Adalimumab in **J**uvenile Idiopathic Arthritis-associated **U**veitis **S**topping **T**rial **(ADJUST)**

Protocol Number: 17-23987

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STATEMENT OF COMPLIANCE

ADJUST will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Eye Institute's Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

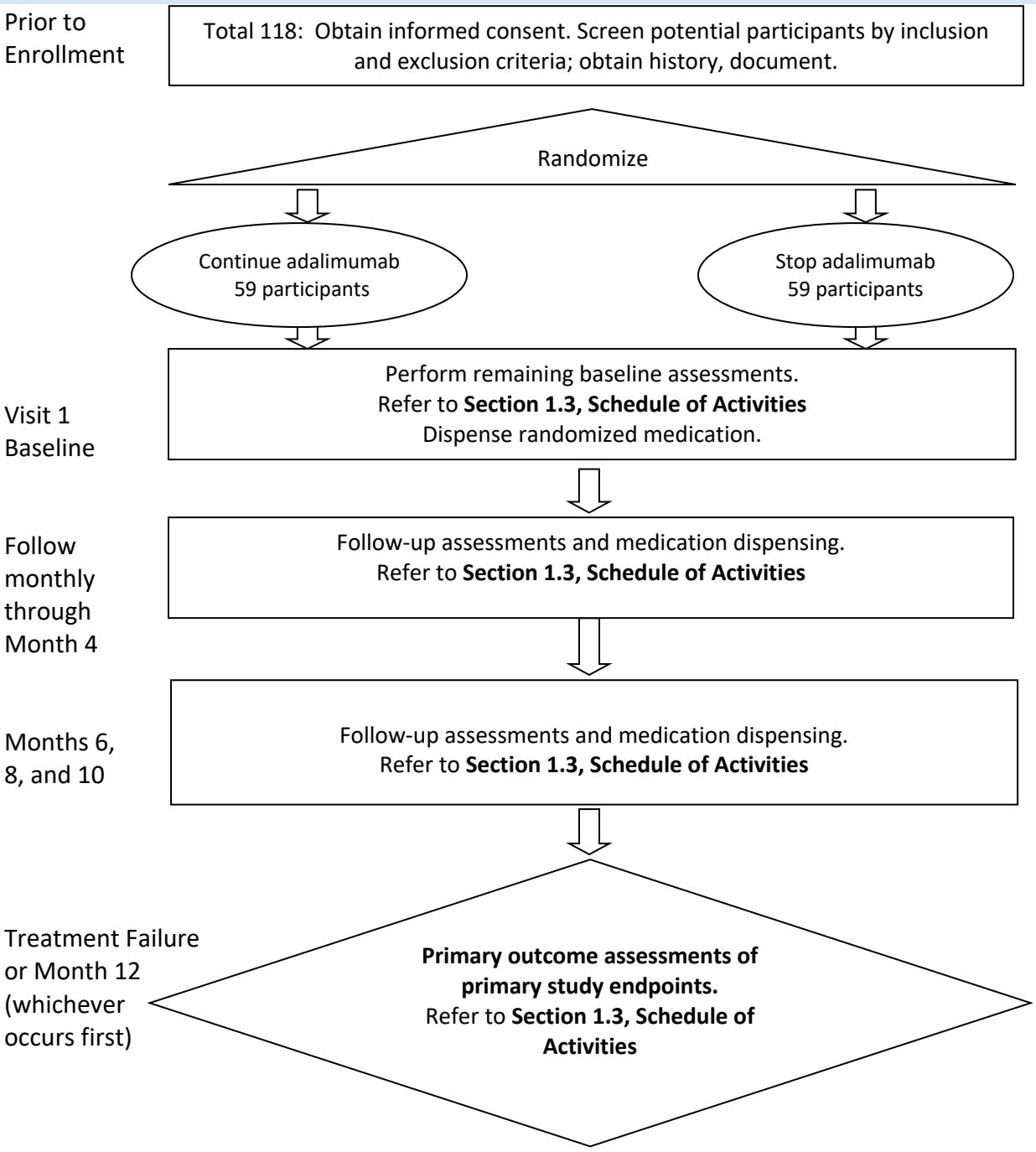
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Adalimumab in Juvenile Idiopathic Arthritis-associated Uveitis Stopping Trial (ADJUST)
Study Description:	Multicenter, block-randomized, double-masked, placebo-controlled trial to compare the safety and efficacy of stopping adalimumab treatment versus continuing adalimumab treatment in patients with uveitis associated with juvenile idiopathic arthritis (JIA) or patients with chronic anterior uveitis (CAU). 118 patients with JIA-associated uveitis or CAU, with control of ocular inflammation on adalimumab will be randomized to either continue adalimumab at their current dose or stop adalimumab. Patients will complete monthly visits for 4 months in addition to visits at 6, 8, 10, and 12 months.
Objectives:	Primary Objective: To compare time to recurrence of ocular inflammation between patients with JIA-associated uveitis or CAU, randomized to stop adalimumab treatment and patients randomized to continue treatment. Secondary Objectives: To determine predictors of JIA-associated uveitis or CAU disease recurrence. To compare 6- and 12-month outcomes between the two treatment groups.
Endpoints:	Primary Endpoint: Time to treatment failure, up to 12 months post-randomization.

Study Population:	118 patients ≥2 years of age in the U.S., UK, and Australia, with a history of JIA-associated uveitis or chronic anterior uveitis. Original diagnosis must have been made prior to 16 years of age (but patients can be >16 at time of enrollment). Patients must have achieved steroid-sparing control of ocular inflammation and inactive arthritis on adalimumab or a biosimilar of adalimumab for ≥12 consecutive months. Patients may not have used systemic corticosteroid or ocular corticosteroid injection within the last 180 days and must be on ≤2 drops daily of 1% prednisolone acetate with stable dose for ≥90 days. The dose of adalimumab must be stable for ≥180 days and should be no greater than 40mg biweekly for patients ≥30kg and 20mg biweekly for patients <30kg. If on a concomitant antimetabolite, dose must be stable for ≥90 days and ≤25mg weekly for methotrexate, ≤3g daily for mycophenolate mofetil, ≤250 mg daily for azathioprine, or ≤ 20 mg daily for leflunomide.
Phase:	IV
Enrollment Centers:	10 centers in the U.S., 9 in the UK, and 1 in Australia. Additional sites may be added during the study to facilitate enrollment.
Description of Study Intervention:	Adalimumab administered subcutaneously or placebo administered subcutaneously. Patients randomized to continue adalimumab will remain on the same dosage at which they entered the trial. Standard dosages in clinical practice are 40mg every other week for patients ≥30kg and 20mg every other week for patients <30kg. The volume-matched placebo will be administered every other week. If on methotrexate or mycophenolate mofetil, patients will continue their same dose during the trial.
Study Duration:	Anticipated project duration of five years with enrollment starting in March 2020 and completion of analysis and publication by December 2025.
Participant Duration:	Each individual participant will complete all study assessments during a 48-week period.

1.2 SCHEMA


Prior to Enrollment
Total 118: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Continue adalimumab 59 participants
Stop adalimumab 59 participants
Visit 1 Baseline
Perform remaining baseline assessments.
Refer to Section 1.3, Schedule of Activities
Dispense randomized medication.
Follow monthly through Month 4
Follow-up assessments and medication dispensing.
Refer to Section 1.3, Schedule of Activities
Months 6, 8, and 10
Follow-up assessments and medication dispensing.
Refer to Section 1.3, Schedule of Activities
Treatment Failure or Month 12 (whichever occurs first)
Primary outcome assessments of primary study endpoints.
Refer to Section 1.3, Schedule of Activities

1.3 SCHEDULE OF ACTIVITIES (SOA)

Visit Schedule

Visit	Code	Week *	Window (weeks)
Baseline	BL	0	
Month 1	M1	4	2 - 6
Month 2	M2	8	>6 - 10
Month 3	M3	12	>10 - 14
Month 4	M4	16	>14 - 18
Month 6	M6	24	>22 - 26
Month 8	M8	32	>30 - 34
Month 10	M10	40	>38 - 42
Month 12	M12	48	>46 - 50
AE check phone call	Other	58	>56 - 60

***** since baseline / first treatment administration

Study Visit Assessment Schedule

	Baseline[a]	Months 1-4	Month 6	Months 8 & 10	Month 12	Treatment Failure[b]	Additional Visit[c]
Informed consent	✓						
Confirmation of eligibility criteria	✓						
Medical history and demographic data collection	✓						
Complete ophthalmic exam	✓	✓	✓	✓	✓	✓	✓
Visual acuity	✓	✓	✓	✓	✓	✓	✓
OCT	✓	✓	✓	✓	✓	✓	✓
Serum chemistry and complete blood count	✓	Month 3[d]	✓	Month 8 or 10[d]	✓	✓[e]	✓[c]
MRP8/14 serum levels	✓		✓		✓	✓	
Anti-adalimumab antibody levels	✓		✓		✓	✓	
Blood draw for biobanking	✓		✓		✓	✓	
Rectal swab	✓				✓	✓	
Pregnancy test for women of reproductive age	✓	✓	✓	✓	✓		✓
Monitoring for arthritis activity	✓	Month 3	✓		✓	✓[e]	
Review of AEs[f]	✓	✓	✓	✓	✓	✓	✓
Quality-of-life questionnaires	✓		✓		✓	✓	
Medication dispensing	✓	✓	✓	✓		(✓)[g]	
Review of treatment adherence and concomitant therapy		✓	✓	✓	✓	✓	✓

[a]All baseline data must be collected at or within 14 days from the date of consent, with the exception of laboratory measurements. The baseline laboratory measurements may be collected no more than 30 days prior or up to 14 days after the date of consent. Baseline data are encouraged to be collected on the date of the Baseline visit, which is when the patient is randomized.

[b]Note that treatment failure can occur at any time, including an unscheduled visit.

[c]90-day follow-up visit is necessary for patients who experience a late treatment failure where there is < 90 days of follow-up remaining in the regular follow-up period. Patient will need standard of care labs if they are on an antimetabolite and if more than 90 days have passed since their last standard of care labs.
[d]Standard of care labs should be checked every 3 months for patients on antimetabolites (Baseline, Month 3, Month 6, on or any time between Month 8 and Month 10, Month 12, and Treatment Failure if it occurs), and every 6 months for patients not on antimetabolites (Baseline, Month 6, Month 12, and Treatment Failure if it occurs).
[e]Assessment does not need to be re-performed if done within 14 days prior to the patient's treatment failure visit.
[f]Adverse Event (AE) check phone call: Patients are contacted approximately 70 days after their last study visit. Only the AE form is completed.
[g]Patients randomized to continue adalimumab and patients randomized to stop adalimumab who have a treatment failure and restart will be provided open-label drug until Month 12 (or Month 15 if treatment failure occurs at Month 12).

Form Completion Schedule

After completing each study visit, study coordinators will review the electronic case report forms for completion and accuracy and submit them electronically via REDCap. If study visit data are recorded on hard copies of the forms, these paper copies should be scanned and emailed to the Coordinating Center (ADJUST@ucsf.edu) and kept in a secure location at the site. All US centers are part of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and submit data to the registry for their JIA patients. As we are collecting similar data on an overlapping patient population, CARRA has allowed us to use their data collection forms. We will collect data using forms developed specifically for ADJUST in addition to several forms from the CARRA registry that are applicable to the study procedures and data collected for this study.

