Protocol Title: A Pilot Study to Investigate Ustekinumab (STELARA®) for the Treatment of Active Sight-Threatening Uveitis

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Human Research Protections Program Investigator and Staff Training:

"Just in time" human subjects protection training courses are required for investigators and staff participating on this protocol: None

Total Requested Accrual:

11 Participants – 5 Participants, ages 18 and older, will be initially enrolled and included in the first cohort. For the second cohort, up to 4 participants, ages 18 and older will be enrolled. Up to an additional 2 participants may be enrolled in the second cohort to account for participants who withdraw from the study prior to the Week 16 visit.

0 Healthy Volunteers

Project Uses Ionizing Radiation: ☒ No ☐ Yes

IND/IDE: ☐ No ☒ Yes

Drug #: 131,716

Sponsor: National Eye Institute

Durable Power of Attorney: ☒ No ☐ Yes

Multi-Institutional Project: ☒ No ☐ Yes

Data and Safety Monitoring Board: ☒ No ☐ Yes

Technology Transfer Agreement: ☒ No ☐ Yes

Samples are Being Stored: ☐ No ☒ Yes

Flesch-Kincaid Reading Level of Consent: 9.9

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Protocol Abbreviation List

≥	Greater Than or Equal To
AC	Anterior chamber
BCVA	Best-corrected visual acuity
CBC	Complete blood count
CC	Clinical Center
CD	Crohn's Disease
EAU	Experimental autoimmune uveitis
ETDRS	Early Treatment Diabetic Retinopathy Study
EVA	Electronic visual acuity
FA	Fluorescein angiography
FDA	Food and Drug Administration
HIV	Human Immunodeficiency virus
IFN	Interferon gamma
IL	Interlukein
IOP	Intraocular pressure
IRB	Institutional Review Board
IV	Intravenous
mL	Milliliter
MTX	Methotrexate
NEI	National Eye Institute
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NLM	National Library of Medicine
NSAIDS	Nonsteroidal anti-inflammatory drugs
OCT	Optical coherence tomography
PPD	Purified protein derivative
PI	Principal Investigator
RCT	Randomized clinical trial
SAE	Serious Adverse Event
SC	Subcutaneous
SOP	Standard operating procedure
SUN	Standard of Uveitis Nomenclature
TB	Tuberculosis
TNF-alpha	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor

Précis

Objective: Uveitis refers to intraocular inflammatory diseases that are an important cause of visual loss. Standard systemic immunosuppressive medications for uveitis can cause significant adverse effects and many patients continue to experience disease flare-ups. Ustekinumab is a human IL-12 and -23 antagonist. The involvement of IL-12 and IL-23 in the pathophysiology of uveitis and other autoimmune diseases known to be associated with uveitis suggests that ustekinumab could be a potential treatment for uveitis. The study objective is to investigate the safety, tolerability and potential efficacy of ustekinumab as a possible treatment for active intermediate uveitis, posterior uveitis or panuveitis.

Study Population: The first cohort will consist of five participants with active intermediate uveitis, posterior uveitis or panuveitis who meet the inclusion criteria. The second cohort will include up to four participants with active intermediate uveitis, posterior uveitis or panuveitis who meet the inclusion criteria. Up to eleven participants may be enrolled, as up to two participants may be accrued in the second cohort to account for participants who withdraw from the study prior to Week 16.

Design: This is a prospective, non-randomized, uncontrolled, single-center, two-arm pilot study to evaluate ustekinumab as a possible treatment for active intermediate uveitis, posterior uveitis or panuveitis. Five participants in the first cohort will receive a 90-mg subcutaneous (SC) injection of ustekinumab at baseline and a second and third injection at Week 4 and 8 for a total of three injections. For the second cohort, up to four participants will receive an initial high, weight-based dose of ustekinumab via intravenous (IV) injection (up to 55 kg, 260 mg (2 vials); greater than 55 kg to 85 kg, 390 mg (3 vials); greater than 85 kg, 520 mg (4 vials)), followed by a single 90 mg subcutaneous injection at Week 8. In participants who demonstrate allergic reaction to the first dose, the second dose can also be administered as IV infusion with pre-infusion desensitization instead of a subcutaneous injection as it allows better control on the rate of drug administration. Participants will continue in the study for a total of 28 weeks and will be able to receive standard of care after the first 16 weeks.

Outcome Measures: For each cohort, the primary outcome is the number of participants who experience treatment response (as defined in Appendix 1) by Week 16. Secondary outcomes for each cohort include changes in visual acuity, the number of participants who experience a recurrence, the number of days to recurrence, presence or extent of macular edema, the amount of retino-vascular leakage, changes in retinal thickening, the length of time to quiescence and the ability to taper concomitant immunosuppressive medications. Safety outcomes for each cohort include the number and severity of systemic and ocular toxicities and adverse events, the proportion of participants who experience vision loss of ≥15 letters as measured by Electronic Visual Acuity (EVA) and the number of participants who experience a substantial rise in elevated intraocular pressure (IOP).

1.0 Introduction/Scientific Rationale

1.1 Uveitis

Uveitis, an inflammatory condition that affects the uvea (iris, ciliary body and choroid) and adjacent structures of the eyes, is an important cause of visual loss in both adults and children. A recent study in Northern California suggests that the incidence and prevalence of uveitis is three times what was previously thought, at 52/100,000 and 115/100,000 respectively.[1,2] It is believed that approximately 100,000 American citizens currently require the use of systemic corticosteroids or other immunosuppressive agents as treatment for ocular inflammation. It is particularly common to use immunosuppressive or immunomodulatory therapy for the treatment of posterior segment uveitis (intermediate, posterior or panuveitis), which are considered to be more likely to be sight threatening.[3] Management and prevention of the iatrogenic complications of immunosuppressive therapy accounts for most of the medical resources devoted to these individuals.[2]

Uveitis is a predominantly T-cell mediated immune disease, and drugs like cyclosporine targeted primarily at T-cells have demonstrated efficacy.[4] The dominant role of T-cells in the pathogenesis of uveitis is also observed in the experimental animal models of uveitis. Both Th1 and Th17 pathways are believed to drive inflammation in uveitis.[4] IL-12 and IL-23 are crucial parts of Th1 and Th17 pathways which have been implicated in autoimmune disorders including uveitis. IL-12, a heterodimer of p40 and p35 subunits, induces $CD4^+$ differentiation into Th1 cells which produce interferon (IFN)-gamma and mediates cellular immunity. IL-23, also a heterodimer with p40 and p19 subunits, induces naïve CD4 cells to differentiate into Th17 cells which produce IL-17, IL-6 and tumor necrosis factor alpha (TNF-alpha) and similarly mediate cellular immunity. In addition, IL-12 and IL-23 each play an important role in the expression of experimental model of uveitis (EAU).[4,5] Anti-IL-12 administration in experimental uveitis models not only prevented the development of disease and pathogenic Th1 cells, but also induced suppressive Th2 cells.[6] Keino et. al. showed that oral administration of a potent IL-12/IL-23 inhibitor abrogated inflammation in an EAU both in afferent and efferent phases of the disease. They also found that IL-12/23 inhibitor administration also reduced the expansion of IL-17 producing cells.[7] Ustekinumab, by targeting the p40 subunit shared by both IL-12 and IL-23, offers a novel mechanism of action; it prevents IL-12/23 interaction with their receptors and blocks signaling through the IL-12β1 receptor, cell differentiation and cytokine production.

