CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Filgotinib in Subjects with Active Noninfectious Uveitis
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	133054
EudraCT Number:	2017-001485-17
Clinical Trials.gov Identifier:	NCT03207815
Indication:	Noninfectious Uveitis
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PPD :	Name: PPD Telephone: PPD Email: PPD
PPD	Name: PPD Telephone: PPD Email: PPD
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Filgotinib in Subjects with Active Noninfectious Uveitis
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	133054 2017-001485-17 NCT03207815
Study Centers Planned:	Approximately 75 centers globally
Objectives:	The primary objective of this study is: • To evaluate the efficacy of filgotinib versus placebo for the treatment of the signs and symptoms of noninfectious uveitis as measured by the proportion of subjects failing treatment for active noninfectious uveitis by Week 24 The secondary objectives of this study are: • To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the time to treatment failure on or after Week 6 • To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in vitreous haze (VH) grade in each eye (National Eye Institute / Standardization of Uveitis Nomenclature [NEI/SUN] criteria), from best state achieved prior to Week 6 to Week 52/ End of Treatment (EOT) visit or Early Termination (ET) visit • To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in anterior chamber (AC) cell grade in each eye, from best state achieved prior to Week 6 to Week 52/ EOT visit or ET visit • To evaluate the effects of filgotinib versus placebo as measured by the change in logarithm of the minimal angle of resolution (logMAR) best corrected visual acuity (BCVA) in each eye, from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in central retinal thickness in each eye, from best state achieved prior to Week 6 to Week 52/ EOT visit or ET visit
- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the time to development of macular edema in at least one eye as determined by optical coherence tomography (OCT) on or after Week 6
- To evaluate the safety and tolerability of filgotinib
- To evaluate the pharmacokinetics of filgotinib and its metabolite GS-829845

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Study Design:	This is a randomized, double-masked, placebo-controlled Phase 2 trial in adult subjects with active noninfectious intermediate-, posterior-, or pan-uveitis in at least one eye despite at least 2 weeks of maintenance therapy with oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent). The study is designed to demonstrate the efficacy and safety of filgotinib in adult subjects requiring high dose steroids for active noninfectious intermediate-, posterior-, or pan-uveitis. Both of the subject's eyes must be clinically evaluable for the purpose of determining eligibility based on inclusion and exclusion criteria, and for the purpose of assessing Treatment Failure. There will be no designated "study eye." Subjects will be randomized in a 1:1 ratio to receive filgotinib 200 mg once daily or placebo to match (PTM) for up to 52 weeks. Subjects that meet criteria for treatment failure or discontinue for any other reason prior to the end of the study will have an EOT or ET visit (as appropriate). Subjects that early terminate should also complete the 4-Week Post-Treatment Follow-Up Visit. It is anticipated that approximately twenty-five percent of subjects will have their uveitis attributed to sarcoidosis. Subjects will be stratified according to whether their uveitis is attributed to sarcoidosis (yes/no), baseline use of immunosuppressant(s) (yes/no), and prior use of anti-TNF therapy (yes/no). All subjects will be administered 60 mg/day of oral prednisone at Day 1/Baseline followed by a protocol-defined mandatory taper schedule in which all subjects continuing in the study will discontinue prednisone no later than Week 15. Subjects who enter the study on topical ocular corticosteroids will undergo a standardized taper schedule until they have completely discontinued topical ocular corticosteroids no later than Week 9. Depending on the topical ocular corticosteroid dose that the subject is on at the baseline visit, the number of drops per day will be decreased every week according to a predefined schedule (Section 3.3.1). Beginning at Week 6 and at all subsequent visits, subjects will be examined for evidence of treatment failure. Treatment failure will be defined as a subject meeting at least one of the elements of failure criteria in at least 1 eye as outlined in Table 3-3. Subjects with evidence of treatment failure at or after Week 6 will be discontinued from study and treated at the discretion of the investigator.
Number of Subjects Planned:	Approximately 248 subjects

Target Population:	Adult subjects 18 years or older with active, noninfectious intermediate-, posterior-, or pan-uveitis
Duration of Treatment:	Subjects will receive a maximum of 52 weeks of study drug in the randomized, double-masked trial
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Section 4.

Main Eligibility Criteria

1) Male or female subjects who are ≥18 years of age, on the day of signing informed consent
2) Subject is diagnosed with noninfectious intermediate-, posterior-, or pan-uveitis
3) Subject must have active uveitic disease at the Day 1/Baseline visit as defined by the presence of at least 1 of the following parameters in at least one eye despite 2 weeks or more of maintenance therapy with oral prednisone (≥ 10 mg/day to ≤ 60 mg/day) or oral corticosteroid equivalent:
   - Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesion
   - ≥ 2+ anterior chamber cells (SUN criteria)
   - ≥ 2+ vitreous haze (NEI/SUN criteria)
4) On oral prednisone ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent) for 2 or more weeks immediately prior to and including Day 1/Baseline
5) No evidence of active tuberculosis (TB) or untreated latent TB (Section 4.2)
6) Subjects with confirmed or suspected infectious uveitis or with clinically significant (as per the judgement of the investigator) active or chronic recurring infection, opportunistic infection, or immunodeficiency syndromes are not eligible to participate

7) Subjects with elevated intraocular pressures and/or severe glaucoma must meet the following criteria within the screening period:

- Intraocular pressure of < 25 mmHg in the absence of therapy or if on a single glaucoma medication
- Intraocular pressure of < 21 mmHg if on 2 or more glaucoma medications
- Subject must have no evidence of glaucomatous optic nerve injury that involves or encroaches on central fixation, regardless of intraocular pressure or number of glaucoma medications
- Subject must have no evidence of glaucomatous optic nerve injury that, in the opinion of the investigator, has the potential for splitting fixation or visual acuity loss during the course of the study, regardless of intraocular pressure or number of glaucoma medications

Study Procedures/ Frequency:

Participating subjects will visit the clinical study center at Screening, Day 1/Baseline, Weeks 1, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52/EOT or ET as applicable. If a subject presents at a site for an Unscheduled visit with symptoms related to a uveitis flare, subjects should be evaluated for treatment failure criteria in both eyes. If treatment failure criteria are met, investigators should complete EOT procedures. If a subject presents at a site for an Unscheduled visit not related to a uveitis flare, investigators should complete unscheduled visit procedures at their discretion.

All subjects will undergo a follow-up visit 4 weeks after the last dose of study drug (4-Week Post-Treatment Visit). Consequently, subjects are planned to be in the study (inclusive of screening and post study treatment follow-up) for up to 60 weeks.

Investigator confirmation of active uveitis in at least one eye (according to the inclusion criteria above) is required at Day 1/Baseline. In addition, information on demographics, medical history/concomitant diseases, as well as both prior and current uveitis medication(s) will be collected at Screening and Day 1/Baseline.

Screening assessments will include a complete physical exam (PE) (including height and weight), vital signs (ie, blood pressure, pulse rate, and temperature) and a standard 12-lead electrocardiogram (ECG). The ECG will be interpreted by the investigator (or qualified designee) for clinical significance. A chest x-ray is also required (if one has not already been obtained within 3 months prior to

screening). Additional screening laboratory assessments include the following:

- Hepatitis B virus (HBV) test
- Hepatitis C virus (HCV) test
- Human immunodeficiency virus (HIV) antigen/antibody combination test (4th generation) to HIV type 1 (HIV-1) and HIV type 2 (HIV-2)
- QuantiFERON® TB Gold in Tube Test
- Syphilis test (either a FTA test or a syphilis IgG test)
- Clinical laboratory tests (hematology, chemistry and urinalysis)
- Urine drug tests
- [redacted]
- Serum pregnancy test for females with childbearing potential or follicle stimulating hormone (FSH) test for females <54 years of age and amenorrhea of ≥12 months, as defined in Appendix 5.

The required screening labs can be obtained either using the sites local lab or by submitting appropriate samples to the central lab. Laboratory tests performed for the purposes of standard medical care can be used to satisfy eligibility criteria as long as they are completed within the allowable screening period (or within the stated period otherwise outlined in Appendix 2). The required study laboratory assessments are outlined in Appendix 2 (Study Procedures Table) and Appendix 6 (Clinical Laboratory Assessment) in detail.

At Day 1/Baseline, after the subject's eligibility for the study has been confirmed, the subject will be randomized into the study to receive filgotinib 200 mg daily or PTM. All subjects will receive a standardized prednisone dose of 60 mg/day at Day 1/Baseline followed by a protocol-defined mandatory taper schedule, as outlined in Section 3.3.1, in which all subjects continuing in the study will be off prednisone by Week 15.

Subjects who enter the study on topical ocular corticosteroids will undergo a standardized taper schedule beginning at Day 1/Baseline. Subjects must be off topical ocular corticosteroids by Week 9. Depending on the dose that the subject is on at the Day 1/Baseline visit, the number of drops per day will be decreased every week at the increments indicated in Table 3-2.

Subjects will be able to continue certain oral uveitis control medications, provided the subject is taking only one of the allowable

medications (within the specified dose range) detailed in Section 5.4.1 (Allowed Concomitant Medications).

Study medication will be dispensed and subjects and/or their care-giver will be instructed on the dosing schedule.

On-treatment assessments will include: adverse events (AEs), concomitant medications, review of study medication compliance through drug accountability, CCI [redacted] physical examination (PE), weight, vital signs, blood and urine sampling for safety laboratory tests CCI [redacted] and urine pregnancy tests for females of child bearing potential only.

Blood samples will be collected for plasma PK analysis of filgotinib and its metabolite GS-829845 at Day 1/Baseline and Week 12 (at least 30 minutes after dosing), within 2 hours prior to dosing on Weeks 4 and/or 6, and anytime at Week 24, 36 and the final assessment visit on Week 52/EOT or ET visit.

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Visual ophthalmologic efficacy assessments are described in Section 6.3.5 and detailed in the procedures table (Appendix 2). These assessments include determination of the following:

Best Corrected Visual Acuity (BCVA), tonometry, slit lamp exams and dilated indirect ophthalmoscopy with assessments for evidence of intraocular inflammation (AC cell grade and VH grade) will be conducted in both eyes at all study visits. AC cell and VH grade will be determined according to the NEI/SUN criteria. BCVA measurements will be performed under standardized lighting conditions by certified study examiners with best refractive correction in place, using standard logarithmic Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts. In the ETDRS system, 15 letters is equal to a change of 3 lines of visual acuity, for example, from 20/40 to 20/20 or vice versa, a halving or doubling of the visual angle; a change of 7.5 letters corresponds to a 25% decrease or 50% increase in the visual angle.

Fundus photographs using standardized protocols will be obtained in both eyes at Day 1/Baseline, at Week 24 and at the Week 52/EOT or ET visit. OCT scans using standardized protocols will be assessed in both eyes at all visits including Screening, on Day 1/Baseline (before dosing), and at Week 52/EOT or ET visit. The presence versus absence of macular edema is determined by OCT.

	Fluorescein angiograms (FA) will be obtained in both eyes on Day 1/Baseline (before dosing), Week 24 and at Week 52/EOT or ET visit. Additional ophthalmologic assessments (including imaging studies) which are done as a part of standard medical care may also be collected. If a subject presents at a site for an Unscheduled visit with symptoms related to a uveitis flare, subjects should be evaluated for treatment failure as detailed in the procedures table (Appendix 2). If treatment failure criteria are met, investigators should complete EOT procedures. If a subject presents at a site for an Unscheduled visit not related to a uveitis flare, investigators should complete unscheduled visit procedures at their discretion. Four week post-treatment follow-up assessments include ophthalmologic assessments, AEs, concomitant medications, PE, weight, vital signs, blood and urine sampling for safety laboratory tests, and urine pregnancy tests for females of child bearing potential only. Post-treatment assessments will occur 4 weeks after the last dose of study drug.
Test Product, Dose, and Mode of Administration:	200 mg filgotinib (1 × 200 mg tablet) administered orally once daily
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-match (PTM) filgotinib (1 tablet) administered orally once daily
Criteria for Evaluation:	
Safety:	Safety will be assessed by documentation of AEs, clinical laboratory tests, vital signs, and physical exams during the study.
Efficacy:	Primary Endpoint • Proportion of subjects failing treatment for active noninfectious uveitis by Week 24 Key Secondary Endpoints • Time to treatment failure at or after Week 6 • Change in VH grade in each eye (NEI/SUN criteria), from best state achieved prior to Week 6 to Week 52/EOT or ET visit • Change in AC cell grade in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit • Change in logMAR BCVA in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit

- Log change in central retinal thickness in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit
- Time to development of macular edema in at least one eye as determined by OCT on or after Week 6

Pharmacokinetics: Plasma concentrations of filgotinib and its metabolite, GS-829845, will be analyzed.

Statistical Methods:

The primary analysis set for efficacy analyses will be the Evaluable Analysis Set, which includes all randomized subjects who receive at least one dose of study drug and do not permanently discontinue from the study prior to Week 6.

The primary endpoint is the proportion of subjects failing treatment by Week 24. The primary analysis will consist of a superiority test of the filgotinib group compared to the placebo group based on the proportion of subjects failing treatment by Week 24. The Cochran-Mantel-Haenszel approach adjusting for the stratification factors will be used for the hypothesis testing of the primary endpoint.

The hypothesis testing of the following secondary endpoints will commence after the primary endpoint reaches statistical significance, and will be tested according to the hierarchical testing principle at the same significance level as the primary endpoint. That means, if a null hypothesis is not rejected for the higher ranked secondary endpoint, formal sequential testing will be stopped and only nominal significance will be reported for the remaining key secondary endpoints.

- Time to treatment failure on or after Week 6
- Change in VH grade in each eye (NEI/SUN criteria), from best state achieved prior to Week 6 to Week 52/ EOT visit or ET visit
- Change in AC cell grade in each eye, from best state achieved prior to Week 6 to Week 52/ EOT visit or ET visit
- Change in logMAR BCVA in each eye, from best state achieved prior to Week 6 to Week 52/ EOT visit or ET visit
- Log change in central retinal thickness in each eye, from best state achieved prior to Week 6 to Week 52/ EOT visit or ET visit
- Time to development of macular edema in at least one eye as determined by OCT on or after Week 6

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) by treatment group. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by treatment group.

Sample size calculations are based on published data from the VISUAL I trial {Jaffe 2016}. Assuming the observed proportion of subjects failing treatment by Week 24 is 70% in the placebo group, 107 subjects per treatment group will provide at least 85% power to detect a reduction of 20% in the proportion of subjects with treatment failure by Week 24 in the filgotinib group using a 2-sided significance level of 0.05. Given an expected attrition rate of 15%, a total of 248 subjects will need to be randomized into the study.