	Baseline	Months 1-4	Month 6	Months 8 & 10	Month 12	Treatment Failure[a]	Additional Visit[b]
Patient Consent Forms	✓						
Eligibility and Screening Form	✓						
Baseline Treatment Assessment Form	✓						
Baseline Demographics Form	✓						
Baseline Ophthalmology Form	✓						
Baseline Rheumatology Form	✓						
Clinical Eye Exam Form	✓	✓	✓	✓	✓	✓	✓
Arthritis Evaluation Form	✓	Month 3	✓		✓	✓	
Visual Acuity Form	✓	✓	✓	✓	✓	✓	✓
OCT Form	✓	✓	✓	✓	✓	✓	✓
Standard of Care Lab Form	✓	Month 3[c]	✓	Month 8 or 10[c]	✓	✓	✓[b]
Research Sample Lab Form	✓		✓		✓	✓	
Adverse Event Checklist	✓	✓	✓	✓	✓	✓	✓[d]
Quality-of-Life Questionnaires (CHAQ, CVFQ, EYE-Q, EQ-5D-Y)	✓		✓		✓	✓	
Treatment Assessment Form[e]	✓	✓	✓	✓	✓	✓	✓
Medication Adherence Log	✓	✓	✓	✓	✓	✓	✓
Patient Dropout Form (if applicable)		(✓)	(✓)	(✓)	(✓)	(✓)	(✓)

Serious Adverse Event Narrative Form (if applicable)		(✓)	(✓)	(✓)	(✓)	(✓)	(✓)
Protocol Deviation Form (if applicable)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)
Interim Masking Decision Form (if applicable)[f]		(✓)	(✓)	(✓)			(✓)

[a]Treatment failure can be declared at any visit, including an unscheduled visit.

[b]90-day follow-up visit is necessary for patients who experience a late treatment failure where there is < 90 days of follow-up remaining in the regular follow-up period. Patient will need standard of care labs if they are on an antimetabolite and if more than 90 days have passed since their last standard of care labs.

[c]This form should be completed when standard of care labs are checked. For patients not on antimetabolites, this means Baseline, Month 6, Treatment Failure if it occurs, and Month 12. For patients on antimetabolites, standard of care labs should also be checked at Month 3, and at or any time between Month 8 and Month 10 visits.

[d]Will also be completed at the AE check phone call, approximately 70 days after the last study visit.

[e]If the patient did not experience Treatment Failure prior to February 14, 2024, the Follow-Up Treatment Assessment form should be completed at all visits going forward, regardless of if/when the patient is later unmasked. If the patient had already experienced treatment failure prior to February 14, 2024, the Unmasked Treatment Assessment form is sufficient for all future visits.

[f]To be completed at the next study visit after February 14, 2024, if the patient had not already been unmasked due to Treatment Failure.

2 INTRODUCTION

2.1 STUDY RATIONALE

Juvenile Idiopathic Arthritis (JIA)-associated uveitis and chronic anterior uveitis (CAU) can lead to significant vision loss early in life. Adalimumab, an anti-Tumor Necrosis Factor alpha (TNF-α) monoclonal antibody, is an effective treatment for refractory, JIA-associated uveitis and CAU. However, there are concerns regarding long-term adverse events associated with adalimumab treatment. In addition to possible detrimental effects of long-term treatment, the financial burden associated with adalimumab is a motivating factor for stopping treatment. There are no prospective studies examining uveitis recurrence rates after stopping adalimumab treatment in patients with JIA-associated uveitis or CAU who have achieved control of inflammation. Identifying potential predictors of recurrence of ocular inflammation could inform treatment decisions for personalized care. The potential for drug resistance further warrants the development of treatment guidelines. The results of this proposed study will provide evidence for the safety and utility of stopping adalimumab treatment in patients with JIA-associated uveitis or CAU.

2.2 BACKGROUND

Chronic, asymptomatic, anterior uveitis occurs in 12-38% of all patients with juvenile idiopathic arthritis (JIA) within 7 years of the onset of arthritis. 20-25% of all pediatric uveitis is associated with JIA.[1–3] There is significant evidence of poor long-term visual outcomes for JIA-associated uveitis, with as many as one third of all patients developing substantial visual impairment and 10-15% becoming legally blind.[4–6]

It is well-recognized that there is a chronic anterior uveitis phenotype in children that looks identical to chronic JIA-associated uveitis, but without the history of arthritis.[7] Chronic anterior uveitis (CAU) does not have systemic manifestations of disease but presents similarly in the eye and can result in identical visual complications as JIA-associated uveitis. A large, population-based analysis using data from the National Paediatric Rheumatological Database in Germany showed that chronic anterior uveitis in children without arthritis appears to take a course similar to that of uveitis in patients with JIA and thus should be managed similarly.[8] It is thought that the arthritis may not have been clinically detected since it is often mild in these patients, or that treatment that was initiated for uveitis masked the symptoms of arthritis. The European Medicines Agency (EMA) also considers pediatric chronic anterior uveitis without systemic symptoms to be comparable to JIA-associated uveitis from a treatment standpoint.[9]

While the primary interest of this study is JIA-associated uveitis, the inclusion of this secondary group of patients with chronic anterior uveitis (henceforth referred to as 'CAU') presenting with the same phenotype will increase generalizability and facilitate enrollment.

While methotrexate is the mainstay of long-term, immunomodulatory therapy for JIA-associated uveitis and CAU, previous studies have shown that anywhere from 15-50% of affected children will have refractory uveitis despite adherence to methotrexate treatment.[10–13] Both human and animal models have suggested the pro-inflammatory cytokine TNF-α may play a role in both JIA and uveitis pathogeneses.[14–16] Given its demonstrated efficacy in clinical trials, adalimumab has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of both JIA and non-infectious intermediate, posterior, and panuveitis.[17] Adalimumab has also been shown to effectively control inflammation in more than 80% of JIA-associated anterior uveitis cases, leading to its approval for use for this indication within the National Health System (NHS) in the UK.[18,19]

Despite strong evidence for adalimumab's short-term efficacy for treating JIA-associated uveitis and CAU, there is a lack of evidence regarding long-term treatment outcomes for such patients.[2,3,18–24] There is some evidence to suggest that patients on adalimumab may have higher rates of adverse events compared to patients on methotrexate alone.[25] In addition, anti-TNF-α therapy may harbor a risk of malignancy and opportunistic infection.[26–34] These health concerns contribute to a growing interest in the possible cessation of adalimumab after a patient with JIA-associated uveitis or CAU has achieved disease control.

Anti-TNF-α therapy is expensive to the patient and healthcare system.[35,36] A single dose of adalimumab costs £350 under NHS England.[36] A 2013 study found that, on average, a person with health insurance coverage in the U.S. pays $26,537 for adalimumab in the first year of treatment.[37] Some patients may lose coverage for the drug, which may cause them to stop treatment for financial reasons. For example, the NHS England interim policy on anti-TNF-α treatment for pediatric uveitis mandates stopping treatment after 18 months and will discontinue financial coverage of adalimumab after this time.[38]

While there is evidence to support the short-term effectiveness of treating JIA-associated uveitis and CAU with adalimumab, there have been no studies reporting on the ability to successfully taper or discontinue treatment when remission is presumed. There are limited data on discontinuation of other immunosuppressive treatments in JIA-associated uveitis and CAU. Data on withdrawal of immunomodulatory therapy in patients with JIA-associated uveitis or CAU and on discontinuation of anti-TNF-α treatment in patients with other autoimmune diseases both suggest a high relapse rate when stopping therapy after control of inflammation.[39–47] Collectively, these studies suggest that discontinuation of adalimumab carries a risk of disease recurrence in patients with autoimmune conditions.

While there has yet to be any clinical trial on discontinuation of adalimumab in patients with JIA-associated uveitis or CAU, other observational studies have suggested that certain clinical characteristics such as duration of treatment or duration of inactive disease may be associated with likelihood of disease recurrence.[39,47] In addition to use of clinical parameters to inform treatment decisions, there is interest in finding potential biomarkers that can predict disease relapse. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in the blood serve as measures of non-specific, systemic inflammation and have been suggested as predictors of flare in JIA.[48,49] The protein complex formed between MRP 8 and MRP 14 (calprotectin) has shown promise as a potential indicator of both relapse of rheumatic disease and response to anti-TNF-α treatment.[50–54] Evaluating MRP8/14 serum levels in JIA-associated uveitis and CAU may uncover a key biomarker for ocular disease relapse or drug response that could inform ophthalmic treatment decisions.

Previous studies have found that between 9.2% and 32% of patients on adalimumab treatment developed antibodies against the drug.[55–57] There is evidence to suggest that patients with uveitis who develop adalimumab antibodies may have worse ocular inflammatory outcomes compared to patients without these antibodies.[56] Furthermore, preliminary data on discontinuation of anti-TNF-α therapy have also raised concerns that patients may exhibit reduced sensitivity when retreated with the anti-TNF-α agent after disease recurrence.[41,43] There are no published data addressing the safety of stopping adalimumab from an ocular standpoint, especially concerning development of reduced efficacy of anti-TNF-α therapy in the eye.

As the use of biologics in uveitis becomes increasingly common, questions regarding the safe and efficient use of anti-TNF-α therapy become increasingly relevant. In this multicenter, observer-masked, randomized clinical trial, we will compare rates of reactivation of ocular inflammation and adverse events

in patients with JIA-associated uveitis or CAU randomized to either continue their current treatment regimen of adalimumab or discontinue adalimumab. Addressing these clinically relevant research aims will provide a stronger evidence base for informing treatment guidelines for long-term use of adalimumab in patients with JIA-associated uveitis and CAU.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Based on product insert information,[58] the risks associated with adalimumab treatment include:

- Serious infections
- Reactivation of tuberculosis or new tuberculosis in patients with latent tuberculosis
- Malignancies
- Hypersensitivity reactions (localized rash, anaphylaxis, and angioneurotic edema)
- Injection-site pain
- Hepatitis B virus reactivation
- Neurologic reactions (multiple sclerosis, optic neuritis, peripheral demyelinating disease)
- Hematologic reactions (thrombocytopenia, leukopenia)
- Congestive heart failure
- Development of lupus-like syndrome (new formation of autoantibodies)
- Liver enzyme and creatinine elevations

Based on product insert information,[59] risks associated with methotrexate treatment include:

- Infection
- Nausea or vomiting
- Mild abdominal pain
- Dizziness
- Diarrhea
- Alopecia
- Leukopenia
- Elevated liver enzymes
- Potential for folic acid deficiency (patients should take folic acid supplements while on methotrexate)
- Rarely, an increased risk of severe opportunistic infection
- Rarely, an increased risk of cancer

Based on product insert information, risks associated with mycophenolate mofetil include:

- Infection
- Nausea or vomiting
- Mild abdominal pain
- Muscle aches
- Fatigue
- Diarrhea
- Hypertension
- Leukopenia

- Elevated liver enzymes
- Sepsis
- Rarely, an increased risk of severe opportunistic infection
- Rarely, an increased risk of cancer

Risks of treatment with placebo injection may include:

- Injection-site pain
- Localized rash

Risks of participating in the study include:

- Possible discomfort while undergoing eye exam
- Possible discomfort or bruising from venipuncture for lab tests

2.3.2 KNOWN POTENTIAL BENEFITS

Potential benefits for adalimumab treatment:

- Reduction in signs and symptoms of JIA or CAU
- Reduction in signs and symptoms of uveitis

Potential benefits for placebo treatment:

- Reduced exposure to adalimumab treatment and its associated risks of adverse events

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Given the lack of information on the risk of recurrence of inflammation after stopping adalimumab, it is reasonable to expose participants to a treatment strategy of stopping therapy. The risks are particularly reasonable, given that patients must have achieved control of inflammation for at least 12 consecutive months while on adalimumab to be eligible for participation in the study.

Because JIA-associated uveitis and CAU are chronic diseases and standard clinical practice is to treat these conditions with long-term immunomodulatory therapy, it is reasonable to expose participants to continuing adalimumab treatment for up to 12 additional months. Adalimumab is FDA-approved in the same formulation and dosage as use in this trial for the indications of polyarticular JIA in children 2 years of age or older and for treatment of uveitis in adults. In addition, the NHS has approved adalimumab for the treatment of pediatric anterior uveitis and JIA-associated uveitis in the same formulation and dosage as used for this trial. Patients will be followed on a monthly basis and can stop treatment at any time if safety or tolerability issues arise that are suspected to be related to the study treatment.