IL-12 is also believed to be responsible for CD4+ cells escaping suppressor effects of regulatory T-cells (Tregs).[8] It is possible that IL-12/23 blockage may, in addition to inhibiting Th1 and Th17, also help expand regulatory T-cells through multiple mechanisms.

1.2 Ustekinumab

Ustekinumab is a human IL-12 and -23 antagonist and is currently approved by the FDA for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Ustekinumab is administered by subcutaneous (SC) injection. For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and four weeks later, followed by 45 mg every 12 weeks. For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and four weeks later, followed by 90 mg every 12 weeks. In a randomized, controlled trial (RCT) of ustekinumab for moderate-to-severe Crohn's disease, clinical response was most notable in infliximab non-responders and sub-optimal responders indicating a different, perhaps more robust, clinical effect. More importantly, adverse events with ustekinumab have been mostly mild and non-serious in clinical trials so far. The most common side effects were upper respiratory tract infections, nasopharyngitis, headache, fatigue and arthralgia.[9] In PHOENIX 1 and 2 randomized, double-masked phase III trials, in which a total of 1,996 patients were enrolled, serious adverse events occurred in 0.8% of the patients receiving the 45 mg dose of ustekinumab, 1.6% of the patients receiving the 90 mg dose of ustekinumab and 0.8% of the patients receiving placebo.[10] Injection site reactions occurred in 1% of patients receiving ustekinumab injections and 0.4% of patients receiving placebo injections.[11] No episodes of anaphylactic or serum-like sickness reactions, lymphoma, tuberculosis or demyelinating diseases were reported.[12]

Ustekinumab has also been used in Crohn's disease (CD) and psoriatic arthritis in large clinical trials. A double-blind, cross-over trial of the clinical effects of ustekinumab in 104 patients with moderate-to-severe CD used a more frequent dosing of 90 mg SC ustekinumab injections weekly for four weeks. In this trial, the investigators allowed concomitant use of prednisolone at a maximum daily dose of 20 mg, azathioprine, 6-mercaptopurine or methotrexate. Concomitant medication doses remained constant during the study except corticosteroids, which could be tapered. Ustekinumab induced a clinical response in patients with CD and helped improve disease activity scores, especially in patients previously given infliximab.

Population pharmacokinetic data analyses indicated that the clearance of ustekinumab was not impacted by concomitant Methotrexate (MTX), nonsteroidal anti-inflammatory drugs (NSAIDs), and oral corticosteroids, or prior exposure to anti-tumor necrosis factor (anti-TNF) agents in patients with psoriatic arthritis. Anti-ustekinumab antibodies were negative in 99 patients that were tested throughout the study duration of 54 weeks. In the PHOENIX 1 and 2 trials, approximately 3-5% of patients showed positive anti-ustekinumab antibodies. For the most part, adverse event rates in the treatment groups (IV or SC ustekinumab) were comparable to placebo groups. The most common adverse events in either group were nausea, headache, abdominal pain, worsening CD and fatigue, some of which were related to underlying disease. Administration-site reactions, interestingly, were more common in the placebo group. Serious adverse event (SAE) rates occurred in 6% of the placebo-treated patients and 4% of the ustekinumab-treated patients. Infections were observed in 23% of the placebo vs. 15% of the ustekinumab-treated patients.[13] Similarly, in a large multi-center, international, double-blind, randomized, placebo-controlled crossover study of psoriatic arthritis patients, weekly-administered ustekinumab significantly reduced signs and symptoms of psoriatic arthritis and skin lesions within 12 weeks.[14] Of note, single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity.[9] Ustekinumab also improved the quality of life in this patient population. It is important to note that in this frequent dosing study, the drug was well-tolerated.[14] More recently, ustekinumab (90 mg SC) was evaluated for the treatment of Ankylosing spondylitis in a proof of concept open-label trial (N=20, TOPAS study) and was shown to be effective in improving the signs and symptoms of active spondyloarthritis when administered at 0, 4, and 16 weeks.[15] In this study too, ustekinumab was well tolerated with no adverse events requiring discontinuation of the study drug.[15] While ustekinumab has not been effective in treating multiple sclerosis it did not cause worsening of the disease -unlike anti-TNF agents- and remains one of the two safe biologics available to patients that have both psoriasis and MS.[16]

More recently, STELARA® is approved for moderate to severely active CD. STELARA® is used for induction in IV infusion form at doses up to 520 mg/infusion (4 vials) for one infusion (at 6 mg/kg/infusion), followed by a single, SC 90 mg dose eight weeks after, and, for maintenance, a SC 90 mg dose every eight weeks thereafter. Mean ±SD peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL following an IV infusion and steady state steady-state trough

concentration was 2.51 ± 2.06 mcg/mL for 90 mg ustekinumab administered every eight weeks following IV infusion. This was higher than steady-state trough serum ustekinumab concentrations observed with SC administration alone (0.69 ± 0.69 mcg/mL to 0.74 ± 0.78 mcg/mL). In these induction studies, a greater proportion of patients treated with STELARA® achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo. Clinical response and remission were significant as early as Week 3 in STELARA®-treated patients and continued to improve through Week 8. This is in keeping with the finding that, in general, higher rates of clinical response and remission are observed in IV ustekinumab groups compared to SC ustekinumab groups in CD patients.[17]

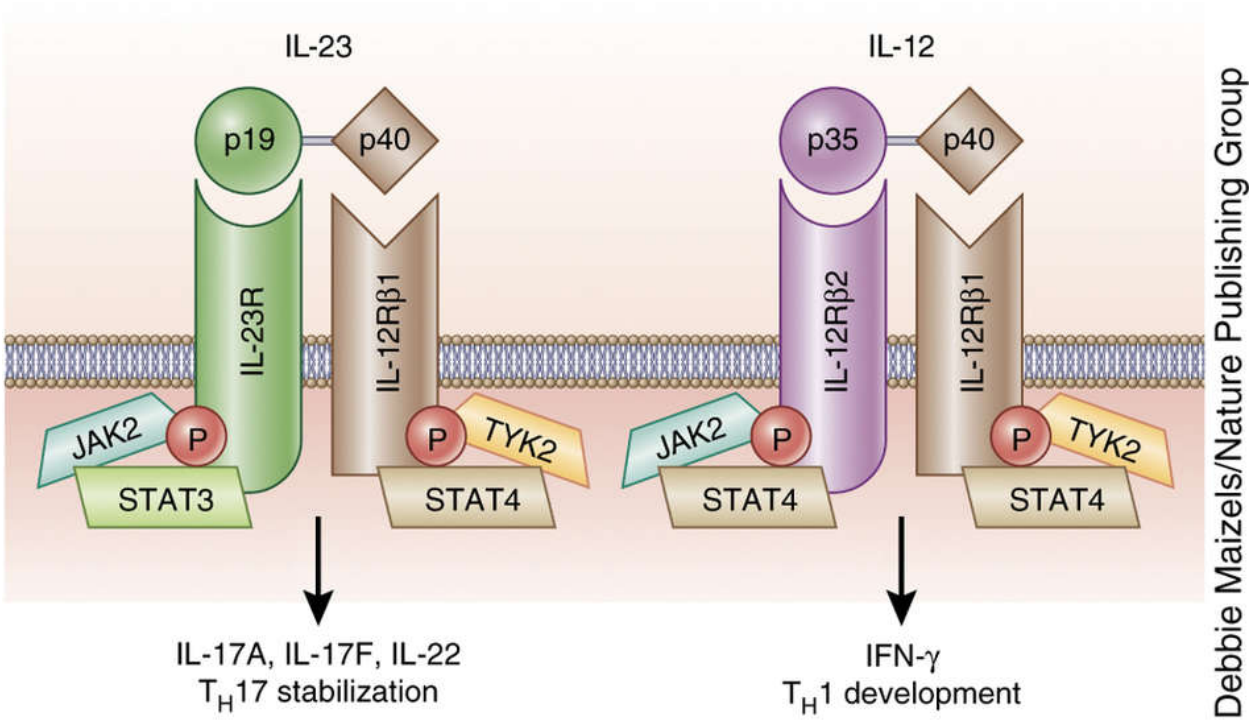
The safety of STELARA® was assessed in 1407 patients that participated in three randomized clinical trials. Overall, the safety profile of STELARA® was consistent with the safety profile seen in the adult psoriasis and psoriatic arthritis clinical studies. Most common adverse reactions with IV dosing in CD trials was vomiting (4% among CD patients vs. 3% in Placebo) and most common adverse reactions during SC maintenance therapy among CD patients observed at a rate >=3% were: nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis. Hypersensitivity reactions with STELARA® has been rare. In CD trials the incidence of hypersensitivity reaction was encountered in two patients, one following SC administration and one following IV administration (0.1% among SC dosing group and 0.08% among IV dosing group). Immunogenicity to ustekinumab (antibodies against ustekinumab) was less common in CD Trials (<3%) than was observed in psoriasis trials (6-12%) (see section 6.2.2 for more information on adverse events in clinical trials using high dose IV administration).