An interim analysis for efficacy and futility will be conducted when approximately 50% of enrolled subjects have either completed their Week 24 visit or discontinued from the study before Week 24. An efficacy analysis will be performed on the proportion of subjects failing treatment by Week 24, using the CMH approach adjusting for the stratification factors. The rejection boundary for efficacy will be based on a significance level of 0.001. A non-binding futility rule is defined as a predictive power (i.e., the probability of obtaining a statistically significant result at the final analysis given the observed interim data) being < 20%. If the Data Monitoring Committee (DMC) recommends early termination of the study, an internal Gilead team who are not involved with the study may perform an unmasked review of the interim data to determine the path forward. Gilead retains final decision-making authority on all aspects of the study.

To control for the overall type I error rate at 0.05, an alpha of 0.001 will be spent for the filgotinib group comparison to the placebo group based on the Haybittle-Peto boundaries at the interim analysis. As a result, an adjusted 2-sided significance level of 0.0498 will be used to declare statistical significance for the final primary analysis.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AC	anterior chamber
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibody
AST	aspartate aminotransferase
AUC	area under the curve
BCVA	best corrected visual acuity
BLQ	below the limit of quantitation
CD	Crohn's Disease
CIA	collagen-induced arthritis
CI	Confidence interval
C_{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
CVEAC	cardiovascular safety endpoint adjudication committee
CXR	Chest X Ray
CYP	cytochrome
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DAS28	Disease Activity Score based on 28 joints
EAU	experimental autoimmune uveitis
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
CCI	[redacted]
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSH	follicle stimulating hormone
FTA	flourescent treponemal antibody
GCP	Good Clinical Practice

Gilead	Gilead Sciences Inc.
GI	gastrointestinal
GLP	Galapagos
HBsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
HR	hazard ratio
HSV	herpes simplex virus
HTLV-1	Human T-Lymphotropic Virus Type 1
HZV	Herpes Zoster virus
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IL	interleukin
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
JAK	janus kinase
logMAR	logarithm of the minimal angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NEI/SUN	National Eye Institute/Standardization of Uveitis Nomenclature
CCI	[redacted]
OAT	Organic Anion Transporters
OCT	optical coherence tomography
PE	Physical exam
PK	Pharmacokinetics
PPD	Purified protein derivative
PT	preferred term
PTM	Placebo to match
PVE	Pharmacovigilance and Epidemiology
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
CCI	[redacted]

SI	International System of Units
SOC	System Organ Class
SOP	standard operating procedure
STAT	signal transduction and activation of transcription
SUSAR	suspected unexpected serious adverse reactions
TB	Tuberculosis
CCI	[redacted]
TEAEs	treatment-emergent adverse events
TNFα	tumor necrosis factor alpha
TYKs	tyrosine kinases
UC	ulcerative colitis
UGTs	uridine 5'-disphosphate glucuronosyltransferases
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
CCI	[redacted]
VH	vitreous haze
CCI	[redacted]

1. INTRODUCTION

1.1. Background

Filgotinib is a selective Janus kinase 1 (JAK1) inhibitor that is being developed for the treatment of multiple inflammatory diseases including rheumatoid arthritis (RA), Crohn's disease (CD) and ulcerative colitis (UC). Uveitis is a syndrome of intraocular inflammation resulting from a heterogeneous group of diseases including infection, systemic immune-mediated diseases, and conditions confined primarily to the eye. Epidemiologic studies estimate the incidence of uveitis in the United States (US) at around 17-52 cases per 100,000 person-years {Gritz 2004}.
The majority of uveitis cases involve the anterior uveal tract and are controlled successfully with topical therapy. However, approximately 20% of uveitis cases involve other areas of the eye, primarily the vitreous (intermediate uveitis), the choroid or retina (posterior uveitis), or the entire eye (panuveitis) {Jabs 2005}. These intermediate-, posterior-, and pan-uveitis subtypes are challenging to control and often require systemic or peri/intraocular corticosteroid therapies. While effective, corticosteroid-based regimens are frequently associated with adverse complications, including glaucoma and cataracts. In addition, these subtypes of uveitis generally represent those forms considered vision-threatening, with uveitis accounting for approximately 10% to 15% of legal blindness cases in the US {Durrani 2004, Nussenblatt 1990}. Noninfectious intermediate-, posterior- and pan-uveitis affects men and women in equal numbers, and occurs in every age group, including children {Gritz 2004, Jabs 2008}. As a result, it has the potential to account for a disproportionately large number of years of potential vision lost when compared to more prevalent sight-threatening diseases in which onset occurs in later years. This places uveitis on par with diseases such as diabetic retinopathy and macular degeneration as a cause of lost years due to visual morbidity and makes it a substantial public health problem.

Noninfectious sight-threatening uveitis occurring posterior to the lens is often treated with corticosteroids, the only globally approved therapeutic for uveitis. Off-label use of other antimetabolite or cytotoxic agents such as methotrexate is also common. Recently, adalimumab (Humira®) was approved for the treatment of noninfectious intermediate-, posterior- and pan-uveitis, and is presently the only US Food and Drug Administration (FDA) and European Medicines Agency-approved non-corticosteroid therapy available for adult patients in this disease population. Adalimumab was associated with significantly lower risk of treatment failure when compared to placebo in 2 pivotal Phase 3 trials, VISUAL-I and VISUAL-II {Jaffe 2016, Nguyen 2016}. In both trials, treatment failure was defined as having one or more of the following components affecting at least one eye: 1) increase in anterior chamber cells or vitreous haze, 2) new inflammatory chorioretinal or retinal vascular lesions, or 3) decrease in visual acuity. In VISUAL-I, subjects with active uveitis on adalimumab were significantly less likely to experience treatment failure when compared to those on placebo (hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.36, 0.70) {Jaffe 2016}. Likewise, in VISUAL-II, adalimumab significantly reduced the risk of treatment failure in subjects with inactive uveitis requiring control with systemic steroids (HR 0.57; 95% CI 0.39, 0.84) {Nguyen 2016}.
However, significant treatment failure rates were still observed within the adalimumab arms of each clinical trial by the end of the respective treatment observation periods (approximately 65%

and 45% in VISUAL-I and-II, respectively). While therapies for sight-threatening uveitis are advancing, it is still a condition associated with significant morbidity, limited safe and efficacious treatment options, and hence a significant unmet therapeutic need still exists globally.

1.2. Filgotinib

1.2.1. General Information

Janus kinases (JAKs) are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors through signal transducers and activators of transcription (STATs) to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors, and hormones, including the pro-inflammatory cytokine interleukin (IL)-6.

Four different types of JAKs are known, JAK1, JAK2, JAK3, and TYK2 which co-interact with different sets of membrane receptors. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions including RA and CD.

Filgotinib (GS-6034, formerly GLPG0634) is a potent and selective inhibitor of JAK1.
The compound has shown good preliminary efficacy in phase 2 RA and CD studies, DARWIN 1 {Westhovens 2017} and DARWIN 2 {Kavanaugh 2017} and Fitzroy {Sandborn 2013}.
In humans, filgotinib is metabolized to form one major metabolite GS-829845 (formerly G254445). Though the potency of this metabolite in inhibiting JAK-1 is lower than the parent molecule, the overall exposure and peak plasma concentration in humans is higher than seen in all tested animal species. As a consequence, dedicated pharmacology and toxicology studies have also been performed with GS-829845. For further information on filgotinib, refer to the current investigator's brochure (IB).

1.2.2. Nonclinical Pharmacology and Toxicology

1.2.2.1. Nonclinical Pharmacology, Absorption, Distribution, Metabolism, and Excretion and Toxicology

Filgotinib and GS-829845 have been extensively characterized in nonclinical studies.
This program includes cellular assays demonstrating potency and selectivity of the compound against JAK1, efficacy studies in rats and mice, repeat dose toxicity studies (up to 26 weeks in the rat and 39 weeks in the dog), *in vitro* and *in vivo* safety pharmacology and genetic toxicology studies, and reproductive toxicology studies in rats and rabbits. Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in support of a definitive rat juvenile toxicity study and a 6-month carcinogenicity study in transgenic (TgrasH2) mice. A pre- and post-natal development study and a 2-year rat oral carcinogenicity study in rats were completed.

1.2.2.2. Primary and Secondary Pharmacology

Filgotinib is an adenosine triphosphate-competitive inhibitor of JAK1. It is highly selective for inhibition of JAK1 over 451 other kinases evaluated *in vitro*. In cellular assays, it inhibits JAK/STAT-driven processes with half maximal inhibitory concentration (IC_{50}) values from 179 nM onwards. In human whole blood, JAK1 is inhibited by filgotinib with an IC_{50} of 629 nM and exhibits approximately 30-fold selectivity over JAK2. Filgotinib demonstrated significant efficacy in the rat collagen-induced arthritis (CIA) model as well as in the mouse dextran sulphate sodium (DSS)-induced colitis model.

Metabolite GS-829845 exhibits a similar JAK1 selectivity profile but is approximately 10 to 20-fold less potent than the parent filgotinib in *in vitro* assays. GS-829845 was as effective as filgotinib in the rat CIA model, but at doses that required a 10-fold higher exposure.

1.2.2.3. Safety Pharmacology

Filgotinib and GS-829845 had no effects on the respiratory system and central nervous system (CNS) in rats up to respectively 40- and 5-fold the exposure in RA subjects given filgotinib 200 mg daily. Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (human ether-a-go-go-related gene and dog telemetry studies), apart from a slight non-adverse increase in heart rate and arterial pressure with GS-829845 at exposures 7-fold that of the C_{max} in subjects with RA treated with 200 mg daily filgotinib. There were no relevant effects on ECG and QT.

1.2.2.4. Nonclinical Absorption, Distribution, Metabolism, and Excretion

Filgotinib demonstrates good oral bioavailability in mice, rats, dogs, and minipigs but less in monkeys. Plasma protein binding is low (< 70%) in all species, including humans.

The pharmacokinetics (PK) of filgotinib is generally dose proportional without gender differences. No accumulation occurs with repeated dosing. The mean terminal half-life after oral administration is 4 and 5 hours (h) in rats and dogs, respectively.

In the rat, filgotinib showed a rapid and even distribution throughout the body.
High concentrations were observed only in the gastrointestinal (GI) tract and urinary bladder.

Filgotinib does not penetrate into central nervous system tissues. The distribution of filgotinib indicates some affinity for melanin-containing tissues. A single oral dose administered to the rat resulted in significant distribution to the eye including the uveal tract. Specifically, quantitative whole body autoradiography data following a single dose of [^{14}C]-radiolabeled filgotinib to partially pigmented rats demonstrated that the eye:blood ratio for total radioactivity was 2.5 and 3.3 at 1 and 5 hours post-dose, respectively.

Excretion is nearly complete within 24 h (rat) and 48 h (dog) post-dosing. In the rat, fecal and urinary excretion accounted for 40% and 53% of the administered dose, respectively, with a bile

secretion of about 15%. In the dog, fecal excretion was the primary route of excretion, accounting for 59% of the administered dose, with urinary excretion accounting for 25%.

In vitro metabolism studies in all species revealed one major metabolite (GS-829845). The formation of GS-829845 is mediated by carboxylesterases and is not dependent on cytochrome P450 (CYP).

In vitro experiments have shown that drug-drug interactions with filgotinib and GS-829845 are unlikely. There is no inhibition or induction of CYPs or uridine 5'-disphosphate glucuronosyltransferases (UGTs), and no relevant inhibition of key drug transporters, including the organic anion transporters (OATs), by filgotinib or GS-829845. Organic cation transporter 2 (OCT2) was inhibited by both filgotinib (IC_{50}: 8.7 uM) and GS-829845 (IC_{50}: 67 uM). The clinical relevance of the IC_{50} values for inhibition of OCT2 will be further evaluated. MATE1 was also weekly inhibited by filgotinib (IC_{50}: 94 uM) and GS-829845 (IC_{50}: >100 uM). Filgotinib is a substrate of p-glycoprotein (P-gp)

1.2.2.5. Nonclinical Toxicology

In repeat oral dose toxicity studies in both rats and dogs, the primary target tissues identified for filgotinib were the lymphoid tissues which is expected based on the pharmacology of JAK inhibition. Additional filgotinib-related findings were observed in the male reproductive organs of both species, and in the incisor teeth of rats only. Ophthalmology and histological evaluations did not reveal any ocular findings. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated partial reversibility, however sperm counts remained low. A dose of 200 mg/day of filgotinib results in an estimated mean clinical AUC of 2.80 µg·h/mL, which represents an exposure margin of 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the no-observed-effect-levels in the 26 week and 39 week chronic toxicity studies, and the 39 week targeted exposure toxicity study, respectively.

GS-829845-related findings in general repeat dose toxicity studies were similar to those of the parent filgotinib, however no testicular toxicity was noted following administration of GS-829845.

Filgotinib and GS-829845 were non-genotoxic when evaluated in the bacterial mutagenicity assay, the *in vitro* mouse lymphoma mutagenicity assay, and the rat bone marrow micronucleus assay.

In embryofetal development studies, filgotinib and GS-829845 caused embryolethality and/or teratogenicity in rats and rabbits at exposures similar to the human exposure at 200 mg daily of filgotinib in subjects with RA. Administration of filgotinib did not affect female fertility but impaired fertility was observed in male rats at exposures approximately 15-fold the human exposure at 200 mg of filgotinib in subjects with RA. GS-829845 did not have any effects on fertility parameters in either male or female rats.

In an *in vitro* phototoxicity study in 3T3 cells, the metabolite GS-829845 was positive for phototoxic potential and results with filgotinib were equivocal. A follow-up *in vivo* rat phototoxicity assay revealed a lack of phototoxic potential for both compounds.

A detailed description of all nonclinical studies conducted with filgotinib can be found in the IB.

1.2.3. Clinical Trials of Filgotinib

Comprehensive data from the Phase 1, 2 and ongoing 3 programs are available to support the development of filgotinib. A detailed description of all clinical studies can be found in Section 4 of the IB.

1.3. Rationale for This Study

Noninfectious intermediate-, posterior- and pan-uveitis is a sight-threatening chronic relapsing-remitting inflammatory ocular disease. Novel oral therapies that are effective and well-tolerated are needed to optimally manage this patient population.

Filgotinib is a potent and selective JAK1- inhibitor that is currently in clinical development for the treatment of multiple inflammatory conditions including rheumatoid arthritis (IND 115500), Crohn's disease (IND 129646), and ulcerative colitis (IND 129646). Comprehensive data from Phase 1 and 2 studies support Phase 3 programs for RA, CD and UC. Gilead has not yet evaluated filgotinib's efficacy for treating uveitis but its mode of action suggests that it may provide therapeutic benefit. Moreover, RA, CD, and UC are all inflammatory diseases which are sometimes complicated by the development of uveitis {Acharya 2013}. Despite the heterogeneity of diseases implicated in immune-mediated uveitis, most are thought to be due to an imbalance between regulatory mechanisms inhibiting the immune system and inflammatory pathways that evolved to fight infection. Animal models of experimental autoimmune uveitis (EAU) implicate an array of cytokines {Horai 2011}. These include anti-inflammatory IL-10, TGF-β, and IL-35 produced by regulatory T lymphocytes designed for immunomodulation. In contrast, IL-6, IL-17, IL-23, IFN-γ, and TNF-α are produced by T-Helper cell populations (Th1 and Th17) resulting in leukocyte recruitment and subsequent tissue damage {Amadi-Obi 2007}. These activation/inhibition processes are mediated by complex signaling pathways that involve JAK and signal transduction and activation of transcription (STAT) signaling. Although there are currently no clinical trials with a JAK inhibitor for the treatment of noninfectious uveitis, topical tofacitinib (a JAK inhibitor) was reported to reduce intraocular inflammation in a rat EAU model {Huang 2013}.