This study will provide data on uveitis recurrence rates in patients with JIA-associated and CAU treated with adalimumab. Additionally, the study will provide further safety data on long-term use of adalimumab. The findings of this study will provide a stronger evidence base to inform safe and effective treatment strategies for patients with JIA-associated uveitis and CAU. The benefits of developing additional evidence-based clinical practice guidelines for this patient population outweigh the risks of participation.

3 OBJECTIVES AND ENDPOINTS

See the Statistical Analysis Plan (SAP) for details about the objectives, endpoints, and analysis.

3.1 TREATMENT FAILURE

Patients can discontinue the study treatment due to lack of efficacy and be declared a treatment failure if they have recurrence of ocular inflammation and/or recurrence of joint inflammation that is persistent and severe enough to necessitate unmasking to manage the arthritis recurrence.

Ocular inflammation is defined as ≥2-step increase in AC cell from baseline, observed at 2 consecutive visits at least 7 days apart; >0.5+ AC cell for ≥28 days; ≥3+ AC cell at a single visit; or >0.5+ vitreous haze, active retinal/choroidal lesions, or macular edema at a single visit.

Macular edema is defined as central subfield thickness on OCT > 2 standard deviations above normal thickness (>320µm on Spectralis or >300µm on Zeiss or Topcon) and having a greater than 20% increase from baseline *and/or p*resence of intraretinal or subretinal fluid.

Patients with ocular inflammation that meets one of the treatment failure thresholds should return for an evaluation to evaluate whether the increased inflammation is sustained (called the Treatment Failure visit), as close to the 7- or 28-day period as possible, but no earlier.

Criteria for recurrence of ocular inflammation (at least one of the following in at least one eye)

Parameter	Definition
Anterior chamber cells*	≥2-step increase** at two separate visits ≥7 days apart >0.5+ cell observed for ≥28 days ≥3+ cell observed at a single visit
Vitreous haze***	>0.5+ haze at a single visit
Choroid & retina	Active retinal / choroidal inflammation and/or macular edema in either eye at a single visit. Macular edema is defined as central subfield thickness on OCT > 2 standard deviations above normal thickness (>320µm on Spectralis or >300µm on Zeiss or Topcon) and having a greater than 20% increase from baseline *and/or p*resence of intraretinal or subretinal fluid

*SUN criteria; **increase is based on inflammation at baseline[60]; ***NEI vitreous haze grading scale[61]

Patients who meet the treatment failure threshold of ocular inflammation at Month 12 will be re-evaluated after the Month 12 visit to assess for sustained inflammation which would result in treatment failure. If inflammation is sustained at the follow-up visit, then treatment failure is declared. At this point, patients and doctors will be unmasked, and doctors can treat per best medical judgement. Patients in the placebo arm will be encouraged to restart adalimumab. The date of treatment failure is defined as the date of the initial visit when the ocular inflammation reached the threshold. A minimum of 90 days of follow-up is required following treatment failure, so if treatment failure is declared with fewer than 90 days remaining in the 12-month follow-up period, follow-up may be extended to up to 15 months. Regardless of the course of treatment pursued after treatment failure, all patients will be followed through Month 12 or a minimum of 90 days, whichever is longer.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypotheses for this trial include:

1) Patients who stop adalimumab will have a shorter time to uveitis recurrence compared to those who continue treatment. Patients randomized to continue treatment will have a higher rate of adverse events compared to patients randomized to stop treatment.
2) Patients with higher serum levels of MRP8/14, higher ESR, higher ADA, and higher CRP will have a higher uveitis recurrence rate compared to patients with lower serum levels. In addition, period of inactive uveitis, age at randomization, and duration of adalimumab treatment before randomization will be associated with uveitis recurrence rate.
3) A smaller proportion of patients who stop adalimumab will have controlled ocular inflammation at Month 6 and Month 12 compared with patients who never stop adalimumab. In addition, among patients who stop adalimumab and have a uveitis recurrence, anti-adalimumab antibodies will be associated with a longer time to regaining uveitis control after restarting treatment. MRP8/14 levels will be associated with the likelihood of establishing control of ocular inflammation after restarting adalimumab treatment following uveitis recurrence.

This study is a phase IV clinical trial.

The study design is a multicenter, randomized, placebo-controlled, superiority trial comparing stopping adalimumab treatment to continuing adalimumab treatment for patients with JIA-associated uveitis or CAU who have achieved corticosteroid-sparing control of inflammation on 12 consecutive months of adalimumab or a biosimilar treatment. Patients randomized to continue adalimumab treatment will receive the standard clinical practice weight-based dose of adalimumab. Patients in both arms will remain on their current dose of concomitant antimetabolite therapy if applicable. Further detail on dosing and administration of study treatment is provided in **Section 6.1.2.**

Randomization will be stratified by use of concomitant antimetabolite therapy and by country. Patients will be treated as originally randomized until treatment failure is declared, at which point, they may be treated per best medical judgement. The primary outcome will be time to treatment failure (as defined in **Section 3** primary endpoint) up to 12 months post-randomization. Rates of disease recurrence and rates of adverse events will also be compared between the two treatment groups. All patients will be followed through Month 12 for the purpose of obtaining secondary, long-term clinical outcome data.

Patients originally randomized to stop adalimumab treatment who experience a treatment failure may restart adalimumab treatment during the trial and will be assessed at Month 12. Primary outcome analysis will be intent-to-treat, but a secondary per-protocol analysis will be performed, and subgroup analyses will be performed on patients who stop and restart adalimumab treatment. Further detail on statistical analysis is provided in **Section 9.4.**

MRP8/14 serum levels, ESR, CRP, and adalimumab antibody levels will also be measured periodically during the trial. These biomarkers will be assessed as potential predictors for disease recurrence in patients with JIA-associated uveitis or CAU.

The trial will have 10 enrollment centers in the U.S., 9 in the UK, and 1 in Australia. Additional sites may be added during the study to facilitate enrollment. U.S. study sites will include the F.I. Proctor

Foundation at University of California San Francisco (UCSF), Children's Hospital of Philadelphia, Cincinnati Children's Hospital, Children's Mercy Hospital in Kansas City, MO, University of Utah Health in Salt Lake City, Colorado Retina Associates in Lakewood, CO, University of California Davis Eye Center in Sacramento, CA, Vanderbilt Eye Institute in Nashville, TN, University of Texas in Austin, TX, and University of Miami, FL. UK study sites will include Great Ormond Street Hospital in London, University Hospitals Bristol, Alder Hey Children's Hospital in Liverpool, Great North Children's Hospital in Newcastle, Sheffield Children's Hospital, Cambridge University Hospital, Royal Manchester Children's Hospital, University Hospital of Leicester, and Norfolk and Norwich University Hospital. The Australian study site is The Royal Children's Hospital in Melbourne.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Justification for placebo treatment: As both patients and those assessing outcomes could introduce bias, complete masking of the treatment is ideal for this study. This concern is especially pertinent for the pediatric population, since it is difficult to prevent young patients from discussing their treatment with their physician. Our primary outcome is time to treatment failure, where treatment failure is defined as a recurrence of ocular inflammation (≥2-step increase in AC cell observed at 2 consecutive visits at least 7 days apart; >0.5+ AC cell for ≥28 days; ≥3+ AC cell observed at a single visit; or >0.5+ vitreous haze, active retinal/choroidal lesions, or macular edema at a single visit) and/or a recurrence of joint inflammation that is persistent and severe enough to necessitate unmasking to manage the arthritis recurrence. While an attempt will be made to ensure the grading of ocular inflammation is as standardized as possible, complete removal of subjectivity in inflammation grading is impossible. Furthermore, we plan to assess adverse events and quality of life as secondary outcomes, which rely on patient self-report. Given that self-report is involved in both the primary and secondary outcome assessments, masking of subjects is also necessary to remove any potential bias in assessing the outcomes for our study.

Justification for superiority: There is clinical utility in determining if one treatment plan is more effective for reducing the risk of recurrence of ocular inflammation. The findings of this trial could provide justification for either stopping adalimumab or continuing adalimumab for long-term management of JIA-associated uveitis and CAU, which are chronic conditions. Therefore, a superiority trial design is warranted.

Potential problems with placebo treatment: We hypothesize that stopping adalimumab will result in a shorter time to treatment failure and higher uveitis recurrence rates compared to continuing adalimumab. In anticipation of this possibility, we have allowed for patients to restart adalimumab or be treated per best medical judgement for the remainder of the study period. The primary analysis will be intent-to-treat, but we will also collect clinical outcome data at Month 12 to assess whether the initial strategy of stopping treatment results in worse outcomes compared to the initial strategy of continuing therapy.

4.3 JUSTIFICATION FOR DOSE

Patients randomized to continue adalimumab will receive the standard clinical practice weight-based dose of adalimumab. The standard clinical practice is self-administration of adalimumab subcutaneously at a dose of 40mg every other week for patients ≥30kg and 20mg every other week for patients <30kg. Patients randomized to stop adalimumab will receive placebo treatment. The volume-matched placebo will be administered subcutaneously for masking purposes every other week.

Patients must be on a stable dose of adalimumab or a biosimilar of adalimumab for a minimum of 180 days prior to randomization at a maximum dose of 40mg every other week. Patients receiving treatment on a weekly basis will not be eligible for the study. Treatment must be decreased to every other week and remain stable for at least 180 days in order to gain eligibility. We expect most patients will be on the appropriate weight-dependent dose of adalimumab. In the event that a patient is on a higher dose than appropriate for their weight (i.e. 40mg biweekly if <30kg), this dose must be tapered to 20mg biweekly and must be stable for at least 180 days prior to enrollment. In the event that a patient is on a lower dose than appropriate for their weight (i.e. 20mg biweekly if ≥30kg), they may enroll in the trial as long as the dose has been stable for at least 180 days and uveitis and arthritis have been inactive (per definitions above) for at least 12 months, and if randomized to continue adalimumab they will receive the standard weight-based dose. During the course of the study, any patient receiving the lower adalimumab dose (20mg biweekly) who reaches the weight of ≥30kg for at least 2 consecutive visits (≥28 days apart) will be switched to the 40mg biweekly dose strength on their second visit. These requirements will ensure that all patients in the trial receive comparable doses of study treatment and have not had any recent changes to treatment that would affect their outcomes during the trial.

If on a concomitant antimetabolite, patients will continue their same dose and route of administration regardless of treatment arm. We anticipate the dose of methotrexate may range from 10 to 20 mg/m^2 with a maximum dosage of 25 mg per week according to standard clinical practice for methotrexate treatment in the setting of JIA.[59] Patients treated with >25 mg/week will not be eligible for the trial. Such patients must decrease the dose to ≤25 mg/week and must be on a stable dose and the same route of administration for ≥90 days prior to enrollment. Similarly, the maximum allowable dose of mycophenolate mofetil is 3 g daily, azathioprine is 250 mg/day, and leflunomide is 20 mg/day and the dose and route of administration must be stable for ≥90 days prior to enrollment. This restriction will limit potential bias from a recent change in concomitant immunomodulatory treatment dose and its therapeutic effects prior to entering the trial. Note, patients should not be on any other immunosuppressive agent.

If on topical corticosteroids, the dose must be ≤2 drops per day of 0.1% prednisolone acetate or equivalent, and dose must be stable for ≥90 days prior to enrollment. This requirement will ensure that all patients in the trial receive comparable doses of topical corticosteroids, a standard first-line treatment for anterior uveitis. In addition, this restriction will limit potential bias from any recent changes to treatment that would affect patient's clinic outcomes during the trial.