The rate of adverse events and serious adverse events was not significantly different between trials using different dose regimens. During the placebo-controlled PHOENIX trials (0, 4 weeks and every 12-week dose regimen), adverse events occurred in 47.9%-54.5% of the patients receiving ustekinumab and 48.2%-49.8% of the patients receiving placebo. Serious adverse events occurred in 1.2%-2% in the treatment group vs. 0.8%-2% in the placebo groups in PHOENIX 1 and 2 trials. In comparison, during the placebo-controlled psoriatic arthritis trial, where a weekly dose regimen was used, adverse events occurred in 61% of patients in the treatment group and in 63% of patients

receiving placebo, and serious adverse events occurred in 0% in the treatment group vs. 4% in the placebo group.[10,11,14]

Overall, while there appears to be a dose-response relationship in terms of effectiveness, the rate of adverse events has not been found to be significantly different between different dosing groups across multiple large RCTs using ustekinumab.[18]

Thousands of patients world-wide are treated for autoimmune disorders with various types of immunosuppressive and cytotoxic agents. Less toxic, more specific, or targeted immunosuppressive modalities are constantly being sought. Attempts to decrease morbidity, or reduce the dose of more toxic immunosuppressive drugs, or reduce the frequency or severity of episodes of recurrence are clearly all important goals. Although previous clinical trials have not generated specific evidence, the involvement of IL-23 and IL-12 in the pathophysiology of uveitis and other autoimmune diseases known to be associated with uveitis and the clinical evidence from autoimmune diseases where ustekinumab has been used successfully suggests that ustekinumab could be a potential treatment for uveitis (as shown below).[19]



2.0 Study Objectives

The study objective is to investigate the safety, tolerability and potential efficacy of ustekinumab as a possible treatment for active intermediate uveitis, posterior uveitis or panuveitis.

3.0 Participants

For the first cohort, five participants with active intermediate, posterior or panuveitis will be initially accrued. For the second cohort, up to four participants with active intermediate uveitis, posterior uveitis or panuveitis who meet the eligibility criteria may be enrolled in this protocol. In the event that a participant in the second cohort withdraws from the study prior to Week 16, a maximum of two additional participants will be accrued in order to obtain the four participants in each cohort completing the primary outcome visit.

3.1 Inclusion Criteria

1. Participant has the ability to understand and sign the informed consent document.
2. Participant is 18 years of age or older.
3. Participant has negative purified protein derivative (PPD) or quantiferon testing done within three months prior to enrollment or had latent tuberculosis (TB) but has completed prophylactic anti-TB treatment.
4. Participant has active intermediate uveitis, posterior uveitis or panuveitis in at least one eye requiring systemic therapy. Active disease is defined as (also listed in Appendix 1):
    - +1 or more vitreous haze (according to Standardization of Uveitis Nomenclature (SUN) criteria[20]) AND/OR
    - Active chorioretinitis or leakage on Fluorescein angiography (FA) (that is in more than one quadrant) that requires treatment.
5. Participant has visual acuity in at least one eye of 20/400 or better.
6. Participant is willing and able to comply with the study procedures.
7. Female participants of childbearing potential must not be pregnant or breast-feeding, have a negative pregnancy test at screening and must be willing to undergo pregnancy testing throughout the study.
8. Both female participants of childbearing potential (see Appendix 2 for definition) and male participants able to father a child must have (or have a partner who has) had a hysterectomy

or vasectomy, be completely abstinent from intercourse or must agree to practice two effective methods of contraception throughout the course of the study and for six weeks after the last investigational product injection. Acceptable methods of contraception for this study include:

- hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring),
- intrauterine device,
- barrier methods (diaphragm, condom) with spermicide, or
- surgical sterilization (tubal ligation).

3.2 Exclusion Criteria

1. Participant has a significant active infection (an infection requiring treatment as determined by the medical team), including active tuberculosis or human immunodeficiency virus (HIV).
2. Participant received a live vaccination within the past six weeks.
3. Participant is expected to receive a live vaccination at any time during the study.
4. Participant received the Bacillus Calmette-Guérin (BCG) vaccine within the past year.
5. Participant is expected to receive the BCG vaccine at any time during the study or up to one year after discontinuing ustekinumab.
6. Participant has a history of cancer (other than a non-melanoma skin cancer) diagnosed within the past five years.
7. Participant has received intraocular (or periocular) steroid or anti-vascular endothelial growth factor (VEGF) injections within the last six weeks.
8. Participant received rituximab within the last six months or another biologic agent (e.g., infliximab, daclizumab, adalimumab) within the last two months.
9. Participant has received alkylating agents (e.g., cyclophosphamide, chlorambucil) within the last nine months.
10. Participant has a known hypersensitivity to ustekinumab or any of its components.

3.3 Choice of Study Eye

Since this is a systemic treatment, a study eye selection does not apply. Any eye meeting the eligibility criteria will be considered in the outcomes.

4.0 Study Design and Methods

This is a prospective, non-randomized, uncontrolled, single-center, two-arm pilot study to evaluate ustekinumab as a possible treatment for active intermediate uveitis, posterior uveitis or panuveitis. The first cohort will receive a 90 mg subcutaneous injection of ustekinumab at Weeks 0, 4 and 8. The second cohort will receive an initial high, weight-based dose of ustekinumab via intravenous infusion, followed by a single, 90 mg subcutaneous injection of ustekinumab at Week 8. In participants who demonstrate allergic reaction to the first dose, the second dose can also be administered as IV infusion with pre-infusion desensitization instead of a subcutaneous injection as it allows better control on the rate of drug administration.