The present study is designed to compare the proportion of subjects with active noninfectious intermediate-, posterior- or pan-uveitis at enrollment who meet the definition of treatment failure at Week 24 in those treated with filgotinib as opposed to placebo, despite the use of systemic corticosteroid therapy. According to published recommendations of an expert panel, the target recruitment population is representative of one in whom immunosuppressive agents should be considered for maintenance therapy of ocular inflammation {Jabs 2000}. The objective is to determine whether filgotinib is effective in controlling uveitis while reducing and discontinuing systemic corticosteroids. Subjects will be allowed to continue on only one other

immunosuppressive agent during the study. Given the lack of a globally-approved highly efficacious therapy, placebo is the most appropriate control group to measure the effectiveness of filgotinib in controlling the subject's uveitis. All subjects randomized will receive a standardized prednisone taper to treat the uveitis present at study entry. Regardless of randomization to filgotinib or PTM, subjects meeting criteria for treatment failure at Week 6 or any visit thereafter will be switched to a standard of care therapy determined by the site investigator.

Subjects enrolled in this study will have active disease despite at least 2 weeks of oral corticosteroid therapy. These subjects are candidates for a systemic immunosuppressive therapy such as filgotinib to allow potential reduction and/or discontinuation of oral corticosteroid therapy.

1.3.1. Rationale for Dose Selection

Enrolled subjects will be randomized to filgotinib (200 mg) or placebo. The 200 mg daily dose regimen of filgotinib is based on the sight-threatening nature of this condition, the desire to achieve efficacious ocular and systemic exposures of filgotinib, and on the efficacy and safety data from the Phase 1 and 2 studies.

Quantitative whole body autoradiography following a single dose of [^{14}C]-radiolabeled filgotinib to partially pigmented rats demonstrated total radioactivity results compatible with significant penetration into the eye, an affinity for melanin-containing tissue (skin and uveal tract), and clearing over time. Altogether, this suggests that oral administration of filgotinib in the proposed study will result in systemic and ocular levels to test the clinical efficacy of filgotinib for noninfectious intermediate- posterior- and pan-uveitis.

In Phase 1 studies conducted in healthy subjects (eg, GPLG0634-CL-101, -102, -103, -104, -105, -107, and -110), filgotinib administered at doses up to 450 mg daily for up to 10 days was safe and well tolerated. In the two Phase 2a studies in subjects with RA (Study GLPG0634-CL-201 and -202), a condition sometimes complicated by uveitis, dosing with filgotinib was well tolerated and achieved a high level of efficacy at a 200 mg daily dose (ACR20 response of 75-92% at Week 4). Administration of a higher filgotinib dose (300 mg) did not demonstrate greater efficacy, therefore, the dose to be tested in this study will be 200 mg daily.

In two Phase 2b studies, filgotinib at total daily doses of 50, 100, or 200 mg, administered in addition to a background therapy with MTX (GLPG0634-CL-203) or as monotherapy (GLPG0634-CL-204) was shown to be safe and efficacious in subjects with moderately to severely active RA who had an inadequate response to MTX alone. Exposure-response analysis based on data from all Phase 2 studies indicated a dose-dependent increase in efficacy (ACR20/50/70, DAS28[CRP]), with a plateau at the 200 mg total daily dose on the dose-response curve. These results are consistent with the relationship observed between filgotinib exposures and pSTAT1 activation (ex-vivo) following single and multiple filgotinib doses, where maximal inhibition of pSTAT1 (~78%) was achieved at or above 200 mg total daily dose {Namour 2015}.

Safety data collected across Phase 2 clinical studies showed no dose-dependent trends in the incidence of AEs or serious AEs (SAEs), including infections, or laboratory abnormalities with the exception of a numerical increase in select GI AEs (eg, nausea, vomiting, abdominal pain, and upper abdominal pain). This numerical increase was observed at 200 mg compared to the 100 mg dose. However, the overall frequency was low and clinical relevance is unknown. Filgotinib, administered at a dose of 200 mg daily was found to be safe and well tolerated. The safety profile was consistent with that observed for an immunomodulatory compound administered to subjects with RA.

Overall, a 200 mg once-daily dose regimen has been proposed based on the safety and efficacy data from the Phase 2 studies and the observed plateau in the pSTAT1 response which indicates doses above 200 mg are unlikely to add additional benefit. Since no difference in filgotinib PK or pharmacodynamics (JAK1 inhibition) is expected between subjects with RA, CD and uveitis, a 200 mg QD filgotinib dose is expected to be well tolerated in subjects with uveitis. This same filgotinib dose is also expected to provide clinical benefit in controlling the intraocular inflammation associated with this sight-threatening condition.

1.4. Risk/Benefit Assessment for the Study

The safety profile for filgotinib is informed by results from nonclinical and clinical studies evaluating a wide range of doses. More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) may be found in the IB. Information on adverse drug reactions associated with filgotinib may be found in Section 6.2.5. of the IB. In general, filgotinib has been well tolerated in all populations studied. An independent data monitoring committee (DMC) appointed to monitor this study will provide an additional level of oversight.

Filgotinib is contraindicated in pregnancy; highly effective contraception is to be used across all clinical studies to mitigate this risk. Measures to minimize other potential risks to subjects will include site/investigator training regarding monitoring for infection, and collection of AEs of special interest, including major adverse cardiac events, malignancies, infections, and specific laboratory abnormalities.

Nonclinical studies in rats and dogs identified lymphoid tissues and testes as target organs for filgotinib in long-term repeat-dose toxicity studies. Although decreased lymphocyte numbers observed in nonclinical studies have not been seen in clinical studies, hematological assessment will be performed throughout the present study to ensure this potential risk is appropriately monitored. In both rats and dogs, microscopic findings in the testes included germ cell depletion and degeneration, with reduced sperm content and increased cell debris in the epididymis and reduction in fertility in rats. The dog was determined to be the most sensitive species.

When using the AUC at the NOELs in dogs in the 26 week and 39-week chronic toxicity studies, and the 39-week targeted exposure toxicity study, the exposure margins compared with the highest proposed clinical dose of 200 mg once daily are 2.3, 1.8 and 3.4-fold, respectively, in subjects with RA. A male safety study in subjects with UC is on-going to examine the potential effect of filgotinib on semen parameters.

Filgotinib has shown an increased risk of embryofetal malformations in rats and rabbits at exposures similar to human doses; the use of highly effective contraception in the subject population is expected to mitigate this risk.

No clinically relevant impact on cardiovascular parameters (including vital signs and ECG), respiratory or neurologic function has been observed in Phase 1 and 2 trials of filgotinib, including a dedicated Phase 1 study to evaluate the effect of filgotinib on the QT / QTc interval in healthy subjects. The QT study evaluated filgotinib at doses of 200 mg and 450 mg; neither dose led to prolongation in the QTc interval or was associated with clinically significant ECG changes. In Phase 2 trials in RA, filgotinib was well tolerated. In the RA studies (including the open label extension DARWIN 3), infections were reported more commonly in the filgotinib groups, including serious infections leading to hospitalization, and even death. The most common system organ classes (SOCs) with AEs were infections and infestations, and GI disorders. Dose dependent decreases in the Phase 2b studies were observed in mean neutrophil counts and platelet counts (but mean changes in both remained within normal laboratory reference ranges) and there were no decreases in lymphocytes or lymphocyte subsets. Hemoglobin levels slightly improved (increased) with filgotinib treatment, confirming that no anemia was induced. Mild and clinically insignificant serum creatinine increases were noted in both Phase 2b studies, with stabilization by Week 24. Neutrophil decreases (in the RA population) and a potential increased risk of infection may be considered risks consistent with the mechanism of JAK inhibition. Overall clinical findings and laboratory changes are consistent with selective JAK1 inhibition.

Preclinical and clinical data of filgotinib indicate that this novel agent has a potential to offer therapeutic benefit in autoimmune and inflammatory diseases including uveitis. Filgotinib has an acceptable level of risk that is consistent with that of other immunomodulatory agents used in patient populations with autoimmune diseases. Given the clinical data to date, as well as the overall safety, tolerability, and PK characteristics, there is a favorable benefit/risk profile for development of filgotinib in noninfectious sight-threatening intermediate-, posterior- or pan-uveitis.

1.5. Compliance

This study will be conducted in compliance with this protocol, GCP, and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of filgotinib versus placebo for the treatment of the signs and symptoms of noninfectious uveitis as measured by the proportion of subjects failing treatment for active noninfectious uveitis by Week 24

The secondary objectives of this study are:

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the time to treatment failure (on or after Week 6)

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in VH grade in each eye (NEI/SUN criteria), from best state achieved prior to Week 6 to Week 52/End of Treatment (EOT) or Early Termination (ET) visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in AC cell grade in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in logMAR BCVA in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in central retinal thickness in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the time to development of macular edema in at least one eye as determined by OCT (on or after Week 6)

- To evaluate the safety and tolerability of filgotinib

- To evaluate the pharmacokinetics of filgotinib and its metabolite GS-829845

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3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- Proportion of subjects failing treatment for active noninfectious uveitis by Week 24

The secondary endpoints of this study are:

- Time to treatment failure on or after Week 6
- Change in VH grade in each eye (NEI/SUN criteria), from best state achieved prior to Week 6 to Week 52/ EOT visit or ET visit
- Change in AC cell grade in each eye, from best state achieved prior to Week 6 to Week 52 / EOT visit or ET visit
- Change in logMAR BCVA in each eye, from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit
- Log change in central retinal thickness in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit
- Time to development of macular edema in at least one eye as determined by OCT on or after Week 6
- Pharmacokinetic characteristics for filgotinib and its metabolite GS-829845

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3.2. Study Design

This is a randomized, double-masked, placebo-controlled Phase 2 trial in adult subjects with active noninfectious intermediate-, posterior-, or pan-uveitis in at least one eye despite at least 2 weeks of maintenance therapy with oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent). The study is designed to evaluate the efficacy and safety of filgotinib in adult subjects requiring high dose steroids for active noninfectious intermediate-, posterior-, or pan-uveitis.

A total of approximately 248 healthy male and non-pregnant or non-lactating female subjects who are ≥ 18 years of age, with active, noninfectious intermediate-, posterior-, or pan-uveitis will be enrolled into the study.

Subjects will be randomized in a 1:1 ratio to receive filgotinib 200 mg once daily or Placebo to Match (PTM) once daily for up to 52 weeks. Subjects that meet the definition of treatment failure (Section 3.5.2) prior to the end of the study (Week 52 visit) will have an EOT visit or ET visit (as appropriate). Subjects that discontinue from the study for any other reason before Week 52 will have an ET visit. Subjects that early terminate should also complete the 4-Week Post-Treatment Follow-Up Visit.

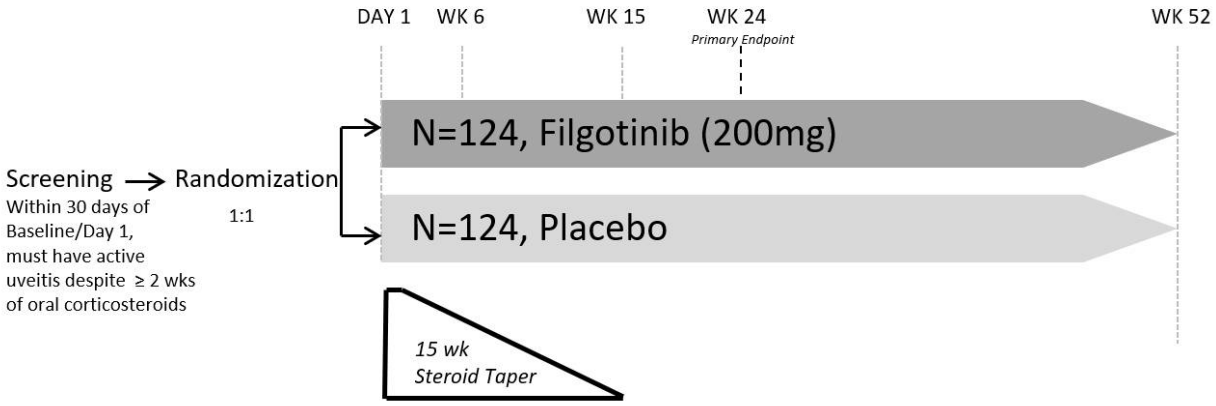
To enhance the safety monitoring during the study, a DMC consisting of independent experts will be convened to periodically review the accumulating safety data for the study.

In addition, an independent adjudication committee governed by a charter will be set up to perform adjudication of potential major adverse cardiovascular events as well as thromboembolic events reported during the study. The adjudication of these events will be performed in a blinded fashion for the purposes of data analysis and not for monitoring of subject safety.

Additional information regarding the logistics of adjudication will be described in the charter.

A schematic of this study is provided in Figure 3-1.

Figure 3-1. Study Schema



3.3. Study Treatments

Eligible subjects will be randomized in a 1:1 ratio to receive filgotinib 200 mg once daily (n 124) or PTM once daily (n 124) for up to 52 weeks.

3.3.1. Dosage and Administration of Prednisone

All subjects will receive a standardized prednisone burst of 60 mg/day at Day 1/Baseline followed by a protocol-defined mandatory taper schedule, as outlined below (Table 3-1), in which all subjects continuing in the study will be off prednisone no later than Week 15.

Table 3-1. Prednisone Taper Schedule

Study Week	Prednisone Dose (mg/day)
Week 0 (Day 1)	60
1	60
2	50
3	40
4	30
5	20
6	15
7	12.5
8	10
9	7.5
10	5
11	4
12	3
13	2
14	1
15	Discontinued Prednisone

Subjects who enroll in the study on topical ocular corticosteroids will undergo a standardized taper schedule beginning at Day 1/Baseline. Subjects must be off topical ocular corticosteroids by Week 9. Depending on the dose that the subject is on at the Day 1/Baseline visit, the number of drops per day will be decreased every week at the increments indicated in Table 3-2 below:

Table 3-2. Topical Ocular Corticosteroid Taper Schedule

Dose Taper Schedule per Week
12 drops per day
10 drops per day
8 drops per day
6 drops per day
5 drops per day
4 drops per day
3 drops per day
2 drops per day
1 drop per day
Discontinue Drops

All subjects will be able to continue their stable dose of oral uveitis control medications provided the subject is taking only one of the allowable medications (within the specified dose range) detailed in Section 5.4.1 (Allowed Concomitant Medications). Study medication will be dispensed and subjects and/or their care-giver will be instructed on the dosing schedule.