4.4 END OF STUDY DEFINITION

Participants are considered to have completed the study when they complete the Month 12 visit or the last scheduled procedure for the Month 12 visit as shown in the Schedule of Activities (SoA), **Section 1.3.** The end of the study is defined as completion of the last patient's visit or procedure shown in the SoA. Note that if inflammation is increased at Month 12 to a treatment failure criterion threshold, a follow-up visit must be conducted to determine whether the treatment failure criteria are met or not. If treatment failure is declared with fewer than 90 days remaining in follow-up, patients will be followed beyond Month 12 so that all patients have a minimum 90 days of follow-up after treatment failure. There will be a 90-day post-treatment failure study visit where the Clinical Eye Exam, Visual Acuity, OCT, and Adverse Event Report will need to be completed in addition to the Month 12 study visit. Standard of care labs will also be drawn only if the patient is on an antimetabolite and if more than 90 days have passed since their last standard of care lab draw. Follow-up could be extended up to 15 months if there is late treatment failure.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Stated willingness to comply with all study procedures and availability for the duration of the study period
- History of JIA or CAU, diagnosed prior to 16 years of age (patient may be older than 16 at time of enrollment)[a]
- ≥2 years of age (per FDA approval for use in children with polyarticular JIA) [b]
- Formal diagnosis of JIA-associated uveitis[c] or CAU[d] with no other suspected etiology
- ≥12 consecutive months of controlled ocular inflammation (≤0.5+ anterior chamber cell, ≤0.5+ vitreous haze, and no active retinal/choroidal lesions in either eye)
- ≥12 consecutive months of controlled arthritis verified by a pediatric rheumatologist (see **MOP Section 3.3.1** for definition of controlled arthritis) if defined as JIA-associated uveitis
- ≥12 consecutive months of treatment with adalimumab[e] and/or a biosimilar of adalimumab[f]
- ≥180 days on a stable dose of adalimumab or a biosimilar of adalimumab; must be biweekly dose of no greater than 20mg (if<30kg) or 40mg (if ≥30kg)
- If on a biosimilar of adalimumab, ≥90 days on the biosimilar
- If on concomitant antimetabolite (injectable or oral methotrexate, mycophenolate mofetil, azathioprine, or leflunomide), dose must be ≤25 mg weekly for methotrexate, ≤3 g daily for mycophenolate mofetil, ≤250 mg daily for azathioprine, or ≤20 mg daily for leflunomide; dose and route of administration must be stable for ≥90 days
- If on topical corticosteroids, dose must be ≤2 drops prednisolone acetate 1% or equivalent per day and stable for ≥90 days
- Willingness to limit consumption of alcohol during the study period
- Agreement to avoid live attenuated vaccinations
- Agreement to use highly effective contraception[g] for ≥28 days prior to screening and throughout study period (for males and females of reproductive age)
- Suitable, in the opinion of the Investigator, to continue treatment with adalimumab or placebo per regional labeling
- No contraindications to receive adalimumab as per the local Summary of Product Characteristics (SmPC)

There are no gender, race, or ethnicity restrictions for this study.

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[a]Patients can be older than 16 years of age at enrollment, but original diagnosis of arthritis must have been made prior to age 16 per the clinical definition of JIA

[b]Adalimumab is FDA approved for use in children ≥2 years of age

[c]By history, chronic or recurrent, relatively asymptomatic (not limiting daily activities or requiring analgesics) unilateral or bilateral anterior uveitis characterized by no or minimal conjunctival injection (no ciliary flush)

[d]If no history of JIA, must have a relatively asymptomatic (not limiting daily activities or requiring analgesics) unilateral or bilateral anterior uveitis characterized by no or minimal conjunctival injection (no ciliary flush)

[e]≤2 weeks of interruption in treatment is allowed (e.g., due to surgery, infection) provided uveitis and arthritis inflammation remains controlled

[f]UK patients on a biosimilar of adalimumab are eligible

[g] Effective contraception includes pharmacologics, devices, and barrier methods

5.2 EXCLUSION CRITERIA

Any one of these excludes the patient:

- Intraocular surgery in the past 90 days or planned surgery in the next 12 months
- Severe cataract or opacity preventing view to the posterior pole in both eyes
- Chronic hypotony (<5mmHg for ≥90 days) in either eye
- Treatment with oral corticosteroids[a] or intraocular corticosteroid injection within the last 12 months
- Use of NSAID eye drops within the last 90 days
- Acute anterior uveitis characterized by redness and symptoms, including but not limited to floaters, pain, and light sensitivity
- Pregnancy or lactation (a pregnancy test will be conducted at baseline and all follow-up visits for females of reproductive age)
- Presence of intraretinal or subretinal fluid in either eye
- Prior safety or tolerability issues with adalimumab
- History of cancer, active tuberculosis, or hepatitis B
- Other medical condition expected to dictate treatment course during the study
- Any of the following laboratory test results on their most recent tests within the past 90 days prior to screening/enrollment[b]: leukocyte count <2500, platelet count ≤75000, hemoglobin<9.0, AST or ALT ≥ 2 times the upper limit of normal range, creatinine ≥1.5

Note that patients with acute anterior uveitis, which is often associated with enthesitis-related arthritis including the HLA-B27 positive subtype, are not eligible. Beyond the tests listed above, the remainder of the work-up is at the discretion of the investigator and should be tailored to the clinical situation. Distinguishing between infectious and non-infectious uveitis is part of standard of care and should be dictated by the patient's clinical exam. A prior attempt at discontinuing adalimumab or other TNF-alpha inhibitor is not an exclusion criterion.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants must:

- Limit consumption of alcohol during the study period
- Avoid live attenuated vaccinations
- Use highly effective contraception for at least 1 month prior to screening, throughout study period, and at least 5 months following the trial (for males and females of reproductive potential)

[a] Oral corticosteroids are permitted if prescribed for conditions unrelated to JIA/CAU (e.g., allergic reaction, asthma) and if not anticipated to need again during the study.

[b] Normal lab readings are required to have been from within 90 days prior to an enrollment if the patient is on an antimetabolite, and can be from within 180 days prior to enrollment if not on an antimetabolite. If there are abnormal labs from within 90/180 days, but their most recent labs are normal, proceed to enroll.

5.3.1 USE OF CONTRACEPTION

A woman of childbearing potential (WOCBP) is defined by the Clinical Trials Facilitation Group as "fertile, following menarche and until becoming post-menopausal unless permanently sterile." Any woman who meets this definition must use highly effective contraception for the timeframe described in Section 5.3.

Highly effective contraception methods as defined by the Clinical Trials Facilitation Group, include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Abstinence from heterosexual intercourse

If abstinence is the selected contraception method, the reliability of this method needs to be evaluated in relation to the preferred and usual lifestyle of the patient.

5.4 SCREEN FAILURES

Screen failures are participants who are considered for trial participation and are included in a conversation about the trial, but do not meet all eligibility criteria, including their willingness to participate and comply with all study procedures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes reason for not enrolling in the trial.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a change in dosing of antimetabolite or adalimumab, use of corticosteroids, or willingness to participate may be screened again at a later time-point if they become eligible.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The sample size for this study is 118 patients. Details on sample size determination are provided in **Section 9.2.** There are limited demographic data available on patients with JIA-associated uveitis and CAU. Based on data from previous studies of this population and JIA populations in general, we expect approximately 77% of study patients will be female,[10] 5% African American, 3% Asian, and 11% Hispanic.[62] There are no restrictions on eligibility related to sex, race, or ethnicity for this study. All patients meeting eligibility criteria will be given information about the study and an opportunity to participate if interested.

With approximately ten planned enrollment centers in the U.S., nine in the UK, and one in Australia, the anticipated accrual rate is 3-4 patients per month across all centers. U.S. study sites will include the Proctor Foundation at UCSF in San Francisco, CA, Children's Hospital of Philadelphia in Philadelphia, PA, Cincinnati Children's Hospital in Cincinnati, OH, Children's Mercy Hospital in Kansas City, MO, the University of Utah Health in Salt Lake City, UT, Colorado Retina Associates in Lakewood, CO, University

of California Davis Eye Center in Sacramento, CA, Vanderbilt Eye Institute in Nashville, TN, University of Texas in Austin, TX, and University of Miami, FL. UK study sites will include Great Ormond Street Hospital in London, University Hospitals Bristol, Alder Hey Children's Hospital in Liverpool, Great North Children's Hospital in Newcastle, Sheffield Children's Hospital, Cambridge University Hospital, Royal Manchester Children's Hospital, University Hospital of Leicester, and Norfolk and Norwich University Hospital. The Australian site is The Royal Children's Hospital in Melbourne. We expect that approximately 51% of participants will be enrolled at the US centers, 43% of participants enrolled at the UK centers, 6% enrolled in Australia. Patients will be identified, screened, and consented in the outpatient clinic setting.

As patients will be followed for 12 months, study coordinators will obtain two phone numbers, email address (if available), and physical address for all study participants. At the conclusion of each visit, coordinators will schedule and confirm the next follow-up study visit with the patient. Coordinators will call patients two days prior to remind them of upcoming study visits. Patients will also receive a travel reimbursement voucher for each completed study visit.

As JIA-associated uveitis and CAU are pediatric conditions, the target population includes children, a group considered as vulnerable participants according to The Office of Human Research Protections (OHRP) definitions. We would not be able to meet the recruitment goals or answer the research aims of this study without the inclusion of children in our study population. An assent form will be provided for children in addition to a consent form to be reviewed and signed by the parent or legal guardian. This informed consent process will ensure children and their parents or guardians understand the risks and benefits of the study and have sufficient information to make an informed decision about whether or not to participate.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Patients randomized to continue adalimumab will receive the standard clinical practice weight-based dose of adalimumab. The dosage and route of administration is self-administration of adalimumab subcutaneously at a dose of 40mg every other week for patients ≥30kg and 20mg every other week for patients <30kg, which is in accordance with standard clinical practice and its FDA approved indication for treatment of JIA.[17] Further detail on justification of dosing is provided in **Section 4.3**.
Patients randomized to stop adalimumab will receive placebo treatment. The volume-matched placebo will be administered subcutaneously for masking purposes every other week.

Adalimumab is commercially available in the U.S. for treatment of polyarticular JIA and non-infectious intermediate, posterior, and panuveitis in children 2 years of age and older at the aforementioned doses. Adalimumab is commercially available in the UK for treatment of both polyarticular and oligoarticular JIA in addition to chronic, pediatric anterior uveitis at the aforementioned doses. Adalimumab is commercially available in Australia for treatment of JIA and CAU at the aforementioned doses, with an exception of patients weighing less than 15kg receive 10mg every other week. Given that the use of adalimumab in patients with oligoarticular JIA and anterior uveitis is technically off-label, the Coordinating Center has obtained an Investigational New Drug Approval from the FDA.

The US formula of adalimumab has recently been changed to be citrate-free, which is the same formula that is in use in the UK. Following this announcement, AbbVie will be providing citrate-free adalimumab and placebo to all clinical study centers.[63–65] To ensure the participants remain completely masked to treatment, the study will provide treatment kits to patients in both arms to standardize the appearance and labeling of adalimumab and the placebo.

6.1.2 DOSING AND ADMINISTRATION

The participant's dose will be selected based on their current weight at the time of randomization. For example, a patient weighing less than 30kg who is randomized to continue adalimumab treatment will receive a dose of 20mg every other week for up to 12 months. If a patient's weight increases during the trial, the patient must hold the larger weight for two consecutive visits (≥28 days apart) before receiving the higher dose of adalimumab (i.e. 40mg biweekly).

Participants randomized to receive placebo treatment will receive a volume-matched placebo dose subcutaneously every other week for up to 12 months.