4.1 Recruitment

Participants will be recruited from the NEI uveitis clinic. In addition, the study will be posted on the National Library of Medicine (NLM) and the NEI and the Clinical Center (CC) web sites. Self-referral and referral from outside physicians will be permitted. The projected recruitment time is approximately 12 months.

4.2 Screening

Participants will be screened under one of the following protocols: NEI Screening protocol (NIH Protocol 08-EI-0102), NEI Ocular Natural History protocol (NIH Protocol 16-EI-0134) or NEI iBank protocol (NIH protocol 16-EI-0046) to establish eligibility. Baseline examinations include a medical/ophthalmic history, a vaccination history, physical examination, vital signs and a concomitant medication assessment. Ophthalmic assessments include best-corrected visual acuity (BCVA) with manifest refraction, slit lamp examination, intraocular pressure (IOP) measurement, dilated fundus examination, color fundus photography, fluorescein angiogram (FA) and optical coherence tomography (OCT). The procedures must be performed on both eyes, where appropriate. Laboratory assessments include a complete blood count (CBC) with differential, acute care, mineral and hepatic laboratory panels, urinalysis, TB screening, HIV screening and pregnancy testing. These are outlined in Appendix 3. Some of the baseline examinations may be performed under the NEI screening, ocular natural history or iBank protocols (see Appendix 3). If determined eligible, the participant will enroll by signing this protocol's consent form and complete any remaining baseline procedures at the first study visit.

4.3 Study Procedures

Following completion of screening procedures and enrollment, eligible participants in the first cohort will receive an initial subcutaneous injection of ustekinumab. Second and third subcutaneous injections of ustekinumab will be given at Weeks 4 and 8. Following protocol Amendment G, eligible participants in the second cohort will receive an initial weight-based intravenous infusion of ustekinumab, followed by a single subcutaneous injection at Week 8. In participants who demonstrate allergic reaction to the first dose, the second dose can be administered as IV infusion with pre-infusion desensitization instead of a subcutaneous injection as it allows better control on the rate of drug administration.

For both cohorts, participants that experience recurrence (or those that are nonresponders) (see Appendix 1 for definition) by Week 16 can receive standard of care. Participants may continue to receive ustekinumab through Week 8 unless there is a medical contraindication (e.g., severe infection or severe allergic reaction). The last injection will occur at the Week 8 visit followed by monthly visits until Week 16 and a final safety visit at Week 28.

The Week 4 and 8 visits must be conducted within a window of ±5 days from the target day and the remaining visits must be conducted within a window of ±14 days. The examinations scheduled at each visit can be completed over 1-3 days (though we expect that they will be completed in one day).

Each participant will be instructed to contact the study investigators upon experiencing any symptoms of flare-up. Such symptoms include: blurred vision, decreased visual acuity, floaters, pain, redness, irritation or photophobia. Participants experiencing flare-up symptoms during the study duration will return to the clinic as soon as possible for evaluation.

A physical examination will be performed at Baseline, Weeks 4, 8 and 28. Vital signs, a live vaccination history query, concomitant medications assessment and an adverse event assessment will be completed at every visit.

BCVA, manifest refraction, a slit lamp examination, IOP, dilated fundus examination and OCT will be assessed at every visit. The imaging (color fundus photography and fluorescein angiogram) will be collected at Baseline, Weeks 8, 12, 16 and 28.

The laboratory assessments (CBC with differential, acute care, mineral and hepatic panels and urinalysis) will be monitored throughout the study at Baseline, Weeks 4, 8 and 28. Women of childbearing potential (see Appendix 2 for definition) will undergo pregnancy testing at every visit.

Research blood (up to 60 mL per study visit) will be collected at Baseline, Weeks 4, 8, 16 and 28. The total amount of blood collected for research purposes will not exceed 360 mL. The research blood will be used for studying soluble and intracellular cytokine expression, proliferative or antibody responses, exosomes and epigenetic changes.

4.4 Ocular and Systemic Evaluations

In this study, examinations will be performed both as clinical care and for research purposes. The following examinations will be performed at the study visits as indicated in the study flowsheet (Appendix 3):

1. Medical/Ophthalmic History
2. Vaccination History
3. Physical Examination
4. Vital Signs
5. Concomitant Medications Assessment
6. Adverse Event Assessment
7. Best-Corrected Visual Acuity (BCVA) using EVA
8. Manifest Refraction
9. Slit Lamp Examination
10. Intraocular Pressure (IOP)
11. Dilated Fundus Examination
12. Color Fundus Photography
13. Fluorescein Angiography (FA)[1]
14. Optical Coherence Tomography (OCT)
15. Complete Blood Count (CBC) with Differential
16. Acute Care Panel
17. Mineral Panel
18. Hepatic Panel
19. Urinalysis
20. Tuberculosis (TB) test (PPD or Quantiferon testing)
21. HIV Test
22. Pregnancy Test for Women of Childbearing Potential (serum) (see Appendix 2)
23. Research Blood Collection

[1]Participants who are allergic to fluorescein dye are exempt from this procedure.

4.5 Follow-up/Termination Procedures

After Week 8, participants will no longer be able to receive investigational product under this protocol. Participants will be followed through Week 28. If the participant withdraws or terminates prior to Week 28, follow-up care will be arranged with an outside ophthalmologist or the participant may continue to be seen at the NIH under another protocol, if available and if the participant is eligible. The participants and their physicians, with written consent, will be informed of the participant's disease status during this study. Clinical data obtained during participation will be shared with the participant and their private physicians (with written permission from the participant). Results from the overall study will be shared once the study team has analyzed the data from all participants.

4.6 Management of Samples and Data

Research blood samples will be stored for this study. The samples will be coded and stored in secured freezers on the NIH campus. The clinical data will be stored in the NEI's research database and The Emmes Company's secured database. All individual data will remain confidential.

Research blood samples may be stored for future use at the NEI as specified in the informed consent document. The participant has a choice to limit sample usage by selecting one of the following consent options:

Your samples may be used for other research projects, including those not related to uveitis if you agree. Please initial on the line below that reflects your choice:

_____*YES My samples and data may be used for other research projects including those not related to uveitis.*

_____*NO I do not want my samples and data used for other research projects. Please destroy my samples once this project is complete.*

4.7 Data and Sample Sharing Plan

If the participant is enrolled in other NEI protocols, identifiable data and samples may be shared with investigators across these studies to help minimize the need to repeat procedures if data and samples are already collected.

Samples and data, including genomic data, will be shared with other sites only after all requirements are met.

Data and samples may also be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases if consent for sharing was obtained. Repositories receiving data and/or samples from this protocol may be open-access or restricted access.

Samples and data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators, but will remain at NIH. Data and samples may be shared with investigators and institutions with an FWA or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

4.8 Study and Concomitant Therapies

4.8.1 Ustekinumab Formulation

Ustekinumab (STELARA®) for subcutaneous injection is supplied as a sterile solution in a single-use, pre-filled syringe with a 27-gauge fixed ½-inch needle, or a single-use 2 mL Type I glass vial with a coated stopper. The pre-filled syringe formulation will be used for this study. The syringe is fitted with a passive needle guard and a needle cover that is manufactured using a dry natural rubber (a derivative of latex).

Each pre-filled syringe contains 90 mg ustekinumab along with: L-histidine and L-histidine monohydrochloride monohydrate (1 mg), polysorbate 80 (0.04 mg) and sucrose (76 mg) to fill to a final volume of 1.0 mL.