3.4. Duration of Treatment

Subjects will receive a maximum of 52 weeks of study drug.

3.5. Discontinuation Criteria

3.5.1. Study Drug Interruption Considerations

The Medical Monitor should be consulted prior to study drug interruption when medically feasible.

Study drug interruption should be considered in the following circumstances; *prior to resumption of study drug, the investigator should discuss the case with the Medical Monitor:*

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug pausing should be determined in consultation with the Medical Monitor
- Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immunocompromised individual, and the subject should be closely monitored

NOTE: During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments, if deemed medically appropriate by the investigator.

3.5.2. Study Drug Discontinuation Criteria

The Medical Monitor should be consulted prior to study drug discontinuation for reasons other than meeting treatment failure criteria or the subject desiring early termination, when medically feasible.

Study drug should be permanently discontinued in the following instances:

- Any opportunistic infection
- Any serious infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)

- Evidence of active HCV during the study, as evidenced by HCV ribonucleic acid (RNA) positivity
- Evidence of active HBV during the study, as evidenced by HBV deoxyribonucleic acid (DNA) positivity
- Any thromboembolic event that meets SAE reporting criteria
- Development of any tuberculosis infection
- Subject has a positive purified protein derivative PPD test or positive (or indeterminate re-test) QuantiFERON®-TB Gold test (or IGRA equivalent)
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest; consultation should be made with the Medical Monitor
- Subject request to discontinue for any reason
- Death
- Subject noncompliance
- Pregnancy during the study; refer to Section 7.7.2.1
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB)/Independent Ethics Committee (IEC)
- Subject use of prohibited concurrent therapy *may* trigger study drug discontinuation; consultation should be made with the Medical Monitor
- Laboratory Criteria: After becoming aware of any of the below described abnormal laboratory changes occurring at any one time, an unscheduled visit (ie, sequential visit) should occur to retest within 3 to 7 days (except creatinine, which should be retested 7 to 14 days apart).

  a) 2 sequential neutrophil counts < 750 neutrophils/mm^3 (SI: < 0.75 x 10^9 cells/L)

  b) 2 sequential (3 to 5 days apart) platelet counts < 75,000 platelets/mm^3 (SI: < 75.0 x 10^9 cells/L)

  c) 2 sequential AST or ALT > 3 times the upper limit of normal range (ULN) and ≥ 1 total bilirubin > 2 x ULN or accompanied by symptoms consistent with hepatic injury

d) 2 sequential AST or ALT > 5 x ULN

e) 2 sequential values for estimated creatinine clearance < 35 mL/min based on the Cockcroft-Gault formula {Cockcroft 1976}

If a subject discontinues study dosing (eg, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

Subjects withdrawing from the study for reasons other than treatment failure should complete the Early Termination Visit and are encouraged to complete the 4-Week Post-Treatment Follow-Up Visit. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Reasonable efforts will be made to contact subjects who are lost to follow-up. All contacts and contact attempts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study medication or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

3.5.3. Study Discontinuation Due to Treatment Failure

Beginning at Week 6 and for all visits thereafter, subjects will be examined for evidence of treatment failure. Treatment failure will be defined as a subject meeting at least one of the following criteria (Table 3-3) in at least 1 eye:

Table 3-3. Treatment Failure Criteria

Parameter	Treatment Failure *	
	Week 6 Visit	**All Visits After Week 6**
Inflammatory chorioretinal and/or inflammatory retinal vascular lesions	New active, inflammatory lesions relative to Day 1/Baseline	New active, inflammatory lesions relative to Day 1/Baseline
Anterior Chamber Cell grade (SUN Criteria)	Inability to achieve ≤ grade 0.5+	2-step increase relative to best state achieved **
Vitreous Haze grade (NEI/SUN Criteria)	Inability to achieve ≤ grade 0.5+	2-step increase relative to best state achieved **
Visual Acuity Early Treatment Diabetic Retinopathy Study (ETDRS)	Worsening of BCVA by ≥ 15 letters relative to best state achieved	Worsening of BCVA by ≥ 15 letters relative to best state achieved

* To be considered a treatment failure, ≥ 1 of these criteria need to be present in at least 1 eye. "Best state" refers to the best measures recorded at all prior visits.

** A 2 step increase is represented by a change of Grade 0 to Grade 2+; or Grade 0.5+ to Grade 3+.

Subjects with evidence of treatment failure (assessed at any scheduled or unscheduled visit at or after Week 6) will be discontinued from the study and should complete the EOT Visit and the 4-Week Post-Treatment Follow-Up Visit per Appendix 2. These subjects will be subsequently treated at the discretion of the investigator.

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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A sufficient number of subjects will be screened to ensure that approximately 248 subjects with active, noninfectious intermediate-, posterior-, or pan-uveitis will be randomized to one of two dosing groups during the masked treatment phase of the study. Both of the subject's eyes must be clinically evaluable for the purpose of determining eligibility based on inclusion and exclusion criteria, and for the purpose of assessing Treatment Failure. There will be no designated "study eye." It is anticipated that approximately 25% of the included subjects will have their uveitis attributed to sarcoidosis.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Judged to be in good health as determined by the investigator based on the results of medical history, laboratory screening profile, physical examination, chest x-ray, and 12-lead electrocardiogram performed during Screening

2) A negative serum pregnancy test is required for female subjects of childbearing potential as outlined in Appendix 5.

3) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5

4) Lactating females must agree to discontinue nursing before the study drug is administered

5) Male or female subjects who are ≥ 18 years of age on the day of signing informed consent

6) Diagnosed with active noninfectious intermediate-, posterior-, or pan-uveitis

7) Active uveitic disease at the Day 1/Baseline visit as defined by the presence of at least 1 of the following parameters in at least one eye despite at least 2 weeks of maintenance therapy with oral prednisone (≥ 10 mg/day to ≤ 60 mg/day) or an oral corticosteroid equivalent:

   a) Active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesion

   b) ≥ 2+ anterior chamber cells (SUN criteria)

   c) ≥ 2+ vitreous haze (NEI/SUN criteria)

8) On oral prednisone ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent) for 2 or more weeks immediately prior to and including Day 1/Baseline

9) Documented prior adequate response to oral corticosteroids (equivalent of oral prednisone up to 1 mg/kg/day)

10) Subjects must meet one of the following 3 TB Screening criteria:

    a) No evidence of active or latent TB:

        - A negative QuantiFERON® TB-Gold In-Tube test at screening, or evidence of negative result within the 3 months prior to screening,

        - A chest radiograph (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review) without evidence of active or latent TB infection,

        - No history of either untreated or inadequately treated latent TB infection

    b) Previously treated for TB:

        - A subject who has previously received an adequate course of therapy as per local standard of care for either latent TB (eg, 9 months of isoniazid in a location where rates of primary multi-drug resistant TB infections are < 5% or an alternative regimen according to local country guidelines) or active TB (acceptable multi-drug regimen). In these cases, no QuantiFERON® TB-Gold Plus In-Tube test (or a centrally reported equivalent assay) needs to be obtained

        - A chest radiograph must be obtained, if not done within 3 months prior to Screening, (with the report or films available for investigator review)

        - It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation

    c) Newly identified latent TB during Screening:

        - A subject who has a newly identified positive diagnostic TB test result (defined as a positive QuantiFERON® TB Gold Plus In-Tube test or equivalent assay), in which active TB has been ruled out and for which appropriate ongoing treatment for latent TB has been initiated for at least 4 weeks prior to the first administration of study drug.

        - Adequate treatment for latent TB is defined according to local country guidelines for immunocompromised patients.

Cases falling under category “b” and “c” must be approved by the Gilead Medical Monitor or designee prior to enrollment in the study. No subject with currently active TB or untreated latent TB may be enrolled in the study.

Subjects with an indeterminate QuantiFERON-TB Gold test result may undergo a repeat test. Subjects with a repeat indeterminate test result (two indeterminate results in total) are, in this study, considered as having a positive QuantiFERON-TB Gold test result. In the event of a negative TB screening test, the results will be interpreted in the context of the subject's epidemiology, history, exam findings, etc.

11) Able and willing to sign the informed consent as approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). Written consent must be provided before initiating any screening evaluations. Subjects must have read and understood the ICF, must fully understand the requirements of the study, and must be willing to comply with all study visits and assessments. Subjects who cannot understand the ICF may not be enrolled by a guardian or any other individual.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) The presence of isolated anterior uveitis

2) The presence of macular edema as the only sign of intermediate-, posterior- or pan-uveitis

3) Intolerance to or prior inadequate response to high-dose oral corticosteroids (equivalent of oral prednisone 1 mg/kg/day or 60 to 80 mg/day)

4) Confirmed or suspected infectious uveitis, including but not limited to infectious uveitis due to TB, cytomegalovirus (CMV), Human T-Lymphotropic Virus Type 1 (HTLV-1), Whipple's disease, Herpes Zoster virus (HZV), Lyme disease, toxoplasmosis and herpes simplex virus (HSV)

5) Presumed ocular histoplasmosis syndrome (as determined by the investigator)

6) Ocular masquerade syndromes such as ocular lymphoma (as determined by the investigator)

7) Serpiginous choroidopathy

8) Corneal or lens opacity that precludes visualization of the fundus or that likely requires cataract surgery during the duration of the trial

9) Subject with elevated intraocular pressures and/or severe glaucoma who is unable to meet the following criteria within the screening period:

   - Intraocular pressure of < 25 mmHg (in at least two consecutive measurements) in the absence of therapy or if on a single glaucoma medication

   - Intraocular pressure of < 21 mmHg (in at least two consecutive measurements) if on 2 or more glaucoma medications

- Subject must have no evidence of glaucomatous optic nerve injury that involves or encroaches on central fixation, regardless of intraocular pressure or number of glaucoma medications

- Subject must have no evidence of glaucomatous optic nerve injury that, in the opinion of the investigator, has the potential for splitting fixation or visual acuity loss during the course of the study, regardless of intraocular pressure or number of glaucoma medications

10) Exposure to a systemic carbonic anhydrase inhibitor within 1 week prior to Screening

11) Best Corrected Visual Acuity (BCVA) less than 20 letters (Early Treatment Diabetic Retinopathy Study) in any eye at the Day 1/Baseline Visit

12) Previous exposure to an approved or experimental JAK inhibitor therapy

13) Any condition preventing the evaluation/assessment of both eyes for eligibility criteria and/or for the presence of treatment failure criteria, as detailed in Sections 3.5.3 (either eye can satisfy active uveitis criteria for eligibility and either eye may meet treatment failure criteria)

14) Exposure to anti-tumor necrosis factor (TNF) therapy or any biologic therapy within 4 weeks of Day 1/Baseline (as per Section 5.4.2)

15) Received intravitreal anti-VEGF therapy within 45 days of the Day 1/Baseline visit [ie, Lucentis® (ranibizumab) or Avastin® (bevacizumab)] or within 60 days of the Day 1/Baseline visit for anti-VEGF Trap (ie, aflibercept)

16) Use of more than 1 accepted immunosuppressive therapy (not counting corticosteroids) at Day 1/Baseline

17) Using concomitant immunosuppressive therapy at Day 1/Baseline other than methotrexate or azathioprine

18) If entering the study on 1 concomitant immunosuppressive therapy, dose has been increased within 28 days prior to Day 1/Baseline visit or is not within the following allowable doses:

    a) Methotrexate (MTX) ≤ 25 mg per week

    b) Azathioprine ≤ 175 mg per day

19) Systemic inflammatory disease requiring continued therapy with oral corticosteroids or a prohibited immunosuppressive agent at screening or Day 1/Baseline

20) Received Retisert® (glucocorticosteroid implant) within 3 years prior to the Day 1/Baseline visit or has had complications related to the device

21) Received intraocular or periocular corticosteroids within 30 days prior to Day 1/Baseline visit

22) Presence of proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy

23) Presence of neovascular/wet age-related macular degeneration

24) Presence of a clinically significant abnormality of vitreo-retinal interface per investigator discretion (i.e., vitreomacular traction, epiretinal membranes, etc.) with the potential for macular structural damage independent of the inflammatory process

25) Presence of severe vitreous haze that precludes visualization of the fundus at the Day 1/Baseline visit

26) Received Ozurdex® (dexamethasone implant) within 3 months prior to the Day 1/Baseline visit

27) Received intravitreal methotrexate within 90 days prior to the Day 1/Baseline visit

28) Use of cyclophosphamide within 30 days prior to the Day 1/Baseline visit

29) Evidence of any clinically significant (as per the judgement of the investigator) active or chronic recurring infection, opportunistic infection, or immunodeficiency syndrome

30) Severe (anaphylactic) reactions to fluorescein or unwillingness to perform fluorescein angiograms

31) Known hypersensitivity to filgotinib, its metabolites, or formulation excipients

32) Contraindication to pupil dilation with mydriatic eye drops

33) History of major surgery (requiring regional block or general anesthesia) or trauma within 30 days prior to screening

34) History of prior ocular surgery (excluding eyelid surgery) within 90 days before Day 1/Baseline with the exception of refractive laser surgery, retinal laser photocoagulation, or neodymium-doped yttrium aluminium garnet posterior capsulotomy. These 3 exceptions are exclusionary within 30 days before Day 1/Baseline

35) Planned (elective) eye surgery (excluding eyelid surgery) within 52 weeks after Day 1/Baseline

36) Any infection requiring hospitalization or treatment with intravenous anti-infectives within 60 days of screening; or any infection requiring oral anti-infective therapy within 30 days of screening

37) A positive test result for HIV-1 or HIV-2 (see Appendix 6)

38) Evidence of active HCV infection. Subjects with positive HCV antibody (Ab) at screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA at screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA are eligible per investigator judgment. Subjects with active HCV during the study, as evidenced by HCV RNA positivity will be discontinued from study drug as outlined in the protocol.

39) Evidence of active HBV infection. Subjects with positive Hepatitis B surface antigen (HBsAg) at screening are excluded from the study. Subjects with positive HBV core Ab and negative HBsAg, require reflex testing for HBV DNA. Subjects with positive HBV DNA at screening will be excluded. Subjects with positive HBV core Ab and negative HBV DNA are eligible per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines/local standard of care and require ongoing monitoring with blood tests for HBV DNA every 3 months. Subjects with evidence of active Hepatitis B during the study, as evidenced by HBV DNA positivity, will be discontinued from study drug as outlined in the protocol.