Patients will take their first dose of study treatment 14 days after their most recent injection prior to entering the trial. Patients in either arm may discontinue treatment at any time for safety, intolerability, or efficacy. Further information on safety, intolerability, and efficacy definitions are provided in **Section 7.1.** After discontinuing treatment, such patients would be treated per best medical judgement and continue to be followed in the study until the completion of the Month 12 visit. If treatment failure is declared with fewer than 90 days left in the 12-month follow-up period, follow-up should be extended up to 15 months. Patients in the placebo arm may restart adalimumab during the study. Patients in the adalimumab arm may continue on adalimumab. The study will provide open-label adalimumab treatment for all patients who restart, regardless of their randomization arm. The advised dose for

restarting adalimumab will be 40mg every other week for patients ≥30kg or 20mg every other week for patients <30kg.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Both adalimumab and placebo study treatments will be provided for patients throughout the duration of the trial. We have a signed contract with AbbVie, Inc. pharmaceutical company to provide the adalimumab and placebo drug supplies for the duration of the trial. The Coordinating Center (CC) will place a product order through AbbVie for starting medication stocks, which will be shipped to the drug supplier. CC will email the drug supplier with details on the expected shipment and arrival dates, treatment kit quantities, lot numbers, and expiration dates. The drug supplier will receive the shipment, record all treatment kit numbers, lot numbers, and expiration dates, and store the treatment kits in a refrigerator designated for medication storage purposes only at a temperature of 36 – 46˚F (2 – 8˚C). The drug supplier will notify the CC of receipt of medication shipment with accurate contents in good condition within 24 hours of the shipment arriving at the site. The drug supplier will repeat the above procedure to ship the treatment kits to the clinical centers. The research pharmacist at each clinical center will notify the CC of receipt of medication within 24 hours of shipment arrival. If there are any issues identified with the shipment, the CC will work with the research pharmacist at the site to resolve the issues. Any damaged stock will be disposed of per local institutional guidelines on safe medication handling and disposal.

The CC will communicate with research pharmacists on a monthly basis for updates on medication stock. The CC will order additional stock from AbbVie to be shipped to the primary country site based on patient enrollment and follow-up and expiration dates of current stock at all clinical centers within the country. Both the CC and research pharmacist at each site will keep a log of medication shipments ordered and received at the site. The research pharmacist will also keep a medication dispensing log with treatment kit number, lot number, expiration date, and study patient ID for each treatment kit dispensed. In addition to the dispensing log, the research pharmacist will keep a log of all damaged and expired medications that have been disposed of. The CC will review medication dispensing and disposal logs as well as adherence to storage and labeling procedures during site-monitoring visits.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Adalimumab solution for subcutaneous injection: Adalimumab 20mg and 40mg is a clear, colorless solution provided in a pre-filled syringe for subcutaneous injection. The formulation is adalimumab, mannitol, polysorbate 80, and water for injection. The formulation is citrate-free. Each prefilled syringe has a fixed 29-gauge thin wall and ½ inch needle with black protective cover and is intended for a single dose to a single patient. The syringe should be discarded in a sharps container after administration. AbbVie, Inc. is the manufacturer of this product.[58]

Placebo solution for subcutaneous injection: The placebo solution is a clear, colorless solution provided in a single-use, prefilled syringe for subcutaneous injection provided in the same volume as the adalimumab injections. The placebo is designed to match the characteristics of the citrate-free adalimumab during injection, but its formulation is different. Each prefilled syringe has a fixed 29-gauge thin wall and ½ inch needle with black protective cover and is intended for a single dose to a single patient. The syringe should be discarded in a sharps container after administration. AbbVie, Inc. will prepare the placebo treatment kits for this study.

Packaging and labeling: Each kit will consist of two prefilled syringes of adalimumab or placebo in a protective carton. Adalimumab is FDA-approved for the treatment of JIA and intermediate, posterior, and panuveitis in patients 2 years of age and older in the U.S., approved by the TGS for the treatment of JIA in Australia, and approved by the NHS for treatment of both chronic anterior uveitis and JIA in the UK. Because this trial includes a placebo arm, both adalimumab and placebo kits will be labeled with adalimumab product information in accordance with GCP and Good Manufacturing Practices (GMP). Labeling will include a kit number and a blank section on the vial and outer packaging for site- and patient-specific details to be completed by the research pharmacist.

6.2.3 PRODUCT STORAGE AND STABILITY

Investigational products are for investigational use only and are to be used only within the context of this study. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label. Adalimumab or placebo-prefilled syringes are to be stored protected from light at 2˚ - 8˚C/36˚ - 46˚F. Study drugs must not be frozen at any time. Any temperature excursion must be reported to AbbVie immediately. Study medication should be quarantined and not dispensed until AbbVie deems the medication as acceptable. In contrast to HUMIRA market product, Adalimumab or placebo pre-filled syringes must not be stored at room temperature until 15 to 30 minutes before injecting (maximum 77˚F/25˚C).

6.2.4 PREPARATION

No preparation is required by the study staff or participants. Both active and placebo treatment kits will be provided in prefilled syringes with fixed needles in protective packaging.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

Both randomization and masking will be used in the study design to minimize bias relating to treatment assignment and outcome assessment.

Randomization: Lists of sequential randomization assignments will be prepared for each site. The randomization lists consist of a unique identifier for each patient, together with the assignments to treatment arms. The assignment of patient ID numbers and treatment randomization will be performed at enrollment. Research pharmacists and emergency contacts will be the only study personnel with access to treatment assignments for currently enrolled patients. These study personnel will only be able to access treatment assignments for their own site. The research pharmacist will perform each randomization for their site and will not know treatment assignments prior to enrolling each new patient. At the time of enrollment, the research pharmacist will log into the online REDCap randomization module and perform the randomization to obtain the treatment assignment.

Masking: A placebo treatment will be used to ensure masking of outcome assessors as well as the patients and caregivers. This process will ensure unbiased assessments of inflammation, adverse events, and other secondary outcomes, such as BCVA and quality of life. All participating physicians have unanimously agreed to the use of placebo injections for this trial. We believe that a sufficient number of patients will be willing to participate in a trial with placebo injections, since many previous JIA biologic trials including SYCAMORE were able to successfully enroll patients with a placebo arm.[25,66–69] Furthermore, these children should be used to receiving biweekly injections because they must be on

adalimumab for a minimum of 12 months prior to enrollment for eligibility in this trial. Adalimumab and placebo will be citrate-free, which eliminates the burning sensation with injections.

6.4 STUDY INTERVENTION COMPLIANCE

The study coordinator will monitor treatment adherence through patient self-report and will record the information on the Medication Log in each patient file.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized clinician. Medications to be reported in the **Follow-Up Treatment Assessment Form** and the **Unmasked Treatment Assessment Form** are concomitant prescription medications, over-the-counter medications, and supplements related to ocular conditions only. In addition, the study coordinator will obtain a complete list of all concomitant medications, including those not related to ocular conditions, at the baseline visit and record the information on **Baseline Treatment Assessment Form.**

The **Treatment Assessment Forms** will collect more detailed information regarding concomitant immunomodulatory therapy and corticosteroid treatments, as these treatments are of particular interest for the trial.

6.5.1 RESCUE MEDICINE

Patients randomized to stop adalimumab treatment who fail treatment will be restarted on adalimumab, unless the investigator deems restarting to not be in the patient's best medical interest. The patient will be restarted on their dose of adalimumab taken prior to randomization. Topical corticosteroids will also be restarted or increased based upon the investigator discretion. Macular edema is part of the definition of treatment failure and can be treated with topical, oral or injectable medications per investigator discretion. All post-primary outcome care will be determined by investigator discretion. The ability to regain control of inflammation when restarting treatment is of interest for Aim 3 of the trial. The study site will supply open-label adalimumab treatment for all who have a recurrence of inflammation and want to either restart (for patients randomized to the placebo arm) or continue (for patients randomized to the adalimumab arm) treatment during the trial.

Patients randomized to continue adalimumab who experience treatment failure for safety, intolerability, or efficacy reasons may be treated per best medical judgement with a medication other than adalimumab. Such patients will continue to be followed until Month 12, but the study will not provide any rescue treatments other than open-label adalimumab. All other rescue treatments will be considered part of standard clinical care.

6.5.2 ANTIMETABOLITE THERAPY

If patients are on an antimetabolite (methotrexate, mycophenolate mofetil, azathioprine, or leflunomide) the dose and route of administration must be stable for at least 90 days prior to randomization in order to be eligible for the trial. Such patients will continue on their same dose and route of administration throughout the trial. The maximum allowable dose of methotrexate is 25 mg weekly in either oral or injectable form. The maximum allowable dose of mycophenolate mofetil is 3 g/daily. The maximum allowable dose of azathioprine is 250 mg daily and for leflunomide it is 20 mg

daily. The dose of azathioprine and leflunomide must also be stable for at least 90 days prior to enrollment. Note, the patient should not be on any other immunosuppressive agent.

The study will not provide antimetabolites. Treating physicians must continue to prescribe the concomitant therapy for patients during the trial. Treatment should be recorded on the Treatment Assessment Form.

6.5.3 CORTICOSTEROIDS

Patients may use topical corticosteroids as long as the dose is ≤2 drops daily of 1% prednisolone acetate or other equivalent and has been stable for at least 3 months prior to randomization. If a patient is exposed to systemic corticosteroids, has an ocular injection of a corticosteroid, or increases topical corticosteroids to more than 2 drops/day during the course of the study, the study coordinator should record this event as a protocol deviation and report it to the medical monitor and CC. Note, systemic corticosteroids are permitted if prescribed for conditions unrelated to JIA (e.g., allergic reaction, asthma) are if not anticipated to be needed again during the trial.

Local corticosteroid injections to the joints are permitted and is the preferred method of treatment if there is a recurrence of arthritis.

6.5.4 EYE DROPS

Investigators may add cycloplegic drops to a patient's medication regimen if the patient has active inflammation and is at risk for synechiae.

Investigators may also add intraocular pressure-lowering (IOP) drops.

Nonsteroidal anti-inflammatory drug (NSAID) eye drops are not permitted to be added to a patient's medication regimen.

All treatment should be recorded on the **Treatment Assessment Form**.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation of study treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated in the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

Discontinuation due to *efficacy*: Patients can discontinue the study treatment due to lack of efficacy and be declared a treatment failure if they have recurrence of ocular inflammation (≥2-step increase in AC cell observed at 2 consecutive visits at least 7 days apart; >0.5+ AC cell for ≥28 days; ≥3+ AC cell on a single visit; or >0.5+ vitreous haze, active retinal/choroidal lesions, or macular edema at a single visit) and/or recurrence of joint inflammation that is persistent and severe enough to necessitate unmasking to manage the arthritis recurrence. Patients with ocular inflammation that meets one of the treatment failure thresholds (see **Section 3.1**) should return for an evaluation to evaluate whether the increased inflammation is sustained (called the Treatment Failure visit), as close to the 7 or 28 day period as possible, but no earlier. Patients who meet the treatment failure threshold of ocular inflammation at Month 12 will be re-evaluated after the Month 12 visit to assess for sustained inflammation which would result in treatment failure. If inflammation is sustained at the follow-up visit, then treatment failure is declared. At this point, patients and doctors will be unmasked, and doctors can treat per best medical judgement. Patients in the placebo arm will be encouraged to restart adalimumab. The date of treatment failure is defined as the date of the initial visit when the ocular inflammation reached the threshold (see **Section 3.1**). A minimum of 90 days of follow-up is required following treatment failure, so if treatment failure is declared with fewer than 90 days remaining in the 12-month follow-up period, follow-up may be extended to up to 15 months. Regardless of the course of treatment pursued after treatment failure, all patients will be followed through Month 12 or a minimum of 90 days, whichever is longer.

Discontinuation due to *intolerability*: Patients may discontinue their current treatment regimen due to side effects. Once side effects resolve, patients may restart their treatment regimen. Discontinuation for intolerability is NOT a treatment failure. Patients should still complete all study visits through Month 12.