Ustekinumab (STELARA®) for intravenous infusion is supplied as a single-dose 26 mL Type 1 glass vial with a coated stopper. Each 26 mL vial contains 130 mg ustekinumab, ethylene diamine tetraacetic acid disodium salt dihydrate (0.52 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

The ustekinumab solution ranges from colorless to slightly yellow in appearance and has a pH of 5.7 – 6.3. Ustekinumab does not contain preservatives.

4.8.2 Ustekinumab Storage

Ustekinumab pre-filled syringes and vials will be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). The investigational product will remain in the original carton to protect it from light until the time of use and will not be frozen or shaken before use. Ustekinumab does not contain a preservative; therefore, any unused portions will be discarded following administration.

4.8.3 Ustekinumab Preparation and Administration

4.8.3.1 Subcutaneous Administration

Prior to administration, the syringe must be visually inspected for particulate matter and discoloration. Ustekinumab ranges from colorless to light yellow and may contain a few small translucent or white particles. The investigational product must not be used if it is discolored or cloudy, or if other particulate matter is present (see Appendix 4 for administration instructions).

The needle cover on the pre-filled syringe contains dry natural rubber (a derivative of latex). The needle cover must not be handled by study personnel sensitive to latex. Each injection will be administered at a different anatomic location than the previous injection (e.g., upper arms, thighs, or any quadrant of abdomen) and not into areas where the skin is tender, bruised, erythematous or indurated.

4.8.3.2 Intravenous Administration

The intravenous solution must be diluted and prepared prior to administration. The dose will be calculated based on the participant's weight as described below. IV administration will be performed in the day hospital of the Clinical Center.

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
More than 55 kg to 85 kg	390 mg	3
More than 85 kg	520 mg	4

Prior to preparing the dose, 20 mL of 0.9% Sodium Chloride, USP from a 250 mL bag will be drawn up and discarded. This is the estimated bag overfill volume. To prepare the dose, a volume of the 0.9% Sodium Chloride Injection, USP from the 250 mL infusion bag equal to the volume of investigational product to be added will be withdrawn and discarded (discard 26 mL sodium chloride for each vial of investigational product needed, for two vials, discard 52 mL, for three vials- discard 78 mL, four vials- discard 104 mL). Twenty-six (26) mL of the investigational product will be withdrawn from each vial needed and added to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL.

The diluted solution must be visually inspected before infusion. The investigational product must not be used if visibly opaque particles, discoloration or foreign particles are observed. The diluted solution should be infused over a period of at least one hour. Once diluted, the infusion solution may be stored for up to four hours prior to infusion. Only an infusion set with an in-line, sterile, non-pyrogenic, low protein binding filter (pore size 0.2 micrometer) will be used. STELARA® will not be infused concomitantly in the same intravenous line with other agents. Any remaining solution will be discarded.

4.8.4 Concomitant Therapy

Participants will be allowed to remain on Prednisone at a maximum dose of 20 mg (if this was their existing regimen) and another nonbiologic immunomodulatory agent (e.g., MTX, azathioprine, cyclosporine, etc.). Tapering of topical treatments and systemic immunosuppressives, including steroids, if needed, may start after Week 16 if the disease is quiet (or anytime if medically indicated such as due to an intolerable side effect). An increase in immunosuppressive therapy in the first 16 weeks will only be done if there is significant vision loss (≥15 letters) from baseline due to worsening inflammation. Treatment for recurrences/worsening disease will be done according to standard of care.

4.8.5 Investigational Product Accountability

The NIH Pharmacy is responsible for the accountability of all unused investigational product. Adequate investigational product accountability records include documentation of all investigational product shipped, received, stored and dispensed by the NIH Pharmacy. The investigator is responsible for the accountability of all used investigational product. Adequate investigational product accountability records include documentation of all investigational product administered by and disposed by the investigator. Used investigational product will be disposed in the hazardous waste disposal bins.

5.0 Risks/Discomforts

5.1 Examination Risks

There are risks associated with the procedures required for participants in this study. However, these are all standard procedures that are performed as part of a normal eye and medical examination, except for the ustekinumab injections and the research blood collection. Some of the discomforts associated with the ocular examination include the following:

1. Dilating drops or anesthetic drops may sting. They can cause an allergic reaction, or if contaminated, can cause an infection, but neither of these problems is very likely to occur. Dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment is available. The participant's IOP will be obtained at each ophthalmic examination to determine whether there is an increased risk of developing glaucoma.
2. Color fundus photographs involve a bright flash to take pictures of the retina. This brief flash may cause temporary discomfort but does not damage the eye.
3. In rare instances, the cornea may be scratched during measurement of IOP or use of a funduscopic contact lens. A corneal abrasion of this sort may be painful, but it heals quickly with no lasting effects.
4. The fluorescein dye used in fluorescein angiography can make a participant's skin turn yellow for several hours. This yellow color is transient and usually disappears in one day. Because the dye undergoes renal excretion, the participant's urine will turn dark orange for

up to 24 hours after the examination. The study team will educate the participant regarding this urine color change. Some participants may be slightly nauseated during the examination, but their nausea usually lasts only a few seconds. If the dye extravasates during the injection, the skin around the injection site may feel mildly uncomfortable or become yellow. The discomfort usually lasts only a few minutes, and the yellow color fades in a few days. There is a chance of ecchymosis at the site of injection and a remote possibility of cellulitis from the needle track. In rare cases, participants may have an allergic reaction to the dye. Treatment typically consists of an oral antihistamine medication, but may require intravenous antihistamine administration if the symptoms are severe. Very rarely a participant experiences anaphylaxis. This would be treated immediately by trained personnel with medications or, if necessary, intubation.

Possible discomforts associated with non-ocular examinations include:

1. Blood draws can cause discomfort and bleeding/bruising at the site of venous puncture. There is a remote risk of fainting or local infection. If any of these discomforts arise, they will be treated.

5.2 Ustekinumab Risks

5.2.1 Administration-related Risks

There is minimal risk associated with subcutaneous injections. Common risks include bruising, itching, swelling, irritation, transient pain or injection site redness and, very rarely, injection site infection. In trials with ustekinumab, injection site reactions occurred in approximately 1% of patients receiving ustekinumab injections and 0.4% of patients receiving placebo injections.

There is minimal medical risk associated with intravenous infusions. Common risks include discomfort and bruising from the needle insertion. The risks of an intravenous catheter include bleeding, infection, or inflammation of the skin and/or vein.

5.2.2 Ustekinumab-related Risks

Ustekinumab may increase the risk of infections and reactivation of latent infections, including serious bacterial, fungal and viral infections. Serious infections include cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia and urinary tract infections. Serious infections from mycobacteria, *Salmonella* and BCG vaccinations have been reported in

patients genetically deficient in IL-12/IL-23. Because of a risk of worsening a latent infection such as TB, all participants will be monitored for TB prior to enrollment.

Participants being treated with ustekinumab should not receive live vaccines. BCG vaccines should not be given during treatment with ustekinumab or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of participants receiving ustekinumab because of the potential risk for shedding from the household contact and transmission to participant. Non-live vaccinations received during a course of ustekinumab may not elicit an immune response sufficient to prevent disease.