40) Positive test for syphilis (fluorescent treponemal antibody or syphilis IgG; See Appendix 6)

41) History of malignancy within the last 5 years prior to screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence)

42) History of lymphoproliferative disorder or current lymphoproliferative disease

43) History of gastrointestinal perforation

44) History of organ or bone marrow transplant

45) History of leukocytapheresis ≤ 6 months prior to screening

46) Use of any prohibited concomitant medications as described in Section 5.4.2

47) Any chronic, uncontrolled medical condition (including, but not limited to, cardiac or pulmonary disease) or psychiatric problem (including, but not limited to alcohol or drug abuse) which would put the subject at increased risk during study participation, such as uncontrolled: diabetes, hypertension, morbid obesity, thyroid, adrenal, pulmonary, hepatic, renal, neurologic or psychiatric disease, or other disease of concern, as per judgment of investigator

48) Administration of a live or attenuated vaccine within 30 days of Day 1/Baseline

49) Not willing to refrain from administration of live or attenuated vaccines during the study and for 6 weeks after last dose

50) Currently on any chronic systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis, cytomegalovirus [CMV], herpes zoster, and atypical mycobacteria).

51) History of disseminated Staphylococcus aureus

52) History of symptomatic herpes zoster or herpes simplex within 12 weeks of screening, or any history of disseminated herpes simplex, herpes zoster, ophthalmic zoster, or central nervous system zoster

53) Current drug use, heavy tobacco use (current use of ≥ 2 packs per day equivalent) or alcohol abuse, per investigator judgment

54) Any condition or circumstances which in the opinion of the investigator or sponsor may make a subject unlikely or unable to complete the study or comply with study procedures and requirements

55) Participation in any clinical study of an investigational drug/device within 4 weeks or 5 half-lives (whichever is longer) of the drug prior to Day 1/Baseline. Exposure to investigational biologics should be discussed with the sponsor.

56) Tests performed at the central laboratory at screening that meet any of the criteria below (out of range lab values may be retested one time, at the discretion of the investigator before subject is considered a screen-failure):

   a) Hemoglobin < 8.0 g/dL (International System of Units [SI]: < 80 g/L);

   b) White blood cells < 3.0 x 10^3 cells/mm^3 (SI: < 3.0 x 10^9 cells/L);

   c) Neutrophils < 1.5 x 10^3 cells/mm^3 (SI: < 1.5 x 10^9 cells/L);

   d) Lymphocytes < 0.5 x 10^3 cells/mm^3 (SI: < 0.5 x 10^9 cells/L);

   e) Platelets < 100 x 10^3 cells/mm^3 (SI: < 100 x 10^9 cells/L);

   f) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 1.5 x ULN;

   g) Total bilirubin level ≥ 2 x ULN unless the subject has been diagnosed with Gilbert's disease and this is clearly documented;

   h) Estimated creatinine clearance < 40 mL/min based on the Cockcroft Gault formula {Cockcroft 1976}

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Masking and Treatment Codes

An Interactive Web Response System (IWRS) will be employed to manage subject randomization and treatment assignments. It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment.

5.1.1. Masking

Subjects and all personnel directly involved in the conduct of the study will be masked to treatment assignment. Specified personnel may be unmasked based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a masked fashion to the subjects. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management, who facilitates the data transfer of PK files between Gilead and vendors, will remain unmasked. Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IWRS system for purposes of study drug inventory management will remain unmasked. Individuals in Pharmacovigilance and Epidemiology (PVE) responsible for safety signal detection, investigational new drug safety reporting and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unmasked to individual case data and/or group level summaries. Separate, external (ie, contract research organizations) Biostatisticians and Programmers will be unmasked for data monitoring committee and PK/pharmacodynamic data merge. Regulatory Quality and Compliance personnel in Research and Development may also be unmasked for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections.

5.1.2. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the masking is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IWRS system for that subject. Gilead recommends but does not require that the investigator contact the Medical Monitor before breaking the masking designation. Treatment assignment should remain masked unless that knowledge is necessary to determine subject emergency medical care. The rationale for unmasking must be clearly explained in source documentation and on the eCRF, along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Medical Monitor promptly in case of any treatment unmasking.

Masking of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead PVE may independently unmask cases for expedited reporting of SUSARs.

5.2. Description and Handling of Filgotinib and Placebo-to-Match Filgotinib

5.2.1. Formulation

Filgotinib tablets, 200 mg, are beige, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "200" on the other. Each tablet contains the equivalent of 200 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient (filgotinib maleate), filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, and magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

PTM filgotinib tablets are identical in appearance to the active filgotinib tablets. PTM filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

5.2.2. Packaging and Labeling

Filgotinib tablets, 200 mg, and matching placebo tablets are packaged in white high density polyethylene bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), European Union (EU) Guideline to Good Manufacturing Practice Annex 13 (Investigational Medicinal Products), and/or other local regulations as applicable.

5.2.3. Storage and Handling

Study drugs (filgotinib tablets and PTM tablets) should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration of Filgotinib

Filgotinib 200 mg or matching placebo tablets will be administered once daily with or without food. Each subject should be given instructions to maintain approximately the same daily time of administration to ensure a similar dosing interval between study drug doses.

For missed dose(s) of study medication, subjects should be instructed to take the missed dose(s) of study medication as soon as possible during the same day. If the missed dose is not taken on the original day, subjects should be cautioned not to double the next dose with the missed dose of study drug under any circumstances. In those cases, the missed dose should be returned to the study drug bottle.

5.4. Prior and Concomitant Medications

All medications taken up to 30 days prior to the screening visit through the end of the study (4 weeks after the last dose of study drug) will be recorded in the source documents and on the eCRF. All prior medication(s) used in the treatment for uveitis, are to be documented in the eCRF. At each study visit, the study center will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription, non-prescription medications, emollients, oral antihistamines, dietary supplements, and minerals.

All uveitis medications should be documented according to the following guidelines:

- Historical Uveitis Medications

  Any systemic or local therapy for uveitis since initial diagnosis (as determined through medical history records or through subject interview) stopped prior to the Screening visit will be recorded on the eCRF. The following information on prior uveitis treatments should be captured:

  - For prior systemic corticosteroids record the highest dose administered and the date range. In addition, the date of the last uveitis flare (the subject's flare prior to the flare at Screening) and the dosage of corticosteroid treatment at the time that the flare began must be recorded. If the subject was completely off corticosteroids when the flare occurred, the date of the last dose of corticosteroid prior to flare must be recorded.

  - For immunosuppressants other than systemic corticosteroids record the highest previously administered dose and the date range.

  - For topical uveitis therapies record the highest previously administered dose and the date range. The medication name should include the strength, if part of the generic name (eg, betamethasone phosphate 0.1%). The dose should be recorded as number of drops.

- Current Uveitis Medications

  Any systemic or local therapy for uveitis that was ongoing during screening or started at or after the screening visit through the end of the study will be recorded on the eCRF.

Effective current therapies should not be discontinued for the sole purpose of participating in this study. Subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician. Should subjects have a need to initiate treatment with any excluded concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the sponsor, the investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication.

5.4.1. Allowed Concomitant Medications

Allowed concomitant medications should be kept stable for the study duration, as much as possible, and include:

- Vitamins and hormonal contraceptive medications are permitted.
- Acetaminophen and ibuprofen may be used intermittently, as needed.
- Inhaled corticosteroids (nasal or oral) are permitted.
- Hormone replacement therapy, thyroid replacement and other chronic therapies (such as those for well-controlled diabetes or hypertension) are permitted during the study and should be kept at a stable dose and regimen, as much as possible.
- One of the concomitant immunosuppressive therapies listed below is allowable upon study entry as long as the dose has not been increased within 28 days prior to Day 1/Baseline visit and is within the following allowable doses at Day 1/Baseline:

  Methotrexate (MTX) ≤ 25 mg per week

  Azathioprine ≤ 175 mg per day

- Dose adjustments for management of toxicity of the above medications are allowed and should be documented, along with documentation of the AE which led to the change in the medication, otherwise the doses must remain unchanged throughout the study
- For subjects with glaucoma, prostaglandin ophthalmic solutions (eg, latanoprost, bimatoprost, travoprost, etc.) cannot be initiated nor discontinued during the study. Dosage of other topical eye drops for glaucoma may be adjusted as medically necessary during the study.
- At study entry topical corticosteroids for uveitis are allowed and will be tapered as described in Table 3-2.

Female subjects of childbearing potential must agree to use highly effective birth-control methods as outlined in Appendix 5 and must agree to continue their use during the study and for at least 35 days after the last dose of study medication. The use of hormonal contraceptives will be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts will be followed.

5.4.2. Prohibited Concomitant Medications

The prohibited medications while on study drug are as follows:

Table 5-1. Prohibited Medications

Drug Class	Agents Disallowed	Prohibited Period
Biologic	All anti-tumor necrosis factor drugs and other biologic therapies; Examples include but are not limited to: Infliximab, etanercept, adalimumab, golimumab, certolizumab, abatacept, anakinra, rituximab, natalizumab, tocilizumab, efalizumab, ustekinumab, belimumab or biosimilar agents	4 weeks prior to Day 1/Baseline through the end of the study or the timepoint at which treatment failure criteria are identified (with permission of the Gilead Medical Monitor), whichever occurs first
	Any other investigational agent	4 weeks prior to Day 1/Baseline through the end of the study or 5 half-lives (whichever is longer)
Prohibited Uveitis and other ocular Medications		
	Intravitreal Anti-VEGF Therapy for Lucentis (ranibizumab) or Avastin (bevacizumab)	45 days prior to Day 1/Baseline through the end of the study
	Intravitreal Anti-VEGF Therapy for anti-VEGF Trap (aflibercept)	60 days prior to Day 1 through the end of the study
	Use of more than one or any other immunosuppressive therapy at Day 1/Baseline other than methotrexate ≤ 25 mg per week, or azathioprine ≤ 175 mg per day	Use at Day 1/Baseline and through the end of the study or the timepoint at which treatment failure criteria are identified (with permission of the Gilead Medical Monitor), whichever occurs first
	Retisert (glucocorticosteroid implant)	Received within 3 years prior to Day 1/Baseline or has had complications with the device and also throughout the study
	Intraocular or periocular corticosteroids (including eyelid injections)	Within 30 days prior to Day 1/Baseline and through the end of the study or the timepoint at which treatment failure criteria are identified (with permission of the Gilead Medical Monitor), whichever occurs first
	Ozurdex (dexamethasone implant)	Within 3 months prior to Day 1/Baseline through the end of the study or the timepoint at which treatment failure criteria are identified (with permission of the Gilead Medical Monitor), whichever occurs first
	Intravitreal methotrexate	Within 90 days prior to Day 1/Baseline and through the end of the study
	Cyclophosphamide	Within 30 days of Day 1/Baseline and through the end of the study

Drug Class	Agents Disallowed	Prohibited Period
	Corticosteroid with the exception of inhaled (nasal or oral) and the mandatory protocol specified prednisone taper and the protocol specified corticosteroid eye drop taper	Prohibited throughout the trial, Reference Section 3.3.1 or the timepoint at which treatment failure criteria are identified (with permission of the Gilead Medical Monitor), whichever occurs first
	Systemic carbonic anhydrase inhibitor	within 1 week prior to Screening visit through the end of the study
Other		
	Live or attenuated vaccines	Within 30 days of Day 1/Baseline or during study and for 6 weeks post last dose of study drug
Strong P-gp Inducers[a]		
Anticonvulsants	Phenobarbital, phenytoin, carbamazepine	21 days prior to Day 1 through the end of the study
Antimycobacterials	Rifabutin, rifapentine, rifampin	
Herbal/Natural Supplements	St. John's wort, danshen (salvia miltiorrhiza)	

a May decrease study drug exposure and are excluded to avoid potential reduction in study drug activity. PK results indicate that filgotinib is a P gp substrate, as a single dose of 200 mg itraconazole (a potent P gp inhibitor) increased filgotinib C_{max} by 64% and AUC_{inf} by 45% and had no effect on the major, active metabolite GS 829845.

For subjects with glaucoma, prostaglandin ophthalmic solutions (eg, latanoprost, bimatoprost, travoprost, etc.) cannot be initiated nor discontinued during the study. Dosage of other topical eye drops for glaucoma may be adjusted as medically necessary during the study.

At study entry topical corticosteroids for uveitis are allowed and will be tapered as described in Section 3.3.1.

5.5. Vaccine Guidelines

Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards.

Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited within 30 days of Day 1/Baseline, throughout the study, and for 6 weeks after the last dose of study drug.

Subjects should be advised to avoid routine household contact with persons vaccinated with live/attenuated vaccine components. General guidelines suggest that a study subject's exposure to household contacts should be avoided for the below stated time periods:

- Varicella or attenuated typhoid fever vaccination avoid contact for 4 weeks
- Oral polio vaccination - avoid contact for 6 weeks following vaccination

- Attenuated rotavirus vaccine - avoid contact for 10 days following vaccination
- Inhaled flu vaccine - avoid contact for 1 week following vaccination

Inactivated vaccines (such as inactivated flu vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of filgotinib and its impact on immune responses following vaccination.

5.6. Accountability for Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug kits
- Record the date, subject number, the study drug kit number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information.

5.6.1. Study Drug Return or Disposal

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with Gilead's requirements. Study drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet Gilead's requirements for disposal, arrangements will be made between the site and Gilead's or its representative for destruction or return of unused study drug supplies.

All drug supplies (if applicable) and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

For additional information about study drug accountability and return, refer to Section 9.1.7.

6. STUDY PROCEDURES

All subjects will have clinic visits at Screening, Baseline/Day 1, and Weeks 1, 4, 6, 8 and then every four weeks until Week 52/EOT or ET (if applicable). Treatment failure status will be assessed at each clinic visit assessment (scheduled and unscheduled) beginning at Week 6. All subjects will have clinic visits and procedures as outlined in Appendix 2.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization.

6.1. Subject Enrollment and Treatment Assignment

Subjects will be appropriately consented by the investigator or a medically qualified member of the investigator's study team (eg, MD, DO, nurse practitioner, or research coordinator) and eligibility will be established at the conclusion of the screening evaluations, within 30 days of Day 1/Baseline. The screening number and subject ID will be assigned for each subject by IWRS.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before randomization. A subject will be considered enrolled once they have been randomized. It is the responsibility of the investigator to confirm the presence of active uveitis that satisfies enrollment criteria; verification by a central reader will not be required. However, independent sequential masked efficacy evaluations by a central reader will be performed for fundus photography and OCT measurements in order to standardize measures and monitor their validity as described below.

Subjects who do not meet the eligibility criteria will be screen failed; however, these subjects may be considered for rescreening in consultation with the Sponsor or its designee and providing that subject undergoes re-consent. All screening procedures with the possible exceptions noted below will be repeated. The subject must meet all inclusion criteria and none of the exclusion criteria at the time of re-screening in order to qualify for participation in this trial. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including the assessment of a QuantiFERON®-TB Gold test and chest x-ray, these tests will not be required to be repeated for re-screening provided the conditions noted in Section 4.2 and Section 6.2.3.7 are met and no more than 30 days have passed. Subjects who originally failed screening due to one of the TB screening tests will not be eligible to re-screen. As appropriate, sites are encouraged to contact the Medical Monitor to confirm if subjects should or should not be re-screened. The Sponsor (including the Medical Monitor) must be contacted if a site plans to screen a subject more than twice.