Discontinuation due to *safety*: Patients who experience abnormal lab results meeting the designated threshold of an AE or other AEs such as an opportunistic infection will immediately stop taking both the study treatment and concomitant antimetabolite therapy if applicable. These AEs are often reversible. In the case of non-serious and serious lab AEs, patients may restart medication when the lab results have normalized. Discontinuation for safety reasons is NOT a treatment failure. Patients should still complete all study visits through Month 12. Patients who develop an illness, such as a febrile illness, ≥101°F/38.3°C or an infection requiring antibiotics, should consult their study physician regarding treatment and may stop taking the study medication and antimetabolite per investigator's discretion. Under the discretion of the investigator, patients should resume treatment as soon as it is determined to be safe. Note, patients should not stop treatment due to milder illnesses such as upper respiratory infections (colds). Additionally, patients who develop any of the following will also discontinue treatment according to the full prescribing information and labeling in the SmPC: serious infections,

opportunistic infections (including invasive fungal infections) or sepsis, Hepatitis B reactivation, new or worsening symptoms of congestive heart failure, or central or peripheral nervous system demyelinating disorders. If the investigator determines it is safe for the patient to restart treatment upon resolution of the disorder, the patient will restart.

Discontinuation due to reactivation of arthritis: Patients with a history of arthritis may experience a recurrence of arthritis while taking the study treatment regimen. The treating rheumatologist will determine per best medical judgement if a patient needs to discontinue their current treatment regimen due to reactivation of arthritis. Every effort should be made to treat the arthritis with NSAIDS or local corticosteroid injections as opposed to changing the study treatment, antimetabolite treatment, or adding systemic corticosteroids. Reactivation of arthritis only results in treatment failure if it cannot be managed with the aforementioned treatment options. Patients will continue to be followed through Month 12 regardless of the treatment course determined by the rheumatologist's best medical judgement. Patients with CAU who develop arthritis during the study should be treated the same as the JIA patients.

7.1.1 EMERGENCY TREATMENT & UNMASKING

In case of an emergency where knowledge of the patient's randomized treatment assignment is essential to the treatment of the patient, the investigator may willingly become unmasked. This decision to unmask resides solely with the investigator. If unmasking is warranted, the investigator will call their unmasked research pharmacist who can readily unmask the patient's treatment assignment. The research pharmacist must notify the Coordinating Center if they provide the treatment assignment to the masked investigator. If the research pharmacist is unable to be reached, the investigator may call the Coordinating Center. The Data Analyst is the best contact for this situation, as they are unmasked. Based on investigator discretion, the investigator should restrict the number of individuals who become unmasked. The patient should remain in the study, regardless of whether they have been unmasked, if the patient's safety is not at risk. As with any unmasking, the investigator must report a Protocol Deviation. See section 10.1.9 for further details on reporting Protocol Deviations.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance that endangers the participant
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded on **Patient Dropout Form**. Subjects who sign the ICF and are randomized but do not receive the study intervention must continue to be followed as part of the study and will be included in the intent-to-treat analysis. Subjects who sign the ICF, are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to continue in the study.
- The investigator or designee will make every effort to reestablish contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Patients are not considered a dropout unless they state they are no longer willing to participate in the study. Study personnel should continue to reach out to the study patient in an effort to schedule a study visit until the end of the Month 12 visit window.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Dilated ophthalmic exam: A study ophthalmologist at each site will be required to perform an eye examination at each study visit. This examination should be similar to that performed in the routine care of patients with uveitis. Several components will be assessed in detail per study protocol. Anterior chamber cell, anterior chamber flare, and vitreous haze will be graded based on Standardization of Uveitis Nomenclature (SUN) Working Group inflammation grading schemes.[60] The study ophthalmologist will also examine the fundus for any sign of retinal or choroidal inflammation and will record any abnormal findings on **Clinical Eye Exam Form**.

Rheumatologic exam: A pediatric rheumatologist will conduct an exam of joint disease activity at Baseline, Treatment Failure (if applicable) and Months 3, 6, and 12. These exams will occur on the same day as, or as close as possible to, the ophthalmic exam. This exam will include assessment of total active joint count, systemic symptoms such as fever or rash, and other tests or examinations deemed necessary by the rheumatologist. Juvenile Arthritis Disease Activity Score (JADAS) for 10 joints and 27 joints will be determined at each visit based on ESR, physical exam, and assessment of patient functioning.[70,71] Findings will be recorded on **Arthritis Evaluation Form**.

Best spectacle-corrected visual acuity (BCVA): Trained visual acuity technicians will use the Electronic Visual Acuity (EVA) protocol developed by the Jaeb Center for Health Research to check best-corrected vision in children. Children 7 years of age or older will be tested using the electronic ETDRS option on the EVA system, while children younger than 7 years of age will be tested on the ATS-HOTV option. Refer to **MOP Section 6.3** for further details on refraction and visual acuity, including acceptable EVA alternative devices (e.g., M&S, VistaVision, Good-Lite).

Optical coherence tomography (OCT): Optical coherence tomography (OCT) is a diagnostic imaging technique that produces cross-sectional tomograms of the posterior segment eye structures. A computer algorithm determines the boundaries of the different layers of the retina and subsequently, retinal thickness and volume data are calculated. Spectral-domain (SD) OCT will be used in this study to monitor the effects of treatment by measuring changes in macular thickness. Heidelberg Spectralis SD-OCT unit, Zeiss Cirrus, and TopCon are the approved OCT imaging machines for study assessments. If there is more than one OCT machine at a site, an effort will be made to use the same machine each time for consistency in measurements. The OCT technician should capture one 20x20 High Speed Volume scan centered on the macula for both eyes at each visit. The study ophthalmologist should record central subfield thickness measurements from the thickness map and structural observations (subretinal fluid, cystoid spaces, epiretinal membrane) on **OCT Form**.

MRP8/14 serum levels: Blood will be drawn to measure MRP8/14 serum levels at Baseline, Month 6, Month 12, and Treatment Failure. See **MOP Section 6.5** for details on storage, transmission, and analysis of samples.

Blood for biobanking: Blood will be drawn at Baseline, Month 6, Month 12, and treatment failure and kept in biobank storage freezers at each site for future analysis in ancillary biomarker studies. See **MOP Section 6.5** for details on storage and transmission of blood samples.

Adalimumab antibody levels: Patients will have blood drawn to test for adalimumab antibody levels at Baseline, Treatment Failure (if applicable), Month 6, and Month 12. Following treatment failure, an

investigator may elect to have one additional sample collected outside of these pre-specified study visit time points if the sample is relevant to the patient's treatment plan. See **MOP Section 6.5** for details on transmission and analysis of samples.

Rectal swab: Patients will provide rectal swabs at baseline, Month 12, and Treatment Failure (if applicable) for gut microbiome and human transcriptomes analyses.

Monitoring for arthritis activity: Patients will be assessed for arthritis activity using the Juvenile Arthritis Disease Activity Score for 10 and 27 joints (JADAS-10 and -27) by a pediatric rheumatologist.

Quality-of-life questionnaires Quality of life will be measured at Baseline, Month 6, Month 12 and Treatment Failure visits. Health-related quality of life (HR-QOL) will be assessed in patients 5 years and older using the Child Health Assessment Questionnaire (CHAQ). The EuroQol 5 Dimension Youth Survey (EQ-5D-Y) will also be completed by patients 4 years and older. Both of these questionnaires can be taken by patients and their caretakers. Vision-related quality of life (VR-QOL) will be assessed in patients using the Children's Visual Function Questionnaire (CFVQ) for patients aged 3-7 years and the Effect of Youngster's Eyesight on Quality of Life (EYE-Q) questionnaire for patients 5 years and older.

8.2 SAFETY AND OTHER ASSESSMENTS

Review of adverse events: The study coordinator will review each item on **Adverse Event Checklist** with patients and their caregivers and record it on the CRF. The study coordinator will also record any adverse events that the study ophthalmologist or rheumatologist have observed during the study visit. See **Section 8** for further detail on classification and reporting requirements for adverse events.

Serum chemistry and complete blood count: Patients prescribed an antimetabolite will have their blood drawn for a complete blood count and serum chemistry panel approximately every 3 months, while patients not prescribed an antimetabolite will have these labs done every 6 months—this is standard of care. The 9-month blood draw for standard of care labs can be completed any time between month 8 and month 10 for patients who are taking an antimetabolite. The study coordinator will review the lab report and record values on **Standard of Care Lab Form**, which the CC will monitor for safety events when CRFs are submitted for data entry. **Adverse Event Checklist** and **Treatment Assessment Form** will guide study coordinators on when to report lab values that are out of reference range and constitute a lab safety event. Study teams will also order **tuberculosis screening** at the baseline visit, if the patient has not been tested within 12 months prior to enrollment. If the test comes back indeterminate, it should be repeated. If it comes back positive, and the patient does not have a history of treatment for latent tuberculosis, then the patient should be evaluated for the need for treatment.

Pregnancy test for women of reproductive age: Serum or urine pregnancy test will be administered at every study visit for women post menarche. Study coordinators are required to notify the CC via **Serious Adverse Event Narrative** in the event of a positive pregnancy test. See **Section 8.3.8** for details on pregnancy reporting.

Patient perception of randomized assignment: Prior to unmasking (either at Month 12 or at the treatment failure visit), patients will be asked which treatment group they believe they were randomized to and reason for their guess. The study coordinator will record this information on the **Treatment Assessment Form** and then the patient and their caregivers will be unmasked.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Examples* may include:

- Increased intraocular pressure (>24 mm Hg)
- Abnormal lab findings (≥ 2 times but < 5 times the upper limit of normal AST or ALT, rise in creatinine to ≥ 1.5 to < 2 mg/dL, reduction of white blood cell count to below 2500)
- Concurrent accident or illness
- Increase in the frequency and severity of symptoms of a pre-existing condition
- Side effects such as gastrointestinal upset, nausea, vomiting, fatigue

*Additional details on adverse event reporting are provided in the case report form: **Adverse Event Checklist**.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Below is a list of thresholds for classifying lab values as non-serious and serious:

	Non-Serious Adverse Event	Serious Adverse Event
Leukocytes	>1,000 to <2,500/µL	≤1,000/µL
Platelets	20,000 ≥ to ≤75,000/µL	<20,000/µL
Hemoglobin	≥ 6.5 to < 9.0 g/dL	<6.5 g/dL
SGOT (AST) or SGPT (ALT)	≥2 to <5 times the upper limit of normal	≥ 5 times the upper limit of normal
Creatinine	≥ 1.5 to < 2 mg/dL	≥ 2 mg/dL

If a lab value surpasses the Non-Serious Adverse Event threshold, the patient must stop their study treatment (adalimumab or placebo), then may resume once levels are below the upper limit of normal. It is recommended to recheck labs weekly following the observation of the elevated lab value. If the lab value remains at the non-serious threshold for more than 28 days, it will be considered an SAE.

If lab values reach the Serious Adverse Event threshold, the patient will stop the study treatment and will not be eligible to restart treatment until the lab value no longer meets the Non-Serious Adverse Event threshold. Patients will continue to be followed through Month 12 regardless of whether or not they regain eligibility to start treatment.

If a patient also stops taking an antimetabolite due to elevated lab values, they are encouraged to restart the antimetabolite as soon as possible, when deemed safe by their provider.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, they must be determined to be Serious or Non-serious, using the definitions in sections 8.3.1 and 8.3.2.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

A determination of the adverse event's relation to the study product will be made by the investigator based on temporal relationship and clinical judgement. The degree of certainty about association will be graded using the World Health Organization's Uppsala Monitoring Centre categories below. In a clinical trial, the study product must always be given consideration.

- **Certain** – The AE occurs in a plausible temporal relationship with the study intervention and cannot be explained by concurrent disease or other drugs.
- **Probable** – The AE occurs in a reasonable time sequence with the study intervention and unlikely to be explained by concurrent disease or other drugs.
- **Possible** – The AE occurs in a reasonable time sequence with the study intervention but could be explained by concurrent disease or other drugs.
- **Unlikely** – The AE occurs in a temporal relationship with the study intervention that makes a causal relationship improbable and concurrent disease and/or other drugs provide plausible explanations.

Regardless of the investigator's decision, patients should continue to be followed through Month 12.

8.3.3.3 EXPECTEDNESS

The Medical Monitor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the information about adalimumab provided in the Summary of Product Characteristics (SmPC).