Because ustekinumab is an immunosuppressant it may increase the risk of malignancy. Although rare, anaphylaxis or serious allergic reactions may occur. The infusion can be preceded by pretreatment with Benadryl, Tylenol and IV solumedrol to minimize infusion reactions. In participants who demonstrate allergic reaction to the first dose, the second dose may be administered as IV infusion with pre-infusion desensitization instead of subcutaneous injection as it allows better control on the rate of drug administration. Although extremely rare, there is a risk of reversible posterior leukoencephalopathy syndrome (RPLS), as one case was reported. RPLS can present with headache, seizures, confusion and visual disturbances. Other risks include upper respiratory infections, headache and tiredness.

In the placebo-controlled clinical studies of psoriasis patients, subject-reported infection rate was 1.39 per subject-year of follow-up in the ustekinumab-treated group, compared with 1.21 per subject-year of follow-up in the placebo-treated group. Serious infections occurred in 0.3% of ustekinumab-treated patients (0.01 per subject-year of follow-up) and in 0.4% of placebo-treated patients (0.02 per subject-year of follow-up). Serious infections were reported in 0.9% of patients (0.01 per subject-year of follow-up).[9]

More than 3,000 psoriasis patients have used ustekinumab, including 2,414 exposed for at least six months, 1,855 exposed for at least one year, 1,653 exposed for at least two years, 1,569 exposed for at least three years, 1,482 exposed for at least four years and 838 exposed for at least five years.[9] Safety data available from these patients are illustrated below. Adverse reactions that occurred at a rate of at least 1% and at a higher rate in the ustekinumab-

treated groups than the placebo-treated groups during the placebo-controlled studies (PHOENIX 1 and 2) are shown below:

	Placebo	STELARA™ 45 mg	STELARA™ 90 mg
Subjects treated	665	664	666
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache and fatigue. Adverse drug reactions that occurred at rates less than 1% included: cellulitis, and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising and irritation).

Adverse reactions occurring in ≥3% of STELARA®-treated patients and higher than placebo during the placebo-controlled CD studies (CD-1 and CD-2) are shown below. Overall, the safety profile of STELARA® was consistent with the safety profile seen in the adult psoriasis and psoriatic arthritis clinical studies.

Common adverse reactions through Week 8 in Studies CD-1 and CD-2occurring in ≥3% of STELARA®-treated patients and higher than placebo:

	Placebo N=466	**STELARA® 6 mg/kg single intravenous induction dose N=470**
Vomiting	3%	4%

Other less common adverse reactions reported in patients in Studies CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Common adverse reactions through Week 44 in Study CD-3 occurring in ≥3% of STELARA®-treated patients and higher than placebo:

	Placebo N=133	STELARA® 90 mg subcutaneous maintenance dose every 8 weeks N=131
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

In CD trials the incidence of hypersensitivity reaction was encountered in two patients, one following SC administration and one following IV administration (0.1% among SC dosing and 0.08% among IV dosing). Immunogenicity to ustekinumab (antibodies against ustekinumab) was less common in CD Trials (<3%) than was observed in Psoriasis trials (6-12%). Rate of incident non-melanoma skin cancers were similar between placebo and STELARA® treated CD patients (0.2%). All other malignancies occurred in 0.2% of STELARA® treated patients (0.27 events per 100 patient years). In CD studies, immunomodulators (6-mercaptopurine, azathioprine, methotrexate) were used concomitantly in approximately 30% of patients and corticosteroids were used concomitantly in approximately 40% of patients. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of STELARA®.[9]

6.0 Participant Monitoring

Participants will be monitored during all study visits for adverse events by the study investigators.

6.1 Withdrawal Criteria

Participants may choose to withdraw from this study for any reason at any time without penalty, without loss of benefits or prohibition from enrolling in other clinical protocols. Reasons for participant discontinuation may include, but are not limited to, the following:

- Investigator determination that study continuation is not in the best medical interest of the participant;
- Findings in the course of the trial that may affect willingness to participate;
- Participant requires additional medicines or intravitreal injections that will interfere with the investigational product;
- Serious suspected adverse reaction;
- Participant requires ocular surgery which cannot safely be postponed until the end of the study;
- Any other safety concerns;
- Inability to keep study visits or to comply with study requirements.

Study staff will request participants complete the study even if they are discontinued from the investigational product. Otherwise, the participant will exit the study and continue his/her ophthalmic care either with an outside ophthalmologist or at the NEI. The participant will be monitored by study investigators and clinical staff at each visit to the clinic.

6.2 Pregnancy Monitoring

If the staff becomes aware that a female study participant became pregnant during the study, the investigator will advise the participant that they will no longer receive the investigational product. The investigator and participant will determine whether to continue any remaining study visits or to exit the study.

If the staff becomes aware that a male study participant impregnates his partner during the study, the investigator will remind the participant of the potential risks to the unborn fetus.

In either case of reported pregnancy, participant will be referred to the NIH OB/GYN consultation service for evaluation and counseling. The investigator must follow the participant (or partner) until the pregnancy outcome.

7.0 Outcome Measures

7.1 Primary Outcome

The primary outcome for each cohort is the number of participants who experience a treatment response (as defined in Appendix 1) by Week 16.

7.2 Secondary Outcomes

The secondary outcomes include the following, as relevant to baseline:

- Mean and median change in visual acuity via EVA at all follow-up visits;
- Number of participants who experience a recurrence (as defined in Appendix 1);
- Mean and median number of days following the baseline injection until first recurrence (of the participants who recur);
- Presence or extent of macular edema as determined by OCT and FA at all follow-up visits;
- Amount of retino-vascular leakage as measured by FA at all follow-up visits;
- Changes in retinal thickening as measured by OCT at all follow-up visits;
- Length of time to quiescence;
- Ability to taper concomitant immunosuppressive medications.

7.3 Safety Outcomes

Safety outcomes include:

- Number and severity of systemic and ocular toxicities and adverse events;
- Proportion of participants with loss of ≥15 letters at any follow-up visit;
- Number of participants experiencing a clinically significant increase in elevated IOP at any follow-up visit. A change ≥10 mmHg as compared with baseline is considered a clinically significant increase.

7.4 Exploratory Outcomes

Participant serum and lymphocytes will be analyzed for soluble cytokines, exosomes and intracellular immune markers as well as RNA-Seq before and after therapy at regular time points. Lymphocyte proliferation prior to and following treatment will be assessed. The changes in epigenetic modification following treatment will also be assessed.

8.0 Statistical Analysis

The primary efficacy analyses will include all participants who receive ustekinumab and complete the Week 16 visit. The secondary and safety analyses will include all participants who receive ustekinumab and complete the Week 16 visit.

8.1 Study Design and Primary Analysis

In this prospective, non-randomized, uncontrolled, single-center, two-arm pilot study, analyses will be primarily descriptive and by participant. As the small sample size does not lend itself to formal statistical analyses, no formal statistical hypothesis tests will be performed. Slit lamp examination will be evaluated at each scheduled visit, with the primary outcome defined as the number of participants who experience a treatment response by Week 16. Treatment response is defined as (all of the below for both/eligible eyes):

- No active inflammatory chorioretinal lesion and/or absent or decreased retinal vascular leakage
- ≤ 0.5+ anterior chamber (AC) cells (SUN criteria)
- ≤ 0.5+ vitreous haze (VH; National Eye Institute [NEI]/SUN criteria)

8.2 Analysis of Secondary Outcomes

In general, secondary outcomes will be monitored throughout the study period in both the study and non-study eyes. The mean and median change in visual acuity via EVA and number of days until first recurrence will be calculated at all follow-up visits. The number of participants who experience a recurrence (as defined in Appendix 1), the presence or extent of macular edema as determined by OCT and FA, the amount of retino-vascular leakage as measured by FA, changes in retinal thickening as measured by OCT, length of time to quiescence and ability to taper concomitant immunosuppressive medications will be tabulated by participant at all follow-up visits.