A retest of screening labs is permitted only if there is reason to believe the retest value will be within accepted parameters, or if the initial value was either due to a sample processing error or an extenuating circumstance.

6.2. Study Procedures Descriptions

6.2.1. Informed Consent

All subjects must sign and date the most recent IRB/ IEC approved informed consent form before any study procedures are performed. Results from certain tests obtained for standard medical care purposes (eg, chest radiograph, TB tests) prior to study enrollment may be utilized to determine eligibility. CCI [redacted]

6.2.2. Medical History

A complete medical history will be obtained by the investigator or qualified designee at screening and recorded on the eCRF. Medical history will include information on the subject's significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior and current uveitis medications and any concurrent illnesses.

A specific uveitis history will be obtained at the Screening Visit. The history will include, but is not limited to, collecting the date of onset of uveitis (first flare), which eye(s) is/are affected, the type of uveitis, subject history of infectious uveitis and cause of previous infection (if applicable), the number of flares within the past 12 months (including the current flare), the date of last flare prior to current flare (present at Screening), the prednisone dose at time of last flare (or equivalent prednisone dose, if subject was on another corticosteroid, refer to Appendix 7), and date of onset of current flare.

6.2.3. Safety

Safety will be assessed by documentation of AEs, clinical laboratory tests, vital signs, and physical exams during the study.

6.2.3.1. Thromboembolic Events

Subjects experiencing a thromboembolic event should be evaluated for the overall risk of recurrent thromboembolism and referred to a specialist for further testing as appropriate (including but not limited to evaluation for an underlying inherited hypercoagulable state).

6.2.3.2. Adverse Events

Subjects will be assessed for AEs per guidelines in the National Cancer Institute (NCI) CTCAE (Version 4.03) at the time points outlined in Appendix 2. Any AEs reported after informed consent is obtained and throughout the study will be recorded on the eCRF with appropriate

source documentation. The subject will be assessed for AEs until 30 days after the last dose of study drug. Please refer to Appendix 4 CTCAE grading criteria.

Please refer to Section 7 for additional information on AE reporting.

6.2.3.3. Prior and Concomitant Medications

All medications taken up to 30 days prior to the screening visit and any supportive therapies given during the course of the study will be recorded as per Section 5.4.

6.2.3.4. Complete and Symptom-Driven Physical Examination

A PE should be performed at the time points indicated in the study procedures table (Appendix 2). Any changes from baseline will be recorded. Height will be measured at screening only. Body weight will be taken at visits outlined in Appendix 2.

At screening and Week 52/EOT or the ET Visit, a complete PE will be performed. A complete PE should include source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; and neurological. A symptom-driven PE will be performed at all other visits.

6.2.3.5. Vital Signs

Vital signs will be measured at the time points indicated in the study procedures table (Appendix 2).

- Vital signs should be taken after the subject has been resting for at least 5 minutes and will include pulse rate, systolic and diastolic blood pressure, and body temperature.

6.2.3.6. 12-lead Electrocardiogram

A resting 12-lead ECG will be performed at the Screening visit only. The ECG should be obtained after the subject has been resting in the supine position for at least 5 minutes and will include heart rate, inter-beat (RR), QRS, uncorrected QT, morphology, and rhythm analysis. QT interval corrected for heart rate according to Fridericia (QTcF) will be recorded. Electrocardiograms will be interpreted by the investigator (or qualified designee) for clinical significance and results will be entered into the eCRF.

6.2.3.7. Tuberculosis Screening:

The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc. and it is the responsibility of the investigator to determine if a subject has previous, active or latent tuberculosis or not in conjunction with a negative TB screening test. Subjects with evidence of a negative TB test result within the 3 months prior to screening will not be required to undergo a re-test at the Screening visit.

QuantiFERON® positive or negative results must not be repeated. An indeterminate result should be repeated once and the second result (if positive or negative) will be accepted. Two sequential indeterminate results constitute a screen failure. Subjects with previously treated TB or newly identified latent TB during Screening require sponsor approval (See Inclusion Criterion No. 10 for details). Subjects who are diagnosed with latent TB before/at Screening must initiate an adequate course of prophylaxis according to local country guidelines for immunocompromised patients for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the Gilead Medical Monitor or designee.

As part of TB screening assessment of a chest x-ray (CXR) is required as described in Section 6.2.3.8.

6.2.3.8. Chest X-Ray

All subjects will undergo a standard CXR (views as per local guidelines) during the screening period to rule out the presence of TB or other clinically relevant findings. If the subject previously had a chest x-ray obtained for clinical care reasons within 3 months of screening, this may be used to satisfy the CXR requirement (as applicable, see Section 4.2).

6.2.3.9. Clinical Laboratory Evaluations

The laboratory analyses will be performed at a local or central laboratory at the Screening Visit. If repeat laboratory tests are required/obtained during Screening, they must be completed at the same location (local or central laboratory) as the original tests. All local tests reference ranges will be supplied by the local laboratory and will be used by the investigator to assess the laboratory data for clinical significance and study eligibility.

For all other visits, laboratory analyses will be performed via a central laboratory. All central tests reference ranges will be supplied by the central laboratory and will be used by the investigator to assess the laboratory data for clinical significance and pathological changes.

Blood samples will be collected by venipuncture CCI [redacted] in the arm at the time points indicated in the study procedures table (Appendix 2). In addition, urine samples for the clinical laboratory assessments will be collected. Subjects only need to be fasted (except ET or EOT visit) on days where lipid profiling is scheduled (Appendix 2).

- Refer to Appendix 6 for table of clinical laboratory tests.

The laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator as indicated.

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and withdrawal from the study, retesting of the affected parameter(s) should be performed promptly (within 3 to 7 days) after the investigator has consulted with the Medical Monitor. A decision regarding subject discontinuation should be made after the results from the retest are available (see Section 3.5 for additional information).

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

6.3. Disease Assessments

Disease assessments will be performed at the time points indicated in the study procedures table (Appendix 2).

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

6.3.5. Visual Ophthalmologic Efficacy Assessments

Visual Ophthalmologic efficacy assessments are detailed in the procedures table (Appendix 2) and include determination of the following:

6.3.5.1. Best Corrected Visual Acuity Testing

Refraction and assessment of BCVA will be assessed at each visit. A qualified and trained health care professional must perform the refraction and BCVA testing. At each visit, subjects should undergo refraction with the result recorded for each eye.

Using the appropriate corrective lenses based on that visit's refraction, subject's BCVA is measured using an ETDRS chart. In the ETDRS system, 15 letters is equal to a change in 3 lines of visual acuity, for example, from 20/40 to 20/20 or vice versa, a halving or doubling of the visual angle; a change of 7.5 letters corresponds to a 25% decrease or 50% increase in the visual angle. The ETDRS chart will be specified and provided by Gilead (if required) with further instructions and training outlined in a visual acuity manual under separate cover. BCVA will also

be collected during the trial if done at unscheduled times for the purposes of standard medical care.

6.3.5.2. Slit Lamp Exam

The slit lamp exam will be completed at each visit. The following findings will be assessed: AC cell count and Age-Related Eye Disease Study (AREDS) lens opacity grading. The AC cell count grading will be performed prior to application of mydriatic eyedrops to dilate subject's pupils for further assessment. AREDS lens opacity grading occurs after dilating the subject's pupils as per Appendix 8. Slit lamp exam results will also be collected during the trial if done at unscheduled times for the purposes of standard medical care. The AREDS classification does not apply if the subject has pseudophakia.

The number of AC cells observed within a 1 mm × 1 mm slit beam will be recorded for each eye. The reported number will be used to determine the grade according to the SUN criteria (Table 6-1).

Table 6-1. Anterior Chamber Cells

Grade	Cells in Field
0	0
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Using the AREDS standard photographs as reference, the degree of lens opacity will be graded for each type: nuclear, cortical, and posterior subcapsular (PSC) (Table 6-2).

See Appendix 8 for further instructions regarding lens opacity grading procedures.

Table 6-2. Lens Opacity Grading

Grading for Nuclear Lens Opacity	
< 1.0	no nuclear opacity, or less than NS Std. No. 1
1.0	opacity similar to NS No. 1
1.5	opacity between NS No. 1 and NS Std. No. 2
2.0	opacity similar to NS No. 2
2.5	opacity between NS No. 2 and NS Std. No. 3
3.0	opacity similar to NS No. 3
> 3.0	opacity greater than NS No. 3
8.0	cannot evaluate
Grading for Cortical Lens Opacity	
< 1.0	no cortical opacity, or opacity obviously less than CO Std. No. 1
1.0	opacity similar to cortical opacity Std. No. 1
1.5	opacity between CO Std. No. 1 and Std. No. 2
2.0	opacity similar to CO Std. No. 2
2.5	opacity between CO Std. No. 2 and Std. No. 3
3.0	opacity similar to CO No. 3
> 3.0	cortical opacity obviously greater than Std. No. 3
8.0	cannot evaluate
Grading for Posterior Subcapsular (PSC) Opacity	
< 1.0	no PSC opacity, or opacity obviously < PSC Std. No. 1
1.0	opacity similar to PSC No. 1
1.5	opacity between PSC No. 1 and Std. No. 2
2.0	opacity similar to PSC No. 2
2.5	opacity between PSC No. 2 and Std. No. 3
3.0	opacity similar to PSC No. 3
> 3.0	PSC obviously greater than PSC No. 3
8.0	cannot evaluate

6.3.5.3. Tonometry

Contact tonometry (Goldmann, Perkins or Tonopen) will be performed at every visit to measure the intraocular pressure for both eyes. Contact tonometry is required for this study. The same technique should be used for all visits for an individual subject. Tonometry results will also be collected during the trial if done at unscheduled times for the purposes of standard medical care.

6.3.5.4. Dilated Indirect Ophthalmoscopy

Subject's eyes should be dilated in preparation for indirect ophthalmoscopy with the examination technique and instrument used remaining consistent for each subject throughout the study.

Dilated indirect ophthalmoscopy is performed to determine the vitreous haze grading and the presence or absence of active, inflammatory, chorioretinal and/or inflammatory retinal vascular lesions. Lesion location(s), number, size(s) and whether the lesions are active or inactive should be documented with a retinal drawing in the subject's source documentation, if a lesion is identified.

Grading of vitreous haze (Table 6-3) will be based on the publication from the NEI which has also been adapted by the SUN working group.

Sites will use the standard photographs given to them by the sponsor and the description in Table 6-3 when determining the grade for vitreous haze.

Table 6-3. Vitreous Haze Grading

Grade	Description
0	No evident vitreal haze
0.5+	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fiber layer cannot be visualized.
1+	Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades)
2+	Permits better visualization of the retinal vessels (compared to higher grades)
3+	Permits the observer to optic nerve head, but the borders are quite blurry
4+	Optic nerve head is obscured

The presence or absence of active inflammatory chorioretinal and/or inflammatory retinal vascular lesions will also be determined via dilated indirect ophthalmoscopy at Screening and Day 1/Baseline. At all subsequent visits, dilated indirect ophthalmoscopy will be performed to determine the presence or absence of new active inflammatory lesions compared to the Day 1/Baseline visit, based on the investigator's clinical judgement. Dilated indirect ophthalmoscopy results will also be collected during the trial if done at unscheduled times for the purposes of standard medical care.

6.3.5.5. Fundus Photography

Fundus photography will be performed in both eyes at Day 1/Baseline, Week 24 and at the time of treatment failure or completion of study (Week 52/EOT or ET). The purpose is to obtain documented evidence of the presence or absence of active inflammatory chorioretinal and/or inflammatory retinal vascular lesions. The same camera should be used for a given subject throughout the study. Fundus photography will also be collected during the trial if done at unscheduled times for the purposes of standard medical care.

All fundus photography images will be sent to the central reader. If there is disagreement between the investigator's assessment for inflammatory lesions based on dilated indirect ophthalmoscopy and central reader's assessment for inflammatory lesions based on fundus photograph, the investigator's assessment will take precedence. However, the reason for the disagreement must be documented by the investigator. The site must have a discussion with the Medical Monitor if the discrepancy is unclear or if further medical discussion is required.

6.3.5.6. Optical Coherence Tomography

OCT will be performed in both eyes at every visit. Sites must use one of two OCT machines for this clinical trial to determine central retinal thickness and the presence of macular edema:

- Cirrus HD-OCT (Carl Zeiss Meditec, Inc.)
- Spectralis (Heidelberg Engineering)

Each subject will undergo OCT measurements of the central retinal thickness (1 mm subfield) to evaluate for macular edema at every visit using the same protocol approved OCT machine throughout the study. OCT measurements at every visit will be captured and sent to the central reader. The central reader will evaluate the OCT images and record these findings. Although it is preferred to complete the OCT measurements following pupil dilation, it is important that the site conducts the scans consistently across each subject (using the same model of OCT device for each subject) throughout the study.

OCT will also be collected during the trial if done at unscheduled times for the purposes of standard medical care.

6.3.5.7. Fluorescein Angiogram

Ultra-wide field fluorescein angiograms are preferred and must be used if this equipment is available at the site. If this equipment is not available at a specific site, standard FA imaging is acceptable. Fluorescein angiograms (FA) will be obtained in both eyes on Day 1/Baseline (before dosing), Week 24, and at Week 52/EOT or ET visit. The severity of fluorescein leakage and of cystoid spaces will be assessed using a modification of the ETDRS protocol. The area of retinal thickening and of cystoid spaces found on concurrently graded FA and color fundus photographs will also be noted. The extent of fluorescein leakage will be noted in disc areas. Additional retinal morphologic features that will be graded include but are not limited to vascular

nonperfusion, choroidal neovascularization, preretinal neovascularization, retinal detachment, optic disc edema, glaucomatous optic disc changes, vitreoretinal interface abnormalities (such as epiretinal membrane) and their relationship to macular edema, and chorioretinal lesions (FA with sweep fields). Morphologic features in most cases are measured as dichotomous variables (present or absent), and if present, their extent is graded. Additional imaging studies done as a part of standard medical care may also be collected. These images will all be sent to the central reader for interpretation. The same instrument should be used for the same subject assessments throughout the study.

6.3.6. Viral Monitoring: HCV and HBV

Subjects with positive HCV antibody (Ab) at screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA at screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA are eligible per investigator judgment. Subjects with active HCV during the study, as evidenced by HCV RNA positivity will be discontinued from study drug as outlined in the protocol.

Subjects with positive HBsAg at screening are excluded from the study. Subjects with positive HBV core Ab and negative HBsAg, require reflex testing for HBV DNA. Subjects with positive HBV DNA at screening will be excluded. Subjects with positive HBV core Ab, and negative HBV DNA are eligible per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines/local standard of care and require ongoing monitoring with blood tests for HBV DNA every 3 months. Subjects with evidence of active Hepatitis B during the study, as evidenced by HBV DNA positivity, will be discontinued from study drug as outlined in the protocol.