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE (encompassing serious adverse reactions, SARs, and suspected unexpected serious adverse reactions, SUSARs, in the UK) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on **Adverse Event Checklist**. All AEs that occur during the study must be documented appropriately regardless of relationship and will be categorized as either serious or non-serious. All AEs will be followed to adequate resolution.

Any medical condition present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 70 days after the last day of study participation and the last dose of study medication. At each study visit, the study coordinator will ask about the occurrence of AE/SAEs

since the last visit. Events will be recorded on **Adverse Event Checklist** at each visit and followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Non-serious AEs will be reported through the **Adverse Event Checklist** at each follow-up visit, which will be submitted along with all other CRFs to the CC for review. Additional modes of reporting AEs are not required unless classified as an SAE.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The site investigator will immediately report any SAE/SUSAR to the sponsor regardless of relatedness to the study intervention. Reportable events include those listed in the protocol and must involve an assessment of the possibility that the study intervention caused the event. SAEs/SUSARs (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All SAEs/SUSARs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the CC or study sponsor and should be provided as soon as possible.

In case of an SAE/SUSAR, **Serious Adverse Event Narrative** will be completed by the Investigator and submitted to the Medical Monitor within 24 hours of study personnel learning of the SAE/SUSAR. Information recorded on this form will include the nature of the event, date of onset, date of resolution, date of notification to Medical Monitor, and action taken. The form will be reviewed and signed by the Medical Monitor. Any significant study drug-related adverse events will be reported by the Data and Safety Monitoring committee (DSMC) as appropriate. IRB offices should also be notified according to the policies of each institution.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

The study sponsor is also responsible for notifying the South Central – Berkshire Research Ethics Committee and the Medicines & Healthcare products Regulatory Agency (MHRA) of the fatal or life-threatening SAE/SUSAR as soon as possible, but no later than 7 days after the sponsor becomes aware. A CTIMPs Safety Report form should accompany the SAE/SUSAR notification to the main Research Ethics Committee. For non-fatal and non-life-threatening SAEs/SUSARs, the sponsor should inform the ethics committee and MHRA within 15 days after becoming aware. All SAEs, regardless of whether they originate in the UK or outside must be reported. The investigator at local UK sites where the SAE/SUSAR occurs is responsible for following local governance procedures, including notifying their Research & Development department.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

If the rate or occurrence of AEs or SAEs changes the risk-benefit ratio for the trial or if new information becomes available that would impact the risk-benefit ratio or patients' willingness to participate in the trial, the CC will prepare a document with standardized language to communicate the information to study participants and IRBs. Study coordinators will provide the study document to participants and notify participants that they may contact the investigator if they have any questions regarding the new finding or change in risk-benefit ratio. Study coordinators will remind patients that participation in the trial is voluntary.

8.3.8 REPORTING OF PREGNANCY

Any pregnancy will be reported to the coordinating center within 24 hours of study personnel learning of the event. The patient should stop study treatment immediately. Patients taking concomitant immunomodulatory therapy should also stop this medication as they have potential teratogenic effects. Every effort should be made to follow up with the patient at the conclusion of the pregnancy to collect any information on congenital abnormalities or other complications.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- 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 ICF; and (b) the characteristics of the participant 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); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB, CC, and Principal Investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs or Protocol Deviations will be reported to the IRB, CC, and PI within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB, CC, and PI within 72 hours of the investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP within 72 hours of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

If the UP affects the study as a whole and changes the risk-benefit ratio for participants in the trial, the CC will prepare a document with standardized language to communicate the information to study participants and IRBs. Study coordinators will provide the study document to participants and notify participants that they may contact the investigator if they have any questions regarding the new finding or change in risk-benefit ratio. Study coordinators will remind patients that participation in the trial is voluntary.

9 STATISTICAL CONSIDERATIONS

See the Statistical Analysis Plan (SAP) for all statistical considerations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND ASSENT DOCUMENTS PROVIDED TO PARTICIPANTS

Consent and assent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Assent form for children 7 – 12 years old
- Assent form for children 13 – 17 years old (13 – 15 years old in the UK and Australia) with additional signature line for a parent or legal guardian
- Informed consent form (ICF) for parents or legal guardians of children ≤12 years old for the main study
- Informed consent form (ICF) for participants who are 18 years or older (16 years or older in the UK and Australia) for the main study
- Consent to donate specimens for parents or legal guardians of children ≤12 years old for providing rectal swabs and drawing extra vials of blood for biomarker analysis
- Consent to donate specimens for participants who are 18 years or older (16 years or older in the UK and Australia) for providing rectal swabs and drawing extra vials of blood for biomarker analysis
- Permission to use health information for Research (HIPAA research authorization in the US)

See **MOP Appendix A** for consent and assent forms.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent and assent forms will be IRB-approved and the participant, and the participant's parent or legal guardian (if under the age of 18 in the US and 16 in the UK or Australia) will be asked to read and review the document(s). At US sites, an assent form with basic language will be given to children 7 – 12 years of age, an assent form with appropriately tailored information will be given to children 13 – 17 years of age, and an ICF will be given to parents or legal guardians of all children ≤12 years old and for participants who are 18 years or older. At UK and Australia sites, patients who are 16 years or older will be given the adult consent form; they do not need a parent or legal guardian to provide consent too. Patients who turn 18 (or 16 in the UK and Australia) while in the trial will be re-consented. Patients willing to donate extra vials of blood at the time of blood draws for biomarker analysis will sign a consent to donate specimens. Patients or their caregivers will sign a HIPAA research authorization form to give permission to use health information for research as well. As UCSF will serve as the single IRB for US sites, consent forms for US patients will be reviewed by UCSF IRB. After approval, the CC will share consent forms with the US sites to alter with their institutional contact information and will send back to the CC and UCSF IRB for final review and recordkeeping. UK and Australia sites will provide assent forms and ICFs in accordance with their local institution's ethics policies. ICFs and assent forms will be adapted from UCSF's model consent documents. The CC will review consent documents prior to study sites submitting their consent documents for ethics approval.

The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant, parent, and/or guardian (whichever is applicable) will sign the consent document(s) prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the consent document(s) will be given to the participants and/or parents or guardians for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and participant's parent or legal guardian (if under the age of 18 in the US or 16 in the UK and Australia), investigators, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and the FDA and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, and any regulatory authorities.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible, primarily in exam rooms at ophthalmology or rheumatology clinics with doors closed.

The study monitor, other authorized representatives of the sponsor, IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the CC at UCSF. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the CC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the CC.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Nisha Acharya, MD, MS	Jeremy Keenan, MD, MPH
Proctor Foundation, UCSF	Proctor Foundation, UCSF
F.I. Proctor Foundation 490 Illinois Street, 2nd Floor San Francisco, CA 94158	F.I. Proctor Foundation 490 Illinois Street, 2nd Floor San Francisco, CA 94158
415-476-8131	415-476-6323
Nisha.Acharya@ucsf.edu	*Jeremy.Keenan@ucsf.edu*

Executive Committee
Dr. Acharya will chair the administrative and executive arm of the clinical trial and will meet with the study team regularly to provide overall oversight for the study and make decisions on day-to-day operation issues as described in the following:

- Monitor study progress and data collection process
- Discuss any quality control issues that have arisen in the CC
- Evaluate and adopt changes in study procedures as necessary
- Communicate with and implement recommendations from the Data and Safety Monitoring Committee
- Make executive decisions on the allocation of resources
- Establish policies on publications and authorship
- Approve and oversee ancillary studies

Coordinating Center
Dr. Ben Arnold from the Proctor Foundation, UCSF will be responsible for directing the CC. The role of the CC includes oversight and coordination of the implementation of the trial at the study sites. Functions include maintaining an up-to-date manual of operations; obtaining human research approvals from Institutional Review Boards; conducting training and certification of all personnel (physicians,

refractionists, OCT technician, etc.); supervising preparation and dispensing of study medication; ensuring proper masking; and monitoring safety, data quality, protocol adherence, and recruitment.

The CC will monitor the recruitment progress with weekly reports from each of the study sites. It will also organize periodic site visits (at least 2 times per year) to conduct chart reviews, training and certification of study personnel. The CC will also be responsible for training/certifying study refractionists and monitoring the refraction protocol at all study sites.

The CC will also be responsible for supervising data collection, data management, data quality control, data analysis, event adjudication, and training and certification of study site staff in the data management systems. The CC will coordinate and support the activities of the DSMC, including preparing interim and final data reports and organizing meetings with the Data Analysis Committee. The CC will also be responsible for the dissemination of datasets for use by the Data Analysis Committee and other investigators. The CC will meet monthly to monitor progress and quality of data entry and data management and address any issues.

10.1.5 SAFETY OVERSIGHT

Safety oversight is under the direction of a DSMC composed of individuals with the appropriate expertise, including bioethics, biostatistics, epidemiology, ophthalmology, and international health care. Members will be appointed by the National Eye Institute (NEI) and is independent from the study conduct and free of conflict of interest. Measures are in place to minimize perceived conflict of interest. The DSMC and NEI program officer convene with CC leadership via conference call or in-person semiannually to assess safety and efficacy data in each arm of the study. The DSMC operates under the rules of an approved charter that was written and reviewed at the organizational meeting of the DSMC. Each data element that the DSMC needs to assess is clearly defined. Ad hoc meetings are convened as needed. All study protocols are subject to review and approval by Institutional Review Boards at each study site and by the DSMC. Committee members monitor any severe or unexpected trend that threatens the safety of the patients. Stopping guidelines were agreed upon, and the DSMC is authorized to end the study if they deem necessary.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement.

- The CC will monitor enrollment and study activities on a weekly basis through email communication with sites. Study coordinators at each site will be required to submit a weekly enrollment report to the CC with any study visits, screenings, and enrollments that have occurred during the one-week period. CC members will also conduct annual, on-site, monitoring of study activities. Site visits will last one week in duration and will involve training and certification of new study personnel, auditing of study patient visits, and 100% verification of data from CRFs, patient medical records, and any additional raw data sources. Appropriate documentation, storage, and maintenance of medication stocks will also be assessed during on-site monitoring visits.
- Independent audits will not be conducted.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation, and completion of research activities.

Quality control (QC) procedures will be implemented through the CC's review of REDCap electronic forms remotely and by review of REDCap data with chart review during in-person site visits. The CC will also run data entry system and data QC checks. Any missing data or data anomalies will be communicated to the sites for clarification and resolution.

The CC will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source documents, and reports in the event of external monitoring by regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data will be captured by electronic REDCap forms. Hardcopies of the CRFs will be provided as a back-up. Data collected should be consistent with data from original sources, such as patient medical records, laboratory blood test reports, and patient's medication diaries.

Clinical data (including AEs, concomitant medications, and exam findings) and clinical laboratory data will be stored on REDCap, a 21 CFR Part 11-compliant data capture system available through UCSF. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from an electronic REDCap survey.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the formal conclusion of the clinical trial. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 24 hours of identification of the protocol deviation, or within 24 hours of the scheduled protocol-required activity. All deviations must be reported and addressed using **Protocol Deviation Form** and submitted to the CC and medical monitor. Protocol deviations must be sent to the reviewing IRB if local institutional policies require it. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. See further details about the handling of protocol deviations in **MOP Section 8**.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting the PI, Dr. Nisha Acharya.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NEI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.1.12 GOOD CLINICAL PRACTICE MONITORING

Monitoring of the trial will reside with the CC, which has over 10 years of experience implementing and monitoring NIH-funded clinical trials. The trial protocol has undergone a rigorous review by the funding agency, the National Institutes of Health, the investigators part of the trial, an internal group of clinicians and biostatisticians at the sponsor's organization, and by the independently-appointed DSMC. During personnel certification, the CC requests proof of Good Clinical Practice and Human Subjects Research certification, and reminds investigators to update their training before it expires.

