder with an estimated incidence of 1 in 60,000. There are currently no FDA-approved medications for the treatment of mucous membrane pemphigoid, highlighting a clear unmet need.

At present, moderate to severe disease requires off-label use of potent immunosuppressive agents, such as oral anti-proliferatives (methotrexate, azathioprine, and mycophenolate), rituximab (RTX) or cyclophosphamide (CyC). Recently, Janus kinase (JAK) inhibition with baricitinib been reported to be successful in one case of ocular MMP. In addition, we have had success with JAK inhibition in 2 cases of ocular MMP after failure of RTX and CyC.

We propose a randomized, single-masked, two-arm study of baricitinib vs anti-proliferatives in 20 patients with ocular MMP.

A2 Primary Hypothesis

Baricitinib is efficacious in the treatment of ocular mucous membrane pemphigoid.

A3 Purpose of the Study Protocol

To conduct a pilot, single-masked, randomized trial comparing the efficacy of baricitinib vs. standard therapy with anti-proliferative to reduce disease activity in patients diagnosed with ocular mucous membrane pemphigoid.

B Background

B1 Prior Literature and Studies

MMP is a chronic, autoimmune disease that affects the mucosal membranes leading to oral, nasal, laryngeal, esophageal, and genital ulcers as well as a cicatrizing (scarring) conjunctivitis of the eyes. This process is thought to be due to auto-antibodies that bind the $\alpha 6\beta 4$ integrin of the basement membrane. Auto-antibody binding activates complement and drives immune cell infiltration into, and ultimately destruction of, conjunctival membranes. Incomplete control of the disease generally leads to a slow but progressive fibrotic process of the conjunctiva over months to years that can progress to severe vision loss and blindness. Ocular MMP affects approximately 1 in 60,000 individuals (*1*) and has no FDA-approved medical therapies. Patients are often treated with off-label use of a variety of immunosuppressants, including steroids, methotrexate, azathioprine, mycophenolate, rituximab, cyclophosphamide, intravenous immunoglobulin (IVIg), and anti-tumor necrosis factor (TNF) agents.

In the Washington University Ocular Inflammation Clinic, patients with ocular MMP are treated collaboratively by ophthalmologists (Drs. Huang and Margolis) and rheumatologists (Dr. Paley and colleagues). We have successfully treated two patients with ocular MMP with a JAK inhibitor (tofacitinib) after both had failed multiple other therapies: methotrexate, mycophenolate, rituximab, and cyclophosphamide as well as IVIg in one patient. Both patients showed an improvement in disease activity by 8 weeks of therapy with tofacitinib. The choice to initiate JAK inhibition was spurred by the prior publication of successful use of baricitinib in a patient with ocular MMP who had failed methotrexate, mycophenolate, rituximab, cyclophosphamide, IVIg, and adalimumab (*2*). Similar to what was observed in our two patients, the report noted improvement at 8 weeks of therapy with baricitinib.

B2 Rationale for this Study

Aside from the published case report and our own experience with refractory ocular MMP that responded to JAK inhibition, there are other reasons to think that baricitinib may be an effective agent in ocular inflammatory disease. Baricitinib is an orally available small molecule JAK inhibitor that is used to treat moderate to severe rheumatoid arthritis. Several inflammatory cytokines that activate JAK/STAT signaling have also been implicated in the pathogenesis of ocular MMP. For example, in conjunctival biopsies, the interleukins IL-6, IL-12, and IL-13 are upregulated in ocular MMP compared to healthy controls (*3, 4*). In the conjunctiva, IL-13 is produced by infiltrating T cells and acts as a chemoattractant for fibroblasts (*4*), likely contributing to the fibrotic phase of the disease. In a contemporaneous process, IL-6 is a pleiotropic cytokine that facilitates the recruitment of immune cells to inflamed tissues (*5*) and promotes their proliferation and differentiation (*6-8*). Of particular importance to ocular MMP, IL-6 is a growth factor for plasmablasts, which have been implicated as a source of auto-antibody production in several autoimmune diseases (*9-11*). As a result, baricitinib blocks multiple pro-inflammatory cytokines involved in the pathogenesis of ocular MMP.

C Study Objectives

C1 Primary Aim

Note: The outcomes for each eye eligible for the study will be assessed independently. See Table 1 for measurement frequency and evaluator.

Primary Endpoint:

- Treatment response of ocular inflammation based on conjunctival injection measured by ophthalmologic exam of the palpebral conjunctiva. This quantitative measurement is adapted from Munyangango *et al.* (*12*): Each eye is divided into quadrants and each quadrant is scored as listed below with the total sum being the sum of all 4 quadrants for a total score of 0-12 for each eye. A clinically meaningful response will be defined as a ≥30% reduction in the score for the eye.
    - 0 (white and quiet)
    - 1 (mild)
    - 2 (moderate)
    - 3 (severe)

C2 Secondary Aims

- A decrease of ocular inflammation to 0 for the eye (based on the primary endpoint score)
    - Only evaluated if primary endpoint is reached
- Change in best-corrected or pinhole distance visual acuity
    - Clinically meaningful improvement or worsening will be defined as a change in 10 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale
- Change in Fibrosis
    - e.g. symblepharon, fornix shortening, ankyloblepharon, entropion, trichiasis
    - Based on Tauber grade: each eye is scored 1-5 and sum is divided by 10.
    - Improvement or worsening will be defined by a change of 0.1 on 0.2 - 1 scale.
- Development of corneal involvement
    - Defined as interval development of punctate corneal epithelial keratitis, corneal epithelial defects, or conjunctivalization of the cornea
    - This will be assessed as present or absent
- Therapeutic response of extra-ocular manifestations, when applicable and available
    - See Table 2 below

C3 Exploratory Analysis

- Treatment response of ocular inflammation based on conjunctiva photography
    - Scored using the same scale as the primary endpoint
    - With and without a red free filter
        - Which offers clearer delineation of fibrosis and blood vessels
- Biospecimens such as blood and impression cytology of the ocular surface will be collected for identification of biomarkers. The biomarker testing may include, but is not limited to, RNA sequencing.
- Patient Reported Outcomes (PROs) will be measured by the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) and Skindex-16

C4 Preclinical Data

Baricitinib is a small molecule that reversibly inhibits Janus associated kinases (JAKs) with some selectivity for JAK1 and JAK2. JAKs execute cytokine receptor signaling by phosphorylation and activation of signal transducers and activator of transcription (STAT) proteins, which subsequently dimerize, enter the cell nucleus, and initiate transcription of numerous inflammatory genes. Topical administration of the JAK inhibitor tofacitinib has demonstrated efficacy in treating ocular inflammation in animal models (*13, 14*) and humans (*15, 16*).