6.4. Pharmacokinetics Assessments

Blood samples will be collected for plasma PK analysis of filgotinib and its metabolite GS-829845 at Day 1/Baseline and Week 12 (at least 30 minutes after dosing), within 2 hours prior to dosing on Weeks 4 and/or 6, and anytime at week 24, 36 and the final assessment visit on Week 52/EOT or ET visit as detailed in Appendix 2.

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6.6. End of Treatment

End of treatment for a subject is defined as the date of the last study-related procedure or the date of death for an on-study subject.

6.7. Unscheduled Visit Attributed to Uveitis Symptoms

If a subject presents at a site for an unscheduled visit with symptoms related to a uveitis flare, subjects should be evaluated for treatment failure criteria. If treatment failure criteria are met, investigators should complete EOT procedures. If a subject presents at a site for an unscheduled visit not related to a uveitis flare, investigators should complete unscheduled visit procedures at their discretion.

6.8. End of Study

End of Study (EOS) is defined as when the last enrolled subject has either completed the Week 52 visit or met the criteria for treatment failure or early terminated (plus the 4-Week Post-Treatment Follow-Up Visit if applicable).

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to investigational medicinal product (IMP) therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the modified CTCAE, version 4.03. For each episode, the highest grade attained should be reported. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1 and Appendix 4.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death related AE

* Activities of Daily Living (ADL) Instrumental ADL refer to opening preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRF: all SAEs and AEs related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug(s). All AEs must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow-up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30-days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow-up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

In the intended study population, Gilead anticipates the occurrence of uveitis-related AEs/SAEs. These uveitis-related events include those that are manifestations of the underlying disease which commonly occur in the study population independent of drug exposure, and/or are components contributing to the study endpoints (e.g., band keratopathy, vitreous hemorrhage). The investigator will determine if a specific AE/SAE is uveitis-related and record it in a specific field in the eCRF.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper SAE reporting form and submit within 24 hours to:

Gilead PVE:	**Fax:**	PPD
	E-mail:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, X-rays, vital signs, ocular assessments) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at: http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3 and as outlined below.

For study-specific interruption and discontinuation criteria, refer to Section 3.5

7.6. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3 and as outlined below. For study-specific interruption and discontinuation criteria, refer to Section 3.5.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Medical Monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be managed as outlined in Appendix 3 and Sections 7.6.2 and 7.6.3.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

For Grades 1 and 2 laboratory abnormalities or clinical events not specified in Section 3.5, continue study drug at the discretion of the investigator.

7.6.2. Grades 3 Laboratory Abnormality or Clinical Event

For Grade 3 laboratory abnormalities or clinical event not specified in Section 3.5, the following toxicity management guidelines apply.

For a Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.

For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2.

If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation and study drug may be continued at the discretion of the investigator.

7.6.3. Grades 4 Laboratory Abnormality or Clinical Event

For Grade 4 laboratory abnormalities or clinical events not specified in Section 3.5, the following toxicity management guidelines apply.

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug, study drug should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 creatine kinase (CK) after strenuous exercise or triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to study drug.

Any questions regarding toxicity management should be directed to the Medical Monitor.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of an investigational product while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of an investigational product by a subject.

Misuse is defined as any intentional and inappropriate use of an investigational product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of an investigational product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to an investigational product as a result of one's professional or non-professional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead investigational product.

Counterfeit or falsified medicine: Any investigational product with a false representation of: a) its identity, b) its source, or c) its history.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows: Email: PPD and Fax: PPD.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the efficacy of filgotinib versus placebo for the treatment of the signs and symptoms of noninfectious uveitis as measured by the proportion of subjects failing treatment for active noninfectious uveitis by Week 24

The secondary objectives of this study are:

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the time to treatment failure (on or after Week 6)

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in VH grade in each eye (NEI/SUN criteria), from best state achieved prior to Week 6 to Week 52/EOT or ET visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in AC cell grade in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in logMAR BCVA in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the change in central retinal thickness in each eye, from best state achieved prior to Week 6 to Week 52/EOT or ET visit

- To evaluate the efficacy of filgotinib versus placebo for the treatment of noninfectious uveitis as measured by the time to development of macular edema in at least one eye as determined by OCT (evaluated at all visits on or after Week 6)

- To evaluate the safety and tolerability of filgotinib

- To evaluate the pharmacokinetics of filgotinib and its metabolite GS-829845

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8.1.2. Primary Endpoint

The primary endpoint is the proportion of subjects failing treatment for active noninfectious uveitis by Week 24 as outlined in Table 3-3.

8.1.3. Secondary Endpoint

The secondary endpoints of this study are:

- Time to treatment failure on or after Week 6
- Change in VH grade in each eye (NEI/SUN criteria), from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit
- Change in AC cell grade in each eye, from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit
- Change in logMAR BCVA in each eye, from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit
- Log change in central retinal thickness in each eye, from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit

- Time to development of macular edema in at least one eye as determined by OCT on or after Week 6
- Pharmacokinetic characteristics for filgotinib and its metabolite GS-829845

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

All Randomized Analysis Set includes all subjects who are randomized in the study. This is the primary analysis set for by-subject listings.

8.2.1.2. Efficacy

8.2.1.2.1. Evaluable Analysis Set

The Evaluable Analysis Set is the primary analysis set for efficacy analyses; which includes all randomized subjects who receive at least one dose of study drug, and do not permanently discontinue from the study prior to Week 6.

8.2.1.2.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who receive at least one dose of study drug.

8.2.1.2.3. Per-Protocol Analysis Set

The secondary analysis set for efficacy analyses will be the Per-Protocol (PP) Analysis Set, which includes all subjects in the Evaluable Analysis Set who do not commit any major protocol violation, including the violation of key entry criteria.

8.2.1.3. Safety

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who receive at least one dose of study drug.

8.2.1.4. Pharmacokinetics

The PK analysis set includes all subjects in the Safety Analysis Set who have at least 1 non-missing plasma concentration data for filgotinib and/or its metabolite GS-829845.

CCI [redacted]

[redacted]

8.3. Data Handling Conventions

PK concentration values and PK parameter values below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listings. BLQ values that occur prior to the first dose will be treated as 0, BLQ values at all other time points will be treated as 1/2 of the lower limit of quantitation.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus one significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group using standard descriptive statistics including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and number and percentages of subjects for categorical variables.

Demographic data will include sex, race, ethnicity, and age.

Baseline characteristics may include uveitis attributed to sarcoidosis (yes/no), baseline immunosuppressant usage (yes/no), prior use of anti-TNF therapy (yes/no), uveitis types (pan-uveitis, posterior uveitis, and intermediate uveitis), affected eye (left eye, right eye or both eyes) and other variables of interest.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint for the study is the proportion of subjects failing treatment by Week 24. The primary hypothesis will consist of a superiority test of filgotinib compared to placebo based on proportion of subjects failing treatment by Week 24. The Cochran-Mantel-Haenszel (CMH) approach adjusting for the stratification factors will be used for the hypothesis testing of the primary endpoint. Subjects who are missing sufficient measurements to establish efficacy at Week 24 will be considered as failures (i.e. non-responder imputation). Sensitivity analyses will be conducted and described in the statistical analysis plan (SAP).

Each component of the primary efficacy endpoint will be compared between filgotinib and placebo groups using the CMH test adjusting for stratification factors. In the event that the number of subjects failing treatment due to any individual component is small, the chi-square test or the exact method will be used. The details of the analyses will be provided in the SAP.

There will be one planned interim analysis when approximately 50% of the enrolled subjects have either completed their Week 24 visit or discontinued from the study before Week 24. To control for the overall type I error rate at 0.05, an alpha of 0.001 will be spent for the filgotinib group comparison to the placebo group based on the Haybittle-Peto boundaries at the interim analysis. As a result, an adjusted 2-sided significance level of 0.0498 will be used to declare statistical significance for the final primary analysis. The details of the interim analysis are provided in Section 8.10.

8.5.2. Secondary Analyses

The hypothesis testing of the following key secondary endpoints will commence after the primary endpoint reaches statistical significance, and will be tested according to the hierarchical testing principle at the same significance level as the primary endpoint. That means, if a null hypothesis for the higher ranked secondary endpoint is not rejected, formal sequential testing will be stopped and only nominal significance will be reported for the remaining key secondary endpoints.

- Time to treatment failure on or after Week 6
- Change in VH grade in each eye (NEI/SUN criteria), from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit

- Change in AC cell grade in each eye, from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit

- Change in logMAR BCVA in each eye, from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit

- Log change in central retinal thickness in each eye, from best state achieved prior to Week 6 to Week 52/EOT visit or ET visit

- Time to development of macular edema in at least one eye as determined by OCT on or after Week 6

For all subjects, the time to treatment failure and the time to OCT evidence of macular edema will be based on the first eye to meet the criteria for treatment failure or macular edema. The change in anterior chamber cell grade in each eye from best state achieved prior to Week 6 to Week 52/ET Visit, change in vitreous haze grade in each eye from best state achieved prior to Week 6 to Week 52/ET Visit, change in best corrected visual acuity (logarithm of the minimum angle of resolution) in each eye from best state achieved prior to Week 6 to Week 52/ET Visit, and change in central retinal thickness in each eye from best state achieved prior to Week 6 to Week 52/ET Visit will be analyzed using data from each eye individually. The definition of 'best state' for the VH grade, AC cell grade, BCVA and central retinal thickness will be provided in the SAP.

The time to treatment failure on or after Week 6 will be compared between the filgotinib group and the placebo group with a stratified log-rank test. A proportional-hazards model with the study group as a factor and stratification factors as covariates will be fitted to estimate the hazard ratio with its 95% confidence interval. As sensitivity analysis, the time to treatment failure between the filgotinib group and the placebo group will be compared using the restricted mean survival time. Treatment failures on or after Week 6 will be counted as events and dropouts due to reasons other than treatment failure at any time during the study will be considered as censored observations at the time of dropping out. The time to macular edema on or after Week 6 will be analyzed in the same way. OCT evidence of macular edema on or after Week 6 will be counted as event. Dropouts due to reasons other than OCT evidence of macular edema will be considered as censored observations at the time of dropping out.

Change in AC cell grade, change in Vitreous Haze grade, change in BCVA (logarithm of the minimum angle of resolution), and change in central retinal thickness will be compared between treatment groups using the repeated measures Analysis of Covariance to control for clustered observations (i.e., observations from each of the subject's eyes), with treatment as a factor, and the stratification factors and baseline values included as covariates. For change in central retinal thickness the analysis will additionally be adjusted for type of OCT machines.

CCI [redacted]

[redacted]

8.6. Safety Analysis

All safety analyses will be performed using the Safety Analysis Set.

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug, unless specified otherwise will be summarized by treatment group according to the study drug received.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the eCRF. Exposure data will be summarized by treatment group.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory AE will be coded using the MedDRA. System Organ Class, High-Level Group Term, High-Level Term, Preferred Term (PT), and Lower-Level Term will be attached to the clinical database.

Treatment-emergent AEs (TEAEs) are:

- Any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or
- Any AEs leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided by treatment group. TEAEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug will be summarized and listed.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group and study visit along with corresponding change from Baseline. The incidence of treatment-emergent graded laboratory abnormalities will be summarized similarly.

Graded laboratory abnormalities will be defined using CTCAE 4.03 grading scale.

8.7. Pharmacokinetic Analysis

Plasma concentrations of filgotinib and its metabolite (GS-829845) will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations over time may be plotted in semi logarithmic and linear formats as mean ± standard deviation and median (Q1, Q3).

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[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

8.9. Sample Size

Sample size calculations are based on published data from the VISUAL I trial {Jaffe 2016}. Assumiung the observed proportion of subjects failing treatment by Week 24 is 70% in the placebo group, 107 subjects per treatment group will provide at least 85% power to detect a

reduction of 20% in the proportion of subjects with treatment failure by Week 24 in the filgotinib group using a 2-sided significance level of 0.05. Given an expected attrition rate of 15%, a total of 248 subjects will need to be randomized into the study.

8.10. Data Monitoring Committee (DMC)

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC will also assess efficacy and futility on the primary endpoint at the pre-defined interim analysis time points.

An interim analysis for efficacy and futility will be conducted when approximately 50% of enrolled subjects have either completed their Week 24 visit or discontinued from the study before Week 24. The efficacy analysis will be performed for the primary endpoint, proportion of subjects failing treatment by Week 24, using the CMH approach adjusting for the stratification factors. The DMC may recommend early termination of the study owing to compelling evidence of efficacy using a pre-specified Haybittle-Peto efficacy boundary with a significance level of 0.001. A non-binding futility rule on the proportion of subjects failing treatment will also be implemented. Based upon the analysis results, the DMC may recommend early termination of the study for futility if the predictive power (ie, the probability of obtaining a statistically significant result at the final analysis given the observed interim data) is < 20%.

If the DMC recommends early termination of the study, an internal Gilead team who are not involved with the study may perform an unmasked review of the interim data to confirm the DMC recommendation and decide the path forward. While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, the timing of planned safety and efficacy analyses, conduct and meeting schedule.

8.11. Ad Hoc DMC Meeting

An ad hoc convening of the DMC may be triggered by the following conditions:

- ≥ 2 subjects develop the same (by PT) related, Grade 4, unexpected AE in the infections and infestations SOC
- ≥ 2 subjects develop any related, Grade 4 thromboembolic event that has been positively adjudicated by the independent adjudication committee (Section 8.12)
- Any subject develops a Grade 5, related, unexpected AE. The definition of an unexpected AE will be based on the Reference Safety Information that is on file at the time the event occurs

8.12. Cardiovascular Safety Endpoint Adjudication Committee (CVEAC)

An independent adjudication committee will be formed to periodically review and adjudicate all potential major adverse cardiovascular events and thromboembolic events in a blinded manner.

The CVEAC's specific activities will be governed by a mutually agreed charter, which will define the CVEAC's membership, conduct, and meeting schedule.

The following events will be adjudicated and classified by the CVEAC:

- Cardiovascular death
- Myocardial infarction
- Stroke
- Arterial thromboembolism
- Venous thromboembolism (eg, deep venous thrombosis, pulmonary embolism)

Further details will be specified in the CVEAC Charter.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

The consent form will inform subjects about genomic testing and/or planned sample retention.