Safety outcomes, including the number and severity of systemic and ocular toxicities and adverse events, will be tabulated by severity, type and assessed relatedness to the study therapy throughout the study period.

8.3 Sample Size/Accrual Rate

For the first cohort, the accrual goal is to have four participants receive three ustekinumab injections and complete at least 12 weeks of follow-up. For the second cohort, the accrual goal is to have four participants receive the high induction dose via IV, followed by one subcutaneous injection and complete at least 12 weeks of follow-up. These are appropriate sample sizes for the

study objectives, since this preliminary investigation will not attempt to definitively determine the safety or efficacy of this treatment.

9.0 Human Subjects Protection

9.1 Equitability

Accrual for this study will be equitable among patients with uveitis meeting the enrollment criteria.

9.1.1 Justification for the Exclusion of Children

Children are not eligible for this study due to the lack of safety information for ustekinumab injection in children.

9.1.2 Justification for the Exclusion of Pregnant or Lactating Women

Pregnant or lactating women are excluded because of the unknown effects of ustekinumab injection on the fetus or nursing baby.

9.1.3 Justification for Exclusion of Persons Who Cannot Consent

Adults unable to understand and sign an informed consent are excluded from this study because they are frequently unable to cooperate with evaluation and testing in the manner standardized for other adult participants. The research question can be answered by enrolling only adults who can provide their own consent and there is no direct clinical benefit for the participant. Thus, the risks will outweigh the benefit for this population.

10.0 Consent Documents and Process

Study investigators with consenting privileges will obtain informed consent. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study. Participants must have the ability to understand and sign an informed consent form, which must be signed prior to enrollment. Participants will have the opportunity to carefully review the consent and ask questions regarding this study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves or benefits lost.

If a participant requires the consent to be in larger font in order to read it well, this will be provided. If a participant is visually impaired to the point of being unable to read the consent, s/he can take

the consent home to read it over with a family member or with the use of magnifying devices. If a participant chooses, the investigator can also read the consent verbatim to the participant and answer any questions that may arise.

Because ustekinumab is commercially-available, participants must be given a current copy of the STELARA® Medication Guide, which describes both subcutaneous and intravenous medication and associated risks in further detail. The Medication Guide will be reviewed with the participant along with the informed consent for this study.

An investigator present during the consent process will document the consent process in the participant's medical record. A copy of the signed informed consent form will be provided to the participant to take home.

11.0 Data and Safety Monitoring

The NEI Serious Adverse Event (SAE) Review Committee is responsible for monitoring data and safety and will exercise oversight of the clinical investigation independently from the study investigators.

11.1 Coordinating Center

The Emmes Company, LLC (Emmes) has been assigned as the coordinating center for this trial to conduct data collection, protocol monitoring, data analysis and reporting. The coordinating center provides routine monitoring of study participants' data. Monitoring visits will occur on a schedule depending on the status of the study. More frequent monitoring visits will be performed at the beginning of the study when enrollment is open. Monitoring will decrease as enrollment closes and as participant follow-up continues.

Although Emmes advises the NEI Clinical Director and Principal Investigator (PI) on data and statistical activities, the coordinating center staff does not have direct access to or interaction with participants.

11.2 NEI Serious Adverse Event Review Committee

The NEI SAE Review Committee, which consists of the NEI Clinical Director and three other NEI physicians, will be responsible for reviewing any reported serious safety events, if they occur under

this protocol. The Committee will review accumulating data on a semiannual basis to determine whether the study should continue. If changes to the protocol are indicated, recommendations will be made to the NEI Director and IRB who will consider and act on such recommendations in a timely manner. Should any serious suspected adverse reactions occur, the NEI Clinical Director may, at his discretion, assemble the Review Committee before the scheduled date to consider whether the study should move forward. The Committee or Principal Investigator can stop the study at any time if it appears there are any unexpected serious suspected adverse reactions that would outweigh any potential benefits of treatment.
In addition, if three or more participants experience non-serious suspected adverse reactions that require temporary or permanent cessation of the investigational product, the Principal Investigator shall report this to the NEI Clinical Director. The NEI Clinical Director may convene the Review Committee before the scheduled time to consider the cessation of the study as a whole. The NEI SAE Review Committee or IRB may recommend temporarily suspending, closing enrollment or stopping the study at any time due to safety concerns, demonstration of efficacy or lack of efficacy or slow recruitment.

12.0 Quality Assurance

The NEI and Emmes maintain quality control by adhering to standard operating procedures (NEI QA program and NEIS standard operating procedures). These procedures cover the full protocol cycle beginning with staff credentialing and training, and protocol development and approval, through database development, data collection, monitoring and analysis, and finally manuscript preparation at the conclusion of the study. Data quality assurance is of the utmost importance to the NEI and Emmes. The two groups use a quality assurance system that relies on real-time data checks and reports throughout the course of a study to ensure the accuracy of information. This system is a secure and confidential data management system that stores data and provides quality assurance and reporting. Emmes has developed a number of routine reports specifically designed for monitors (e.g., listings of serious adverse events, etc.).

Additionally, Emmes has developed summary reports of discrepancies, as well as reports of the exceptions databases, which include requests and reasons for exceptions. The results of the reports are communicated back to site staff, and, along with protocol compliance issues, to the NEI Serious Adverse Event Review Committee (if applicable).

Following the monitoring plan for this study, Emmes will perform monitoring activities, including on-site audits, review of database entries and the resolution of study issues. In addition to monitoring, Emmes performs various detailed automated and manual data quality checks. The results from these checks and any protocol compliance issues are communicated back to site staff and to the NEI Project Officer, NEI Clinical Director and applicable regulatory bodies.

13.0 Reportable Events

Reportable events will be tracked and submitted to the IRB as outlined in Policy 801.

14.0 Alternative Therapies

Alternatives to participation include continuation with the current standard-of-care, which includes the use of systemic steroids, periocular steroids and systemic immunosuppressive agents.

As ustekinumab is commercially available, participants may be able to receive this drug from their physician for "off-label" use.

15.0 Privacy

All research activities will be conducted in as private a setting as possible.

16.0 Confidentiality

Blood samples will be stored for the purposes of this study. The samples will be coded and stored in secured freezers on the NIH campus. All medical records will be kept confidential and will only be reviewed by the participating investigators. Data will be kept in password-protected computers held at the NEI and the coordinating center. Only study investigators and authorized coordinating center staff will have access to the study data. The participants' names will not appear on any of the data forms reported to the coordinating center. A unique identifier, without personally identifying information but linked to a code retained by the investigators, will be assigned to data if participant information is shared with the coordinating center for research purposes. The participants' names will not appear in any publication of the study results. Participants' personal information will be kept as private as possible. However, records can be inspected by organizations for quality assurance and data analysis. These include the members of the IRB, coordinating center and NEI Serious Adverse Event Review Committee.

17.0 Conflict of Interest

The NIH guidelines were distributed to all the investigators and none of the investigators had any conflicts of interest.

18.0 Technology Transfer

There are no technology transfer agreements for this study.