There are no preclinical models of ocular mucous membrane pemphigoid.

C5 Clinical Data to Date

JAK inhibition with baricitinib has been successful in the treatment of ocular MMP for one patient who had failed methotrexate, mycophenolate, rituximab, cyclophosphamide, IVIg, and adalimumab (*2*). This report noted improvement at 8 weeks of therapy with baricitinib. Similarly, we have successfully treated two patients with ocular MMP with a JAK inhibitor (tofacitinib) after both had failed multiple other therapies: methotrexate, mycophenolate, rituximab, and cyclophosphamide as well as IVIg in one patient (James H *et al., in preparation*). Both patients showed an improvement in disease activity by 8 weeks of therapy with tofacitinib. Collectively, these cases suggest clinical efficacy of JAK inhibitors in the treatment of ocular MMP.

Baricitinib is an FDA-approved medication for the treatment of rheumatoid arthritis. Treatment with baricitinib leads to a clinical response starting 2-8 weeks after initiation of therapy (*17*). Administration of baricitinib is approved for 2mg daily for rheumatoid arthritis, however, the 4mg daily dose has demonstrated greater clinical efficacy (*18*).

C6 Dose Rationale and Risk/Benefits

Ocular MMP is a vision-threatening disease that risks permanent disability if left uncontrolled. This protocol is designed to demonstrate proof of concept that baricitinib is efficacious for ocular MMP. The 4mg dose of baricitinib was selected for several reasons. First, this was the dose used in prior publication of efficacy for the treatment of ocular MMP (*2*). Second, the 4mg dose of baricitinib is superior to the 2mg dose in the treatment of inflammatory disease such as rheumatoid arthritis (*17*). Third, the 4mg dose has a similar safety profile to anti-TNF agents (*18*), which are used off-label to treat ocular MMP. Thus, the 4mg dose was chosen to maximize the potential for efficacy while maintaining a similar risk profile to alternative off-label therapies.

D Study Design

D1 Overview or Design Summary

Since the safety profile of baricitinib is well established, we propose a pilot randomized trial focused on efficacy of baricitinib monotherapy compared to standard anti-proliferative monotherapy in the reduction of disease activity in ocular MMP.

Subjects with active ocular MMP based on ophthalmologic exam will be enrolled (*19*). Patients will be evaluated for eligibility criteria and enrolled at a screening visit (week 0). To minimize confounding contributors to active disease such as dry eye, trichiasis (trauma to ocular surface from inward turned eyelashes), and subclinical infection, patients will be treated empirically with lubricating drops (daytime) and ointment (night time), trichiatic eyelash removal, and antibiotic drops for 1 week prior to their baseline exam. This week of ocular surface optimization will also serve as a washout period for previous topical therapy. Patients will initiate therapy (baricitinib or anti-proliferative) after the baseline exam at week 1. Patients will be evaluated for disease activity at weeks 1 (baseline), 5 and 9. The evaluating cornea specialist will be masked with respect to the treatment arms. Our primary endpoint will be evaluated at week 9 (8 weeks of therapy) based on (a) the rate of response to JAK inhibition in our 2 previous patients, (b) rate of response to baricitinib in a prior report (one case) (*2*), and (c) the rapid clinical effect of JAK inhibition in other autoimmune diseases. The primary objective is to estimate clinical response in the baricitinib group compared to standard of care.

Patients will be treated with monotherapy in both study arms for weeks 1 through 9. After week 9, patients will have the opportunity to transition to an open-label extension of baricitinib 4mg daily for a period of 104 weeks. Combination therapy with anti-proliferatives (methotrexate, azathioprine, mycophenolate) will be allowed during the open label extension for active disease at or after week 9. Changes to anti-proliferatives are not allowed during week 0 through week 9, but are allowed during the open label extension. Steroids will not be used as this is not a part of our practice pattern at Washington University.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Patients are eligible to be included in the study only if they meet all the following criteria:

Type of Patient and Disease Characteristics

1. Are at least 18 years of age
2. Have a clinical diagnosis of Ocular Mucous Membrane Pemphigoid
    a. The treating ophthalmologist will have excluded alternative etiologies that can cause cicatrizing conjunctivitis such as:
        - Rosacea
        - Atopic dermatitis
        - Lichen Planus
        - Iatrogenic interventions, e.g. glaucoma eye drops
        - Stevens-Johnsons Syndrome
        - Graft vs Host Disease
3. Have active disease based on ophthalmologic exam

Patient Characteristics

4. Nonpregnant, nonbreastfeeding female or male patient
    a. Female patients of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with the opposite sex.
    b. Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 1 week following the last dose of investigational product. Periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.
    c. Otherwise, female patients of childbearing potential must agree to use 2 effective methods of contraception, where at least 1 form is highly effective, for the entirety of the study and for at least 1 week following the last dose of investigational product.
    d. The following contraception methods are considered acceptable (the patient should choose 2, and 1 must be highly effective [defined as less than 1% failure rate per year when used consistently and correctly]):
        - Highly effective birth control methods:
            - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
            - Progestogen- only containing hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
            - intrauterine device (IUD)/intrauterine hormone-releasing system (IUS)
            - vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
        - Effective birth control methods:
            - Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
                - Diaphragm with spermicide
                - Cervical sponge
                - Cervical cap with spermicide

Note: When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed.