10.1.12.1 INVESTIGATORS AND CLINICS

The CC identified and only included highly qualified clinics and investigators to be part of the trial. The CC will train and certify all personnel engaged in study activities. Examinations will be delivered to study personnel to assess knowledge of the protocol and check the quality of study procedures, including but not limited to, randomization, CRF completion, and visual acuity measurements. Investigators will be required to disclose any conflicts of interest, including financial. The CC will visit each clinic at the start of the trial to ensure the facilities and equipment required to implement the study are adequate at the site. The CC will also perform regular in-person site monitoring visits throughout the trial.

The CC will maintain routine communication with each site through weekly reports of study enrolment and other study progress information. Clinics will also be responsible to submit reports to the CC at routine intervals. In-person and/or teleconference research group meetings will also be held annually for the duration of the trial. These meetings will serve to reinforce the trial protocol, review progress and any changes to the trial, and ensure that all study personnel remain up-to-date on their certifications.

10.1.12.2 DATA QUALITY AND RECORD KEEPING

Clinics will be required to submit electronically captured data to REDCap within 5 days of the study visit. The CC will review the REDCap data as they are submitted for completeness. The CC will follow up with sites on missing and incomplete data. Each clinic will maintain physical copies of all consent/assent documents, as well as the CRFs (if any paper-based forms are used) for a minimum of 2 years following the end of the trial (see section 10.1.8.2). The CC will hold the electronic REDCap data indefinitely.

During the CC's in-person site monitoring visits, the REDCap data will be reviewed and arbitrated against study patient's medical charts to ensure accuracy. Between in-person visits, the CC will perform remote data audits on a regular basis to continually assess data quality.

10.1.12.3 QUALITY OF DRUG SUPPLY

All packaging and labeling of the drug supply will be completed at AbbVie, which has decades of experience producing clinical drug supply. The CC will review the labeling of the drug supply to ensure it's compliant with trial protocol and national regulations. Drug supply records will be maintained by the drug supplier and at each site (research pharmacist and coordinator). Temperature read-outs following drug supply shipments will be electronically delivered to the CC to ensure correct handling of the drugs. The research pharmacist and the coordinator at each clinic will maintain accountability logs of the drug supply inventory, including information on date of receipt, date of expiry, batch/serial numbers, and details of when drugs are dispersed to enrolled patients. The CC will audit the accountability logs, referencing the research pharmacy's inventory, during in-person site monitoring visits and confirm the drug supply is being stored and dispensed properly.

10.1.12.4 PROTOCOL COMPLIANCE

Study personnel will be required to pass a general knowledge assessment prior to trial implementation. If deviations to the protocol occur, the event and a description of it will be reported to the CC (see section 10.1.9). The CC may observe study visits during in-person site monitoring visits to verify adherence to the protocol.

10.1.12.5 TRIAL SAFETY

A masked medical monitor at the CC has been appointed to evaluate the safety of the trial. All serious adverse events experienced by enrolled patients will be reported to the medical monitor in a timely manner, as defined in section 8.3.6. The medical monitor will determine expectedness of the patient's treatment and the reported event. The medical monitor will report his findings to the relevant entities defined in section 8.3.6.

The NEI's appointed DSMC will also review serious adverse events and general trial data on a 6-month basis, or as deemed necessary. Progress reports will be prepared for all scheduled DSMC meetings. An interim analysis will be performed and presented to the DSMC by the trial's unmasked biostatistician when approximately 40% of the trial's anticipated events have occurred. Whether or not to continue the trial will be based on this interim analysis. See **SAP section 3.7** for details on stopping.

On February 14th, 2024 the DSMC met, stopped enrollment and provided the following guidance for patients still completing follow-up in the trial:

- Patients should be told by the study investigator the results regarding efficacy of the continued administration of adalimumab for preventing recurrence of uveitis or arthritis.
- Patients are encouraged to remain in their assigned treatment group and complete follow-up, per protocol.
- Patients in active follow-up who have not yet been unmasked to their treatment assignment can be asked if they want to know their current treatment assignment.
- Patients receiving placebo may opt to discontinue their injections.

10.2 ABBREVIATIONS

AC	Anterior Chamber
ADA	Anti-drug Antibodies (to adalimumab)
AE	Adverse Event
BCVA	Best-corrected Visual Acuity
CAU	Chronic Anterior Uveitis
CC	Coordinating Center
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-reactive Protein
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
ESR	Erythrocyte Sedimentation Rate
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IND	Investigational New Drug Application
IRB	Institutional Review Board
JIA	Juvenile Idiopathic Arthritis
MOP	Manual of Operating Procedures
NEI	National Eye Institute
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
OHRP	Office for Human Research Protections
PDF	Portable Document Format
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
TGS	Therapeutic Goods Administration
TNF	Tumor Necrosis Factor
UCSF	University of California, San Francisco
UK	United Kingdom
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Changes
1.1	22 October 2019	1. Corrected the formulation of the study medication (adalimumab and placebo) being donated by AbbVie (Section 6.2.2) 2. Updated Section 6.2.3 to include required language by AbbVie on study medication storage and stability
1.2	10 April 2020	1. Removed the Baseline Medication Form (Section 1.3) 2. Clarified that there must be at least 28 days between the two consecutive study visits before the study medication dose can be increased to 40 mg due to a weight increase (Section 4.3) 3. Expanded permitted concomitant antimetabolites to azathioprine and leflunomide (Sections 4.3, 5.1, and 6.5.2) 4. Extended the time period of which a planned intraocular surgery would disqualify a patient from 180 days to 12 months (Section 5.2) 5. Added that the use of NSAID eye drops within the past 90 days prior to enrollment would disqualify a patient (Section 5.2) 6. Clarified that prior attempts at discontinuing adalimumab or other TNF-α inhibitors do not disqualify a patient (Section 5.2) 7. Clarified that patients who are prescribed oral corticosteroids for conditions unrelated to JIA are still eligible (Sections 5.2 and 6.5.3) 8. Removed that patients will bring back unused pre-filled syringes of study medication to assess for medication adherence. Adherence will be measured through patient self-report alone (Section 6.4) 9. Added that patients will be assessed on their perception of randomized treatment group prior to unmasking (Section 8.2) 10. Included age thresholds for obtaining assent/consent from patients and their parents in Australia (Section 10.1.1)
1.3	21 October 2020	1. Updated study duration (Section 1.1) 2. Clarified time window for the Baseline laboratory measurements (Section 1.3) 3. Specified a time window for when a rheumatology exam and a standard of care blood draw do not need to be reperformed at a treatment failure visit if recently conducted (Section 1.3) 4. Added The Children's Hospital at Westmead and Queensland Children's Hospital as enrolling centers in Australia (Sections 4.1 and 5.5) 5. Added that route of concomitant antimetabolite administration (injectable or oral methotrexate, mycophenolate mofetil, azathioprine, or leflunomide) must remain stable for ≥90 days (Sections 4.3 and 5.1) 6. Clarified the type of JIA-associated uveitis that can be enrolled (Section 5.1) 7. Added that an additional anti-adalimumab antibody sample may be collected post treatment failure per investigator's discretion (Section 8.1)

		8. Updated F.I. Proctor Foundation address to Mission Bay location (490 Illinois St, 2nd Floor, San Francisco, CA, 94158) (Section 10.1.4)
1.4	22 April 2021	1. Updated address of Colorado Retina Associates as it moved to Lakewood, CO. (Section 4.1 and 5.5) 2. Reduced the recency requirement for screening labs for patients not on an antimetabolite, from within 90 days, to within 180 days. If on an antimetabolite, then screening labs recency requirement remains within the past 90 days. (Section 5.3) 3. Reduced the frequency requirement for standard of care labs to every 6 months for patients not taking an antimetabolite. For patients prescribed an antimetabolite, there is no change to the frequency of standard of care labs conducted. (Section 1.3, 5.3, and 8.2) 4. Removed the requirement for patients to return empty/used treatment kits to the study coordinator. (Section 6.4) 5. Removed the inclusion criteria regarding a negative tuberculosis test within the past 12 months (Section 5.1) Added tuberculosis testing at Baseline (if a test has not been completed in the 12 months prior), and general guidance for responding to an indeterminate or positive result. (Section 8.2)
1.5	01 October 2021	1. Changed the number of active sites in the synopsis (Section 1.1) 2. Added an explanation about ANA-positive chronic anterior uveitis (CAU) to the synopsis, study background, and study rationale. (Section 1.1, 2.1, and 2.2) 3. Changed the inclusion criteria to include CAU in juveniles (presenting <16 years old) (Section 5.1) 4. Added CAU when describing JIA-associated uveitis in various descriptions throughout the document including the objectives, study design, exclusion criteria, recruitment, and statistical analysis sections (Sections 3, 4, 5.2, 5.5, and 9.4) 5. Added a description that CAU will be treated identically to JIA in regard to rheumatology visits (Section 7.1) 6. Added plan for subgroup analysis of patients with and without JIA (Section 9.4.6) 7. Incorporated patient-centered language throughout the document, describing “patients with JIA or CAU” instead of “JIA and CAU patients”.
1.6	01 April 2022	1. Added presence of intraretinal or subretinal fluid as exclusion criteria (Section 5.2) 2. Clarified that occurrence of vitreous haze, retinal or choroidal inflammation, or macular edema at a single visit constitutes treatment failure. (Section 3.0) 3. Clarified the criteria for macular edema as a CST of 2 standard deviations greater than the mean *and* having a greater than 20% increase in CST from baseline, *and/or* having intraretinal or subretinal fluid on the OCT scan (sections 3.0, 4.2, 6.5, 7.1)

		4. Added University Hospital of Leicester and Meyer Children's Hospital in Florence as study sites and removed Duke University and Johns Hopkins Wilmer Eye Institute (sections 4.1, 5.5) 5. Changed number of enrollment centers to include Italy and included them in the consent procedures and study closure (sections 1.1, 5.5, 10.1.1.2, 10.1.2) 6. Added the Good-Lite machine as an acceptable alternative for the EVA device (section 8.1)
1.61	28 September 2022	1. Removed ANA positivity requirement for CAU (sections 1.1, 2.1, 2.2, 5.1, 9.4.5) 2. Removed Meyer Children's Hospital in Florence as a study site (sections 4.1, 5.5) 3. Changed number of enrollment centers to remove Italy and included them in the consent procedures and study closure (sections 1.1, 4.1, 10.1.1.2, 10.1.2)
1.7	27 June 2023	1. Removed Seattle Children's Hospital, Spokane Eye Center, Children's Hospital at Westmead, Queensland Children's Hospital, and University Hospitals Southampton as study sites (sections 4.1, 5.5) 2. Changed number of enrollment centers to remove Seattle Children's Hospital, Spokane Eye Center, Children's Hospital at Westmead, Queensland Children's Hospital, and University Hospitals Southampton (sections 1.1, 4.1, 5.5) 3. Added 70-day post trial Adverse Event phone call to the study visit schedule (section 1.3) 4. Specified when the interim analysis would take place and revised the section number to correspond with the updated SAP (section 10.1.12.5) 5. Clarified abnormal lab exclusion criteria (section 5.2) 6. Stated the assessments that will be conducted at the 90-day follow-up visit for patients who experience late treatment failure (section 1.3, 4.4) 7. Removed age cap for quality of life questionnaire (section 8.1)
1.8	14 February 2024	1. Clarified which Treatment Assessment Form to fill out before/after treatment failure. (section 1.3) 2. Included Treatment Failure Criteria table instead of referring to the MOP, for ease of reference. (section 3.1) 3. Removed 3 repetitive footnotes. (sections 3.1, 4.2, 6.5.1, 7.1) 4. Clarified list of acceptable OCT imaging machines. (section 8.1) 5. Referred to the Statistical Analysis Plan for all statistical considerations (section 3, 9) 6. Included more details about our Good Clinical Practice and Human Subjects Research certification requirements. (section 10.1.12) 7. Added DSMC's recommendation for Investigators to discuss the Interim Analysis results with every patient and give masked patients the opportunity to unmask. (section 10.1.12.5)

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