19.0 Compensation

For this study, there is no compensation for participation. This protocol does not include reimbursement for travel and subsistence. Participants needing financial assistance will be able to receive supplemental reimbursement based upon need. Requests for supplemental reimbursement will be evaluated on a case-by-case basis for valid financial and/or medical need through a standardized process.

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Appendix 1: Definitions of Disease Activity

Active disease is defined as:

- +1 or more vitreous haze (according to SUN criteria[18]); and/or
- Active chorioretinitis or leakage on FA (that is in more than one quadrant) that requires treatment.

Recurrence is defined as presence of one of the following four parameters in at least one eye:

1. New active inflammatory chorioretinal lesion and/or retinal vascular leakage.

2. A 2+ increase in AC cells relative to Baseline (SUN criteria). This is represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

3. A 2-step increase in vitreous haze relative to Baseline (NEI/SUN criteria). This is represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

4. Worsening of BCVA by ≥ 15 letters (ETDRS) relative to Baseline.

Treatment response is defined as (all of the below for both/eligible eyes):

- No active inflammatory chorioretinal lesion and/or absent or decreased retinal vascular leakage
- ≤ 0.5+ anterior chamber (AC) cells (SUN criteria)
- ≤ 0.5+ vitreous haze (VH; National Eye Institute [NEI]/SUN criteria)

Appendix 2: Determining Childbearing Potential

A female participant who is considered non-childbearing due to a medical condition (i.e., participant has previously undergone a hysterectomy) does not need a pregnancy test, Follicle-stimulating Hormone (FSH) test or contraception.

If a female participant is considered non-childbearing due to menopause, it must be in accordance with the IRB/NIH Ob-Gyn guidance on the definition of menopause. This guidance defines menopause as:

Women over age 55 who have not had a period for one year will be considered menopausal and do not need a pregnancy test, FSH test or contraception.

Women between 50 and 55, who have not had a period for one year, should have an FSH test. If their FSH level is ≥ 20 mIU/mL, they will be considered menopausal and do not need pregnancy testing or contraception. If their FSH level is < 20 mIU/mL, they will need pregnancy testing and contraception as required by the protocol.

Women between 45 and 50 who have not had a period for one year will need both an FSH test and a pregnancy test. If they are not pregnant and their FSH level is ≥ 20 mIU/mL, they will be considered menopausal and will not require contraception or additional pregnancy testing. If their FSH test is < 20 mIU/mL, they will need pregnancy testing and contraception as required by the protocol.

Appendix 3: Study Flowsheet

Visit Schedule (Weeks)	0[1]	4	8	12	16	28[2]
Visit Number	000	004	008	012	016	028
Target Day from Baseline	0	28	56	84	112	196
Visit Window (days)	N/A	± 5	± 5	± 14	± 14	± 14
Investigational Product						
Intravenous Ustekinumab*	X				Primary outcome assessment	Safety visit
Subcutaneous Ustekinumab**			X			
General Assessments						
Medical/Ophthalmic History	X					
Vaccination History[3]	X	X	X	X	X	X
Physical Examination	X	X	X			X
Vital Signs	X	X	X	X	X	X
Concomitant Medications Assessment	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X
Ophthalmic Assessments						
BCVA (EVA)	X	X	X	X	X	X
Manifest Refraction[4] (MRx)	X	X	X	X	X	X
Slit Lamp Examination	X	X	X	X	X	X
Intraocular Pressure (IOP)	X	X	X	X	X	X
Dilated Fundus Examination	X	X	X	X	X	X
Color Fundus Photography	X[6]		X	X	X	X
Fluorescein Angiogram[5] (FA)	X[6]		X	X	X	X
Optical Coherence Tomography (OCT)	X[6]	X	X	X	X	X
Laboratory Assessments						
CBC with Differential	X[7]	X	X			X
Acute Care, Mineral and Hepatic Panels	X[7]	X	X			X
Urinalysis	X[7]	X	X			X
TB Test (PPD or quantiferon testing)[8]	X					
HIV Testing[7]	X					
Pregnancy Testing (serum)[9]	X	X	X	X	X	X
Research Blood Collection	X	X	X		X	X

* Participants who enroll in the second cohort (subsequent to Amendment G) will receive one intravenous infusion at Week 0, followed by one subcutaneous injection at Week 8. In participants who demonstrate

allergic reaction to the first dose, the second dose may be administered as IV infusion with pre-infusion desensitization instead of subcutaneous injection as it allows better control on the rate of drug administration.

** Participants who enrolled prior to Amendment G received subcutaneous injections at Weeks 0, 4 and 8.

[1] All visits can be completed over one to three days.

[2] This visit represents the final safety visit.

[3] At each study visit, the participant will be asked whether they have received a live vaccine. The participant will be reminded to avoid live vaccines while on ustekinumab, including a reminder of the risks of infection from exposure to household members who receive a live vaccine.

[4] BCVA with manifest refraction must be performed when scheduled and when there is a change in visual acuity of ≥ 10 ETDRS letters (≥ 0.20 logMAR) from relevant baseline.

[5] Participants who are allergic to fluorescein dye are exempt from this procedure.

[6] These examinations can be performed within 7 days prior to enrollment under NIH protocols 08-EI-0102, 16-EI-0134 or 16-EI-0046.

[7] These laboratory assessments can be performed within 14 days prior to enrollment under NIH protocols 08-EI-0102, 16-EI-0134 or 16-EI-0046.

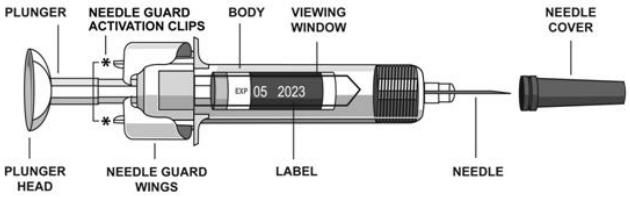
[8] Testing performed within three months prior to enrollment can be used to determine TB status.

[9] For women of childbearing potential only.

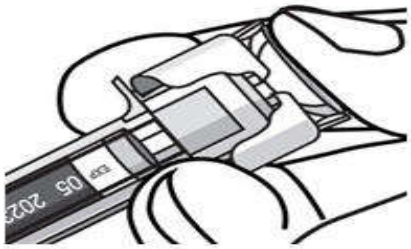
Appendix 4: Subcutaneous Injection Instructions

Refer to the diagram below for the provided instructions.

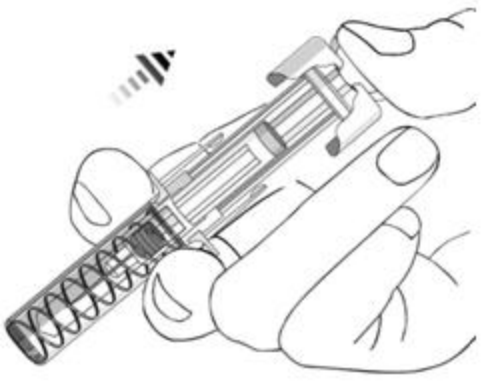
To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.



1. Hold the BODY and remove the NEEDLE COVER. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE COVER or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE COVER in place.**
2. Inject ustekinumab subcutaneously.
3. Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the needle guard wings. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard.**



4. After injection, maintain the pressure on the PLUNGER HEAD and remove the needle from the skin. Slowly take your thumb off the PLUNGER HEAD to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by the illustration below:



5. Used syringes should be disposed of in the hazardous waste bin.