Female patients of non–child-bearing potential are not required to use birth control and they are defined as:

- Women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation)
- Post-menopausal – defined either as
  - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has either
    - Cessation of menses for at least 1 year
    - At least 6 months of spontaneous menorrhea with follicle-stimulating hormone >40 mIU/mL
  - Women aged 55 years or older who are not on hormone therapy, and who have had at least 6 months of spontaneous amenorrhea
  - Women aged 55 years or older who have a diagnosis of menopause

Informed Consent

5. Must read and understand the informed consent approved by the institutional review board (IRB)/ethics review board (ERB) governing the site and provide written informed consent.

2.a Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

Disease Characteristics

6. Have rapidly progressive disease, as determined by the treating ophthalmologist, that places the patient at an unacceptable risk for participating in the study

Medical Conditions

7. Have had any major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator would pose an unacceptable risk to the patient.
8. Have experienced any of the following within 12 weeks of screening: VTE (DVT/pulmonary embolism [PE]), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure.
9. Have a history of recurrent (≥ 2) VTE (DVT/PE).
10. Have a history or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders or any other serious and/or unstable illness that in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data.
11. Have a history of lymphoproliferative disease; have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years prior to randomization.

    The following may be exempted:

    a. Patients with cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease for at least 3 years may participate in the study.

b. Patients with basal cell or squamous epithelial skin cancers that have been completely resected with no evidence of recurrence for at least 3 years may participate in the study.

12. Have a current or recent (<4 weeks prior to randomization) clinically serious viral, bacterial, fungal, or parasitic infection or any other active or recent infection that in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.

    Note: For example, a recent viral upper respiratory tract infection or uncomplicated urinary tract infection need not be considered clinically serious.

13. Have symptomatic herpes simplex at the time of randomization
14. Have had symptomatic herpes zoster infection within 12 weeks prior to randomization
15. Have a history of disseminated/complicated herpes zoster (for example, ophthalmic zoster or CNS involvement).
16. Have a positive test for hepatitis B virus (HBV) defined as:
    a. positive for hepatitis B surface antigen (HBsAg), or
    b. positive for hepatitis B core antibody (HBcAb) and positive for hepatitis B virus deoxyribonucleic acid (HBV DNA)

       Note: Patients who are HBcAb-positive and HBV DNA-negative may be enrolled in the study but will require additional HBV DNA monitoring during the study.

17. Have hepatitis C virus (HCV) infection (hepatitis C antibody-positive and HCV ribonucleic acid [RNA]-positive).

    Note: Patients who have documented anti-HCV treatment for a past HCV infection AND are HCV RNA-negative may be enrolled in the study.

18. Have evidence of HIV infection and/or positive HIV antibodies
19. Have had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB
20. Have evidence of active TB or latent TB
    a. Have evidence of active TB, defined in this study as the following:
       - Positive purified protein derivative (PPD) test (≥5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, clinical features, and abnormal chest x-ray at screening
       - QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB

    Exception: patients with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray at screening (i.e., chest imaging performed within the past 6 months will not be accepted).

    b. Have evidence of untreated/inadequately or inappropriately treated latent TB, defined in this study as the following:

- Positive PPD test, no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening; or
- If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines). If the test results are not negative, the patient will be considered to have latent TB (for purposes of this study); or
- QuantiFERON®-TB Gold test or T- SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. If the test results are positive, the patient will be considered to have latent TB. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study).

Exception: Patients who have evidence of latent TB may be enrolled if he or she completes at least 4 weeks of appropriate treatment prior to randomization and agrees to complete the remainder of treatment while in the trial.
Exception: Patients with a history of latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray at screening (i.e., chest imaging performed within the past 6 months will not be accepted).

21. Have received any of the following medications:
    a. Cyclophosphamide (or any other cytotoxic agent) within 4 weeks of screening.
    b. Rituximab or any other B cell depleting therapies within 12 weeks of screening.
22. Have been treated with probenecid that cannot be discontinued for the duration of the study.
23. Have been exposed to a live vaccine within 12 weeks of randomization or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination).

    Note: All patients who have not previously received the herpes zoster vaccine by screening will be encouraged (per local guidelines) to do so prior to randomization; vaccination with live herpes zoster vaccine must occur >4 weeks prior to randomization and start of investigational product. Patients will not be randomized if they were exposed to a live herpes zoster vaccination within 4 weeks of planned randomization. Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination of patients ≥18 years of age with nonlive vaccines intended to prevent infectious disease prior to entering patients into the study.

24. Are currently enrolled in or have discontinued within 4 weeks of screening from any other clinical trial involving an investigational product or nonapproved use of a drug or device or any other type of medical research judged not to be scientifically or medically compatible with this study.
25. Have screening laboratory test values, including thyroid-stimulating hormone (TSH), outside the reference range for the population that, in the opinion of the investigator, pose an unacceptable risk for the patient's participation in the study. Patients who are receiving thyroxine as replacement therapy may participate in the study, provided stable therapy has been administered for ≥12 weeks and TSH is within the laboratory's reference range.

Patients who have TSH marginally outside the laboratory's normal reference range and are receiving stable thyroxine replacement therapy may participate if the treating physician has documented that the thyroxine replacement therapy is adequate for the patient

26. Have any of the following specific abnormalities on screening laboratory tests from the central or local laboratory
    a. ALT or AST >2 x upper limits of normal (ULN)
    b. alkaline phosphatase (ALP) ≥2 x ULN
    c. total bilirubin ≥1.5 x ULN
    d. hemoglobin <10 g/dL (100.0 g/L)
    e. total white blood cell count <3000 cells/μL (<3.00 x 10^3/μL or <3.00 billion/L)
    f. neutropenia (absolute neutrophil count [ANC] <1500 cells/μL) (<1.50 x 10^3/μL or <1.50 billion/L)
    g. lymphopenia (lymphocyte count <1000 cells/μL) (<1.00 x 10^3/μL or <1.00 bilion/L)
    h. thrombocytopenia (platelets <100,000 cells/μL) (<100 x 10^3/μL or <100 billion/L)
    i. eGFR <60 mL/min/1.73 m^2 (Bedside Schwartz formula 2009)

    In the case of any of the aforementioned laboratory abnormalities, the tests may be repeated once during screening, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion

Other Exclusions

27. Are largely or wholly incapacitated permitting little or no self-care, such as being bedridden or confined to wheelchair
28. In the opinion of the investigator, are at an unacceptable risk for participating in the study
29. Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study
30. Have a history of intravenous drug abuse, other illicit drug abuse, or chronic alcohol abuse within the 2 years prior to screening or are concurrently using, or expected to use during the study, illicit drugs (including marijuana)

    Note: Patients who are prescribed medical marijuana by a physician are not excluded from the study.

31. Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures
32. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

2.b Ethical Considerations

There are no currently FDA-approved medications for the treatment of ocular mucous membrane pemphigoid.

We have designed this study to compare baricitinib monotherapy with anti-proliferative monotherapy. One ethical concern is that subjects enrolled in this study may be placed at risk of ocular damage due to uncontrolled disease if baricitinib is not efficacious. We believe the design of this study minimizes those risks for the following five reasons. (1) In most cases, ocular MMP is a slowly progressive disease with accumulation of ocular damage occurring over years. (2) The study design measures disease activity at an early time point that limits accumulation of irreversible scarring while still being able to measure changes in disease activity. (3) Subjects with residual disease activity at week 9 will be transitioned to

combination therapy with baricitinib and anti-proliferatives as rescue therapy. (4) Subjects with rapidly progressive disease (as determined by the treating ophthalmologist) are excluded from the study. (5) We will perform an interim analysis after half the patients have reached the primary endpoint in order to evaluate whether to terminate the trial early due to lack of efficacy. As a result, this study design reduces the risk of lack of efficacy to study participants.

While a placebo-controlled study can provide the strongest evidence for efficacy, use of a placebo arm (either alone or in addition to anti-proliferatives) creates ethical concerns for patients with active disease. In contrast, our study design provides active therapy for all participants. In order to be able to enroll as many patients as possible, this proposal offers several anti-proliferatives for standard of care so that patients will not be prescribed a previously-failed therapy.

2.c Subject Recruitment Plans and Consent Process

Patients seen in the clinical offices of the Department of Ophthalmology & Visual Sciences and the Division of Rheumatology at Washington University will be consented in a private room within the clinical office.

2.d Randomization Method and Blinding

Subjects will be randomized using sealed envelopes in a 1:1 ratio to either baricitinib 4mg daily or to standard of care with an anti-proliferative, such as methotrexate, azathioprine, or mycophenolate. Small block sizes will be used. The Biostatistics core in the Department of Ophthalmology and Visual Sciences will prepare a randomization schedule. A duplicate randomization schedule will be retained in a REDCap HIPAA-compliant database.

For participants randomized to the anti-proliferative group, the anti-proliferative they receive (methotrexate, azathioprine, or mycophenolate) will be decided based on comorbidities and treatment history. If no contraindications, we typically use methotrexate first, mycophenolate second, and azathioprine third; however this will be decided by the physician.

2.e Risks and Benefits

As with other immunosuppressive treatments to control autoimmune diseases, the patients will be at increased risk of serious infections, which may result in hospitalization and/or fatality. Infections are more likely to develop in patients receiving concomitant immunosuppressive agents (e.g., methotrexate, corticosteroids), which is only applicable during rescue therapy. Other risks include upper respiratory infection (16%), nausea (3%), herpes zoster infection (1%), and laboratory abnormalities (1-2%). Laboratory abnormalities include:

- Hematologic toxicity, including lymphopenia, anemia, and neutropenia
- ALT and AST elevation

Lymphoma and other malignancies have been reported in patients receiving baricitinib.

Tuberculosis (pulmonary or extrapulmonary) has been reported in patients receiving baricitinib. Standard laboratory screening is performed in all patients to assess for latent / chronic infection, such as TB.

Thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis have been observed in patients receiving baricitinib; these may be serious and life-threatening. Patients at increased risk of DVT/PE are excluded from the trial.

There is a risk associated with lack of efficacy. Patients will have the opportunity to switch to rescue therapy with combined baritinib and anti-proliferative treatment.

Potential benefits include improved control of the ocular inflammatory disease and prevention of permanent vision loss. The participants may also derive satisfaction from contributing to medical research.

2.f Early Withdrawal of Subjects

Participants may withdraw at any time from the study. They will be asked to undergo an Early Exit Visit. The Early Exit Visit will include the following procedures:

- If prior to week 9, the visit will include medication collection, ocular exam, photography, patient survey, adverse event collection, and biospecimen collection.
- If after week 9 during open label extension, the visit will include adverse event collection.

2.g When and How to Withdraw Subjects

Participants will contact the researcher if they wish to withdraw.

2.h Data Collection and Follow-up for Withdrawn Subjects

Participants who withdraw will no longer be followed in the study.

2.i Temporary Discontinuation of Therapy

i Indications for temporary discontinuation of therapy

In some circumstances, patients may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to baricitinib.

Abnormal laboratory findings:

1. ANC < 1 x 10^9 cells/L
2. ALC < 0.5 x 10^9 cells/L
3. Hb < 8 g/dL
4. ALT or AST > 5x ULN

Clinical events:

5. Symptomatic Herpes Zoster
6. Infection that, in the opinion of the investigator, merits baricitinib being interrupted

ii Monitoring after temporary discontinuation of therapy

Abnormal laboratory findings:
Serial CBC and/or CMP will be obtained every 1 to 4 weeks at the discretion of the treating physician.

Clinical events:
Patients will be monitored as clinically indicated until resolution of infection and the completion of antivirals or antibiotics.

iii Reinitiation of therapy

Abnormal laboratory findings:

1. Return of ANC to > 1 x 10^9 cells/L
2. Return of ALC to > 0.5 x 10^9 cells/L
3. Return of Hb to > 8 g/dL
4. Return of ALT and AST to < 2x ULN and baricitinib is considered not to be the cause of the enzyme elevation

Clinical events:

5. All skin lesions have crusted and are resolving
6. Resolution of infection that, in the opinion of the treating physician, merits baricitinib being restarted.

2.j Permanent Discontinuation of Therapy

i Indications for cessation of therapy

1. The patient or the patient's designee requests to discontinue investigational product.
2. Abnormal laboratory findings:
   a. ALT or AST >8 x ULN
   b. ALT or AST >5 x ULN for more than 2 weeks after temporary interruption of investigational product
   c. ALT or AST >3 x ULN and total bilirubin level (TBL) >2 x ULN or international normalized ratio (INR) >1.5
   d. ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
   e. ALP >3 x ULN that is deemed to be of liver origin and drug-related
   f. ALP >2.5 x ULN and TBL >2 x ULN
   g. ALP >2.5 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
   h. White blood cell count <1000 cells/μL (1.00 x 103/μL or 1.00 billion/L)
   i. ANC <500 cells/μL (0.50 x 103/μL or 0.50 billion/L)
   j. Lymphocyte count <200 cells/μL (0.20 x 103/μL or 0.20 billion/L)
   k. Hemoglobin <6.5 g/dL (<65.0 g/L)

   Note: Temporary interruption rules must be followed where applicable. For laboratory values that meet permanent discontinuation thresholds, investigational product should be discontinued. However, if in the opinion of the treating physician, the laboratory abnormality is due to intercurrent illness such as cholelithiasis or another identified factor, laboratory tests may be repeated. Only when the laboratory value meets resumption thresholds following the resolution of the intercurrent illness or other identified factor may the treating physician restart baricitinib after consultation with the independent medical monitor, Dr. Musiek.

3. Clinical events:
   a. Pregnancy
   b. Malignancy

c. HBV DNA detected with a value above limit of quantitation
d. Development of a VTE (DVT/PE) during the study

ii Monitoring after treatment cessation

Patients who permanently discontinue baricitinib treatment will remain in the study and be followed to obtain safety data.

2.k Adjustment of therapy

Indications for adjustment of therapy

1. Patients who develop impaired renal clearance (GFR 40 to 60 mL/minute/1.73 m2).

Adjustment therapy

1. The dose of baricitinib will be held or reduced (e.g. from 4mg to 1 or 2mg daily) at the discretion of the treating physician.

D3 Study Drug

3.a Description

Baricitinib is a small molecule that inhibits Janus kinase (JAK). Specifically, it inhibits JAK1 and to a lesser extent JAK2. This inhibition occurs downstream of multiple pro-inflammatory cytokines, such as IL-2, IL-6, & IFN, and explains the anti-inflammatory effects of baricitinib. It has demonstrated clinical efficacy in rheumatoid arthritis.

3.b Treatment Regimen

Study Drug: Baricitinib will be taken as 4mg daily orally.

Antiproliferatives: The target dose of methotrexate, azathioprine and mycophenolate will be 20mg weekly, 2mg/kg daily, and 1g twice daily, respectively, all in oral formulation. Dosing of anti-proliferatives may be adjusted (e.g. decreased) based on toxicity and tolerability.

3.c Method for Assigning Subjects to Treatment Groups

Subjects will be assigned to treatment groups by the research coordinator using sealed envelopes in a 1:1 provided by the Biostatistics core in the Department of Ophthalmology and Visual Sciences. A duplicate randomization schedule will be retained in a REDCap HIPAA-compliant database.

3.d Preparation and Administration of Study Drug

Preparation is not required. Baricitinib will be provided by Eli Lilly, the manufacturer of the drug. The research team will provide pre-packaged bottles to the patients. Antiproliferatives will be prepared by the pharmacy. Patients will self-administer baricitinib and antiproliferatives.

3.e Subject Compliance Monitoring

Patients will be asked to present empty medication bottles to demonstrate adherence during regular clinical follow-up.

3.f Prior and Concomitant Therapy

During Masked Trial Period

Due to the need to maximize the number of eligible patients to meet recruitment goals, no type of prior therapy is prohibited. Prior therapy, however, must be discontinued upon study enrollment. Concurrent systemic immunotherapy is not allowed until the patient requires rescue therapy at week 9.

Patients will have eye lubricant and topical antibiotics to use prior to visits associated with weeks 1, 5, and 9.

Ocular surface optimization will be achieved with lubricating drops (daytime), lubricating ointment (night time), and antibiotic drops for the 7 days preceding visits 2 (week 1), 3 (week 5), and 4 (week 9). Recommended formulation (and dosing) is preservative-free artificial tears (1 drop, four times per day), lubricating ophthalmic ointment (applied at bedtime), and moxifloxacin 0.5% (1 drop, four times per day); however, the selection and dosing of therapy will ultimately be up to the treating ophthalmologist.

Patients will undergo trichiatic eye lash removal (epilation) at week 0 and subsequently as needed by the treating ophthalmologist.

During Open Label Extension and Rescue Therapy

Combination therapy with baricitinib and anti-proliferatives (methotrexate, azathioprine, and mycophenolate) is allowed if the patient requires rescue therapy at week 9.

Patients will undergo trichiatic eye lash removal (epilation) as needed by the treating ophthalmologist.

3.g Packaging

Packaging will be provided by Eli Lilly, the manufacturer of the drug.

Packaging of antiproliferatives will be performed by the pharmacy.

3.h Masking of Study Drug

This is a single masked study where the evaluator of disease activity is masked to treatment.

3.i Receiving, Storage, Dispensing and Return

The baricitinib will be shipped to the PI who will store the drug in a locked room at room temperature. An established and validated local temperature management system with temperature logs will be used to record the storage temperature. The research team will dispense baricitinib to the patients during their clinical visit.

Antiproliferatives will be dispensed to the patients from the pharmacy.

E Study Procedures

E1 Screening for Eligibility

Clinicians and research coordinators on the research team will identify potential participants via a computerized search for relevant diagnoses and via clinical identification of ocular MMP during patient encounters. The clinician and/or research coordinator will discuss the study with potential participants during the patient encounter. Consent will be signed prior to drug administration.

E2 Measurements

- Visual Acuity is measured with the ETDRS chart.
- Intraocular pressure will be measured by Goldmann Applanation Tonometer.
- Disease activity (of the eye) is measured by ophthalmology exam.*
- Fibrosis is measured by ophthalmology exam.*
- Patient Reported Outcomes are measured by the NEI VFQ-25) and Skindex-16.
- Biospecimens to be collected at blood, tears, and impression cytology of the conjunctival surface.
    - Blood will be collected in 4 purple top tubes and processed in the Yokoyama Lab
    - Tears wil be collected with a glass micropipette and processed in the Yokoyama Lab
    - Impression cytology will be collected with filter paper and processed in the Huang Lab or Yokoyama Lab.

* Drs. Huang and Margolis are ophthalomogists with subspecialty training in corneal disease. These two investigators will perform all slit-lamp examinations.

E3 Schedule of Measurements

Schedule of measurements are listed in Table 1.

E4 Initial Visit (Week 0; screening)

- Informed consent
- Inclusion/Exclusion criteria verification
- Medical history and Demographics
- Concomitant Medication collection
    - Dose of medications used to treat increased intraocular pressure
    - Dose of topical and/or systemic medications
- Ophthalmology data
    - Visual Acuity
    - Intraocular pressure
    - Disease activity assessment
    - Fibrosis assessment
    - Corneal Disease
    - Extraocular Manifestations
- Provide Subject Study Handout
- Provide Drug Package Insert
- Randomization

- Laboratory blood draw
- Chest Xray if prior history of TB (laboratory or clinical evidence)
    - To be obtained during visit or prior to week 1 visit
- Undergo trichiatic eye lash removal (epilation); this may also be done subsequently throughout their participation as needed by the treating ophthalmologist

Patients will have eye lubricant and topical antibiotics to use prior to visits associated with weeks 1, 5, and 9.

At the time of consent, participants will be asked in the consent form if they agree to allow data and biospecimens to be stored for use in future studies.

E5 Baseline Visit (Week 1)

- Concomitant Medication collection
    - Dose of medications used to treat increased intraocular pressure
    - Dose of topical and/or systemic medications
- Ophthalmology data
    - Visual Acuity
    - Intraocular pressure
    - Disease activity assessment
    - Fibrosis assessment
    - Corneal Disease
    - Extraocular Manifestations
- Conjunctiva photography
- Patient Survey / Patient Reported Outcomes
- Collection of Biospecimens (blood, tears, and impression cytology)
- Dispense Study Drug

E6 Subsequent visit (Week 5)

- Concomitant Medication collection
    - Dose of medications used to treat increased intraocular pressure
    - Dose of topical and/or systemic medications
- Ophthalmology data
    - Visual Acuity
    - Intraocular pressure
    - Disease activity assessment
    - Fibrosis assessment
    - Corneal Disease
    - Extraocular Manifestations
- Conjunctiva photography
- Patient Survey / Patient Reported Outcomes
- Adverse Event Collection
- Dispense Study Drug

E7 Subsequent visit (Week 9)

- Concomitant Medication collection
    - Dose of medications used to treat increased intraocular pressure
    - Dose of topical and/or systemic medications

- Ophthalmology data
    - Visual Acuity
    - Intraocular pressure
    - Disease activity assessment
    - Fibrosis assessment
    - Corneal Disease
    - Extraocular Manifestations
- Conjunctiva photography
- Patient Survey / Patient Reported Outcomes
- Adverse Event Collection
- Collection of Biospecimens (blood, tears, and impression cytology)
- Dispense Study Drug for participants continuing on open label extension treated with study drug

E8 Open-Label Extension

- Research visits will occur in conjunction with clincal visits as per standard of care
- Adverse Event Collection
- Dispense Study Drug for participants continuing on open label extension treated with study drug
- Patients will undergo trichiatic eye lash removal (epilation) as needed by the treating ophthalmologist.

Participants who take part in the Open-Label Extension will be asked if they agree to optional biospecimen collection that would occur approximately every 6 months. The first collection will occur approximately 6 months after they start the trial, and would occur approximately every 6 months after that. The exact timing of when the biospecimens are collected would be dependent on when participants have standard of care visits.

E9 E-mail and Text Message Communication

Participants may be contacted through e-mail or text message to facilitate execution of the study. For example, participants may be contacted regarding scheduling appointments, appointment reminders, need to contact the study team / treating physician about labs or imaging.

E10 Safety and Adverse Events

10.a Safety and Compliance Monitoring

Safety and compliance monitoring will be performed by research coordinator at weeks 5 and 9 and in conjunction with clinical visits during open label extension.

Patients will return empty bottles of baricitinib to demonstrate compliance.

10.b Medical Monitoring

i Data Safety Monitoring

The independent medical monitor Dr. Amy Musiek will review the study data every 6 months until study completion.

ii Hepatitis B Virus DNA Monitoring

Hepatitis B virus DNA testing will be performed in enrolled patients who tested positive for HBcAb at screening.

Patients who are HBcAb-positive and HBV DNA-negative (undetectable) at Visit 1 will require HBV DNA monitoring every 3 months and at the patient's last visit, regardless of their hepatitis B surface antibody (HBsAb) status. The every 3 month monitoring would only be for those who choose to also take part in the open-label extension portion.

The following actions should be taken in response to HBV DNA test results

- If a single result is obtained with a value "below limit of quantitation," the test should be repeated within approximately 2 weeks.
- If the repeat test result is "target not detected," monitoring may resume according to the study schedule.
- If the patient has 2 or more test results with a value "below limit of quantitation" during the study, HBV DNA testing should be performed approximately once per month for the remainder of the study and referral to a hepatologist is recommended.
- If a result is obtained with a value above limit of quantitation at any time during the study, the patient will be permanently discontinued from investigational product and should be referred to a hepatology specialist immediately

10.c Definitions of Adverse Events (AEs)

An adverse event is any untoward medical occurrence (including an abnormal laboratory finding), in a patient or clinical trial subject administered a medicinal product temporally associated with the use of a study agent(s), whether or not related to the study agent(s), occurring as soon as the patient has signed the informed consent form and at any time during the study. All adverse events always must be recorded in the CRF. AEs also include an undesirable medical condition occurring, even if no study treatment has been administered Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect

10.d Definition of Serious Adverse Events (SAEs)

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

10.e Pregnancy

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

10.f Classification of Events

i Relationship

For all AEs, the investigator will assess the causal relationship between baricitinib and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE:

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to baricitinib, taking into account the disease, concomitant treatment or pathologies.

A “reasonable possibility” means that there is a cause and effect relationship between baricitinib and the AE. The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

ii Severity

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

iii Expectedness

Unanticipated problems are defined as:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.g Data Collection Procedures for Adverse Events

Patients will be interviewed about adverse events during scheduled follow-up for the duration of the study. Laboratory studies will be reviewed at each visit per protocol for the first 9 weeks and then per standard of care for the open label extension.

10.h Reporting Procedures

Information on serious adverse event reporting will be provided in letter of agreement with Eli Lilly.

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at any Washington University or Barnes Jewish Hospital institution

- Any unanticipated problems that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

10.i Serious Adverse Event Reporting Period

These events must be reported to the IRB within 10 working days of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within 1 working day of the occurrence of the event or notification to the PI of the event

10.j Post-study Adverse Event

Post-study adverse events will be identified through routine follow-up of these patients with chronic diseases by their treating rheumatologist for 60 days after study completion.

E11 Study Outcome Measurements and Ascertainment

1. Visual acuity will be measured by Early Treatment Diabetic Retinopathy Study chart
2. Intraocular Pressure will be measured by tonometry
3. The primary endpoint (disease activity) will be a calculated score as described above based on ophthalmologic exam by a cornea specialist
4. Fibrosis will be based on Tauber grade from ophthalmologic exam by a cornea specialist
5. Corneal involvement will be based on ophthalmologic exam by a cornea specialist
6. Therapeutic response of extra-ocular manifestations will be measured via a skin exam and calculated based on Table 2
7. Conjunctiva photography will be obtained using a slit-lamp-mounted camera
8. Patient Reported Outcomes (PROs) such as the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) and Skindex-16 will be collected by the research coordinator via patient survey

F Statistical Plan

F1 Sample Size Determination and Power

The study is mainly designed as a pilot study to estimate the treatment response and variability of ocular MMP to baricitinib for induction of low disease activity. The sample size of 20 (10 per group) was selected to collect data to determine if further studies of baricitinib would be justified. The study was not powered to provide sufficient power for a formal test of therapeutic effect, but to detect a signal for efficacy. The rationale for *n* of 20 assumes a two-sided alpha error rate of 0.10 rather than 0.05 and statistical power of 0.4, 0.7, and 0.9 for effect sizes ranging from 0.6, 1.0, and 1.3 respectively. Effect size is the ratio of the mean difference between active vs. placebo groups divided by their common standard deviation. An effect size of 0.2 would be considered a small therapeutic effect, 0.5 a medium effect, and 0.8 a large effect (*20*).

F2 Interim Monitoring and Early Stopping

An interim analysis will be conducted after 10 patients have been assessed for disease activity at week 9. The review will be conducted by the biostatistician Dr. Gordon, the independent medical monitor, Dr. Musiek, and consultant, Dr. Strand. Collaborators, including Drs. Paley, Huang, and Margolis, will be masked to the interim results, except in the event of early termination of the study. No formal statistical test will be conducted at the time of the interim analysis. We will determine if further recruitment is justified based on all data, in particular effect size, from 10 patients. If the standard care group is superior to the baricitinib group, then a decision to terminate the study will be considered. In this manner, the number of patients exposed to inferior experimental treatment is minimized (*21*). A formal interim analysis is not justified given the low statistical power of the study and the uncertainties of parameters needed to estimate statistical power.

F3 Analysis Plan

The statistical analysis plan focuses on the detection of a signal for efficacy-an estimate of effect size and variance of efficacy outcomes. The primary outcome measure will be disease activity determined by the sum of inflammation scores of each eye.

F4 Statistical Methods

The primary hypothesis will be analyzed using data from both eyes of each patient in a nested, repeated measures analysis of variance model with randomization as a fixed effect. Data will be transformed if needed to meet assumptions of parametric modeling.

F5 Missing Outcome Data

Patients with missing outcome data in the primary endpoints will be censored for the initial analysis for efficacy.

F6 Unmasking Procedures

The data will be unmasked at the conclusion of the trial. Drs. Paley, Huang, and Margolis, will be masked to the interim results, except in the event of early termination of the study.

G Data Handling and Record Keeping

G1 Confidentiality and Security

Consents will be scanned into the medical record. Original hard copies of consents will be secured under two keys and two locks in a locked file-cabinet within a locked office. Prospective clinical data will be collected during the study and entered into RedCap (a HIPAA-compliant and password-protected database.) All aspects of the medical record will be analyzed including age, sex, office visit data, phone number, MRN, chief complaint, history of present illness, past medical and surgical history, past ocular history, medications, allergies, exam findings, studies including clinical images, ultrasound, and radiographic studies, laboratory and pathology data, diagnosis, assessment and plan as well as clinical outcomes. Data sent to Eli Lilly will be de-identified.

Biospecimens will be de-identified and labeled with study number, tissue isolate, and date of collection. Blood and tear samples are stored in a locked freezer in the Yokoyama Lab. Impression cytology samples will be stored in the Huang Lab.

G2 Training

All researchers have undergone confidentiality and ethical training through Washington University.

G3 Records Retention

Electronic records of patient treatment will be stored in the electronic medical record (EMR) and in REDCap. Consents will be scanned into the EMR. These will be saved for the lifespan of the EMR and REDCap. Hard copies of records (e.g. consents) will be kept in compliance with the University policies.

H Study Monitoring, Auditing, and Inspecting

H1 Study Monitoring Plan

The investigators will meet every 4 weeks to review study data to detect early evidence of unanticipated harm to subjects. The review will focus on safety data including but not limited to serious adverse drug events, drug exposure, laboratory test results, and vital signs measurements as well as the rate of treatment failure.

H2 Auditing and Inspecting

2.a Audits

In order to guarantee that the conduct of the study is in accordance with good clinical practice and national laws, audits may be performed at the study sites to be carried out by an independent auditor. In addition, for-cause audits may be scheduled. The investigators agree to give the auditor access to all relevant documents for review.

2.b Inspections

Inspections of the study sites may be performed by the local or regulatory authorities at any time during or after completion of the study. The investigators agree to give the inspectors access to all relevant documents for review.

I Study Administration

I1 Organization and Participating Centers

Principal Investigator: Michael Paley MD, PhD

See IRB submission for complete list of participating clinicians and research coordinators.

This is a single-site study at Washington University.

I2 Funding Source and Conflicts of Interest

This trial is sponsored by Eli Lilly. The research team members do not currently have any financial conflicts of interest. The PI will maintain records during the trial regarding whether any research team members have financial conflicts of interest.

I3 Subject Stipends or Payments

Subjects will receive stipends of $50 for each study visit, 4 in total.

I4 Study Timetable

Planned Start Date: November 1st, 2020
Planned Completion Date: December 31st, 2022

J Publication Plan

The results of this study will be submitted for publication to a peer-reviewed journal.

K Attachments

K1 Tables

Table 1

Measurement	Timepoints	Grader
1^{ary}: Disease activity	Weeks 0, 1, 5, & 9	Drs. Huang and Margolis*
2^{ary}: Visual Acuity	Weeks 0, 1, 5, & 9	Research Coordinator
2^{ary}: Fibrosis	Weeks 0, 1, 5, & 9	Drs. Huang and Margolis*
2^{ary}: Corneal Disease	Weeks 0, 1, 5, & 9	Drs. Huang and Margolis*
2^{ary}: Extraocular Manifestations	Weeks 0, 1, 5, & 9	Dr. Paley
Intraocular Pressure	Weeks 0, 1, 5, & 9	Research Coordinator
Exploratory: Photographs	Weeks 1, 5, & 9	Research Coordinator
Exploratory: Biospecimens / Biomarkers	Weeks 1 and 9	Dr. Paley
Exploratory: PROs (NEI & Skindex)	Weeks 1, 5, & 9	Research Coordinator
Laboratory monitoring (CBC, CMP, Lipid)	Weeks 0 & 9	Dr. Paley
Infection monitoring (T.spot & HBV/HCV)	Week 0	Dr. Paley
Adverse Event Collection	Weeks 1, 5 & 9	Research Coordinator
Concurrent Medication Collection	Weeks 0, 1, 5, & 9	Research Coordinator
Medical History and Demographics	Week 0	Research Coordinator

*Drs. Huang and Margolis are ophthalomogists with subspecialty training in corneal disease. These two investigators will perform all slit-lamp examinations.

Table 2: Adapted scoring from Munyangango *et al.* for grading of extraocular disease:

Surface	Score	Definition of Activity	Score	Definition of Damage
Gingiva [a]	0	No Erythema	0	No erythema
	1	Erythema in 1 segment with no erosion	2	Scar(s) in 1 segment
	2	Erythema in 1 or 2 segments or erosion(s) in 1 segment	4	Scars in 2 segments or atrophy in 1 segment
	3	Erythema in 3 or 4 segments or erosions in 2 segments	6	Scars in 3 segments, atrophy in 2 segments or synechia(e) in 1 segment
	4	Erythema in 5 or 6 segments or erosions in 3 segments	8	Scars in 4 segments, atrophy in 3 segments or synechiae in 2 segments
	5	Generalized ulcerative 'desquamative gingivitis'	10	Scars in 5 segments, atrophy in 4 or 5 segments or synechiae in > 2 segments
Nongingival segments [b]	1	Erythema in 1 segment with no erosion		
	2	Erythema in 2 segments or erosion(s) in < 25% of 1 segment		
	3	Erythema in 3 segments, erosions in 25–49% of 1 segment or erosions in < 25% of 2 segments		
	4	Erosions in 50–75% of 1 segment, erosions in 25–49% of 2 segments or erosions in < 25% of 3 segments		
	5	Erosions in > 75% of 1 segment, erosions in 50–75% of 2 segments, erosions in 25–49% of 3 segments or erosions in < 25% of 4 segments		
Nose	0	No Erythema		
	1	Erythema with no erosion		
	2	Erosions present		
Genital Mucous Membrane [c]	2	Erythema in 1 segment with no erosion	2	Scar(s) in 1 segment
	4	Erythema in 1 or 2 segments or erosion(s) in 1 segment	4	Scars in 2 segments
	6	Erythema in 3 or 4 segments or erosions in 2 segments	6	Scars in 3–5 segments
	8	Erythema in 5 segments or erosions in 3 segments	8	Synechiae in 1–5 segments
	10	Erosions in > 3 segments	10	Stenosis

Surface	Score	Definition of Activity	Score	Definition of Damage
Anal Mucous Membrane [d]	2	Erythema in 1 segment	2	Scar in 1 segment
	4	Erythema in 2 segments or 1 erosive segment	4	Scars in 2 segments
	6	Erythema in 3 or 4 segments or 2 erosive segments	6	Scars in 3 or 4 segments
	8	Erythema in 5–7 segments or 3 erosive segments	8	Scars in 5 segments
	10	≥ 3 erosive segments	10	Stenosis

[a] Gingiva is divided into six segments: upper and lower anterior segments, defined as extending in front of the incisors and the canines, and left and right posterior segments (×4).
[b] Oral non-gingival segments include buccal mucosae (×2), soft palate, hard palate, tongue and floor, lips.
[c] Genital mucous membrane includes five segments: clitoris–vestibule, labia majora (×2)/minora (×2) for women, meatus, glans (two halves), prepuce (two halves) for men.
[d] Anal area includes seven segments: perianal quadrants (×4), anal canal, posterior line, perineal segment.

K2 Informed consent documents

See separate informed consent document in IRB submission.

K3 Questionnaires or surveys

Patients will be asked to complete the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) and Skindex-16 at baseline and on return visits while on therapy.

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