CCI [redacted]

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator's brochure, this protocol, eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, paper or electronic completed subject CRFs, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification;
- Documentation that subject meets eligibility criteria; ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an electronic case report form (eCRF) casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines (CCGs) provided by the Sponsor. Subsequent to data entry, a study monitor will perform source data verification (SDV) within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site investigator or site coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authority(ies), IRBs, and ECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Filgotinib in Subjects with Active Noninfectious Uveitis

GS-US-432-4097, Amendment 4, 17 March 2020

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD (Printed)

PPD

PPD

20-MAR-2020
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Investigator Name (Printed) _____ Signature

Date _____ Site Number

Appendix 2. Study Procedures Table

	Screening	Day 1 / Baseline	Wk 1	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Unscheduled Visit related to Uveitis Symptoms[u]	Wk 52 / End of Treatment –or– Early Termination Visit	4-Week Post-Treatment Follow-Up Visit [t]
Visit Window	**Within -30 days**		**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**			**(+7 days)**
Written Informed Consent	X																		
Review Inclusion/Exclusion		X																	
Medical History	X																		
Complete/ Symptom Driven Physical Examination[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																		
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 lead ECG	X																		
TB Test and Chest X ray[c,d]	X																		
Hematology[d]	X[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Chemistry[d]	X[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Lipid Profile (Fasting)[e]		X								X								X	
ANA Test[f]		X																	
Syphilis Test[d,g]	X																		
Serology Testing[h]	X[v]																		

	Screening	Day 1 / Baseline	Wk 1	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Unscheduled Visit related to Uveitis Symptoms[u]	Wk 52 / End of Treatment –or– Early Termination Visit	4-Week Post-Treatment Follow-Up Visit [t]
Visit Window	**Within -30 days**		**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**			**(+7 days)**
HBV Viral Monitoring[h]							X			X			X			X		X	
Urine drug test[i]	X[v]																		
Urinalysis[d]	X[v]	X					X		X									X	X
Urine or Serum Pregnancy Test[j]	X[v]	X		X		X	X	X	X	X	X	X	X	X	X	X		X	X
Serum FSH[k]	X[v]																		
CCI																			
CCI																			
CCI																			
CCI																			
CCI																			
PK[m]		X		X	X		X			X			X					X	
Best Corrected Visual Acuity Testing (BCVA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Day 1 / Baseline	Wk 1	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Unscheduled Visit related to Uveitis Symptoms[u]	Wk 52 / End of Treatment –or– Early Termination Visit	4-Week Post-Treatment Follow-Up Visit [t]
Visit Window	**Within -30 days**		**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**			**(+7 days)**
Dilated Indirect Ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Color Photography (both eyes)		X								X								X	
Fluorescein Angiogram (both eyes)		X								X								X	
Optical Coherence Tomography (OCT) Scan (both eyes)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Current Uveitis Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																			
CCI [redacted]																			
In Clinic Study Drug Dosing[r]		X		X	X		X												
Study Drug Dispensation[r]		X		X		X	X	X	X	X	X	X	X	X	X	X			
Prednisone Dispensation[s]		X			X	X													

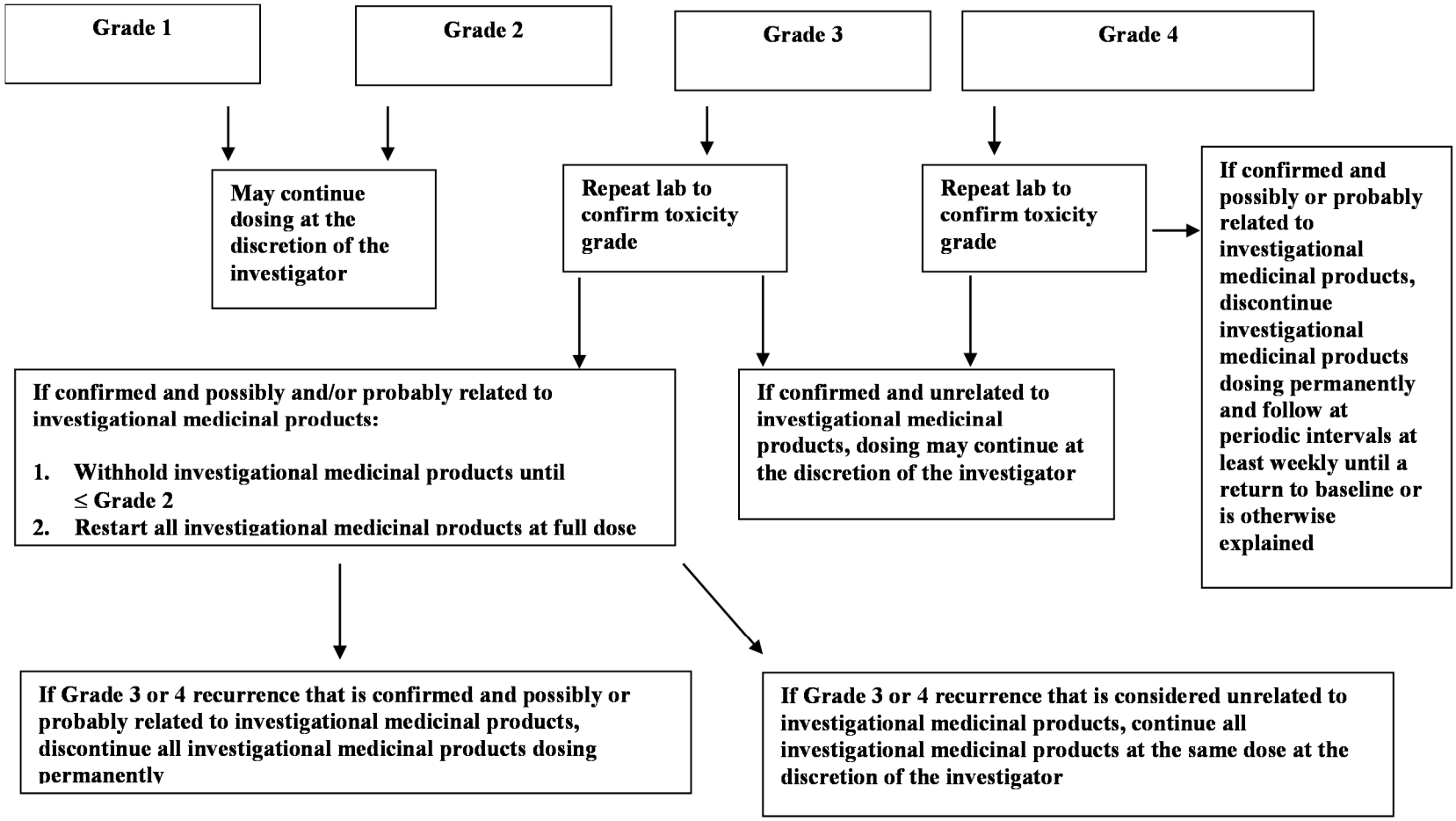
	Screening	Day 1 / Baseline	Wk 1	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Unscheduled Visit related to Uveitis Symptoms[u]	Wk 52 / End of Treatment –or– Early Termination Visit	4-Week Post-Treatment Follow-Up Visit [t]
Visit Window	**Within -30 days**		**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**			**(+7 days)**
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Complete PE will be performed at Screening and Week 52 or ET/EOT. Symptom driven PE will be performed at all other visits.
b Vital signs include resting blood pressure, pulse, and temperature.
c Subjects must have the QuantiFERON® TB Gold In Tube test AND a chest radiograph (views as per local guidelines) taken at screening or within 3 months prior to screening (with the report or films available for investigator review). Subjects with evidence of a negative QuantiFERON® TB Gold In Tube test result within 3 months will not require a re test at Screening. QuantiFERON® TB Gold can be processed locally.
d The required screening labs can be obtained either using the sites local lab or by submitting appropriate samples to the central lab. For Chemistry panel, Uric acid to be tested at screening only per Appendix 6. Refer to list provided in Laboratory assessment table (Appendix 6).
e Fasting lipid on Day 1 and Week 24. Week 52/EOT or ET visit lipid can be obtained fasting or non fasting.
f Study personnel will collect a sample for antinuclear (ANA) and reflex double stranded DNA antibody testing at the Day 1/Baseline visit. A repeat ANA/Anti ds DNA would be warranted if a subject has clinical signs and symptoms suggestive of lupus. The Anti ds DNA antibody testing will be performed in case of positive ANA result.
g Subjects whom underwent syphilis screening (either a FTA test or a syphilis IgG test) for standard of care purposes within 3 months prior to Screening and evidence of a nonreactive FTA or syphilis IgG test result will not require a re test at Screening.
h HBsAg and core Ab (if positive core Ab, then reflex HBV DNA and ongoing monitoring as applicable per Section 6.3.6), Hepatitis C Ab, (if positive then, reflex HCV RNA), HIV 1/2 antigen/antibody combination test (4th generation, as per Appendix 6). The required screening labs can be obtained either using the sites local lab or by submitting appropriate samples to the central lab. Subjects with positive HBV core Ab, and negative HBV DNA are eligible per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines/local standard of care and require ongoing monitoring with blood tests for HBV DNA every 3 months.
i Drug screen to be conducted at screening only per Appendix 6. The required screening labs can be obtained either using the sites local lab or by submitting appropriate samples to the central lab.
j Females of childbearing potential only. Serum pregnancy test at Screening and Urine pregnancy test to be conducted every 4 weeks during the dosing period through 35 days after their last dose of study drug. The required screening labs can be obtained either using the sites local lab or by submitting appropriate samples to the central lab.
k For female subjects <54 and amenorrhea ≥12 months. The required screening labs can be obtained either using the sites local lab or by submitting appropriate samples to the central lab.
[redacted]
m Day 1/Baseline and Week 12 PK sample to be drawn at least 30 minutes post dose. Week 4 and/or 6, PK sample to be drawn within 2 hours prior to dose. Weeks 24, 36 & 52/EOT or ET PK can be drawn at any time.
[redacted]

[redacted]

r Study drug will be dispensed to subjects every 4 weeks until Week 48 or prior to the ET/EOT study visit.
s Prednisone will be dispensed to subjects at Day 1/Baseline (Dose strengths 20 mg and 10 mg), Week 6 (Dose strengths 5 mg and 2.5 mg) and Week 8 (Dose strength 1 mg).
t 4 Week Post Treatment Follow Up Visit to be completed at the end of the Randomized Double Masked study.
u If a subject presents at a site for an Unscheduled visit with symptoms related to a uveitis flare, subjects should be evaluated for treatment failure criteria. If treatment failure criteria are met, investigators should complete EOT procedures. If a subject presents at a site for an Unscheduled visit not related to a uveitis flare, investigators should complete unscheduled visit procedures at their discretion.
v Tests obtained for standard of care purposes within 30 days of Day 1/Baseline may be used to satisfy eligibility criteria. Refer to list provided in Laboratory assessment table (Appendix 6).

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

CTCAE v4.03 can be accessed from the below link:

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

The only modification to the CTCAE criteria is the addition of a Grade 1 upper respiratory infection as follows:

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Upper respiratory infection	Mild symptoms; symptomatic relief (eg, cough suppressant, decongestant)	Moderate symptoms; oral intervention indicated (eg, antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

The administration of filgotinib in embryo-fetal animal development studies resulted in decreased numbers of viable rat fetuses, increased resorptions, and visceral and skeletal malformations. Similar effects were noted in the rabbit. A safety margin relative to human exposure has not been identified. Therefore, filgotinib is contraindicated during pregnancy.

For participation in this study, the use of *highly effective* contraception is required as outlined below for all subjects of childbearing potential. In addition, women of childbearing potential should have a urine pregnancy test every 4 weeks during the study.

1. Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, women <54 with amenorrhea of $\geq$ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b) Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or medical documentation of permanent male infertility.

2. Contraception for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Filgotinib is contraindicated in pregnancy as there is a possibility of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. Data from a drug-drug interaction study of filgotinib and hormonal contraceptives (GS-US-417-3916) demonstrated that filgotinib does not alter the pharmacokinetics of representative hormonal contraceptives levonorgestrel/ethinyl estradiol. Results from this study may be found in the Investigator's Brochure (Section 4.1.3.2.4).

For female subjects, hormonal contraceptives will be permitted as a form of contraception when used in conjunction with a barrier method (preferably a male condom). For male subjects, male condom should be used; for their female partners of childbearing potential, an accepted contraceptive method should also be considered. Details are outlined below.

Please refer to the latest version of the filgotinib IB for additional information.

b) Contraception for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Women must have a negative serum pregnancy test at screening and a negative urine pregnancy test on the Day 1/Baseline visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. In the event of a delayed menstrual period (> one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for women of childbearing potential with infrequent or irregular periods. Female subjects must agree to use one of the following methods from screening until 35 days following the last dose of study drug.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  Intrauterine device (IUD) with a failure rate of < 1% per year

  Tubal sterilization

  Essure micro-insert system (provided confirmation of success 3 months after procedure)

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure, with documentation of sperm-free ejaculate)

These above described methods are considered *preferred methods* of highly effective contraception in this protocol.

Female subjects, who wish to use a hormonally based method, must use it in conjunction with a barrier method; the barrier method is to be used either by the female subject or by her male partner. Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study dosing. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method *must* be used with a barrier method, preferably male condom)

  Oral contraceptives (either combined estrogen/progestin or progesterone only)

  Injectable progesterone

  Implants of levonorgestrel

  Transdermal contraceptive patch

  Contraceptive vaginal ring

- Barrier methods (each method *must* be used with a hormonal method)

  Male or female condom with or without spermicide

  Diaphragm with spermicide

  Cervical cap with spermicide

  Sponge with spermicide

All female subjects must also refrain from egg donation and in vitro fertilization during study participation and until at least 35 days after the last study drug dose.

3. Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during study participation and for 90 days after the last study drug dose. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the end of dosing.

4. Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5. Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 35 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study are to report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

6. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period through 35 days after their last dose of study drug. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

Appendix 6. Clinical Laboratory Assessment Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count Differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils Reticulocyte count Mean corpuscular volume (MCV)	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transpeptidase (GGT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Serum creatinine Creatinine clearance CC&G[a] Glucose Phosphorus Magnesium Potassium Sodium Amylase Lipase Uric Acid (screening) Lipid Profile (Fasting, if applicable) triglycerides, cholesterol and its subfractions (high-density lipoprotein [HDL] and low-density lipoprotein [LDL]) Creatine Phosphokinase (CPK)	Appearance: Blood Color Glucose Specific gravity Nitrites Leukocyte esterase pH Protein Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal **Serology** Hepatitis B surface antigen (HBsAg) and core Ab, (if positive core Ab, then reflex HBV DNA) Hepatitis C Ab (if positive, then reflex HCV RNA) HIV 1/2 antigen/antibody combination test (4th generation) **Pregnancy** *In females of childbearing potential:* Serum pregnancy Urine pregnancy *In females of non childbearing potential:* Follicle Stimulating Hormone (FSH) Test	Urine drug screen (screening) for: Amphetamines Cocaine Methadone Opiates QuantiFERON® TB – Gold In-Tube Analysis Antinuclear antibody (ANA) test and Anti-ds-DNA reflex in case of positive ANA result (Day 1/Baseline) Syphilis Test (FTA or syphilis IgG test)

a Creatinine clearance is calculated by the Cockcroft Gault equation {Cockcroft 1976} using actual body weight (BW).

Male: $\frac{CL_{cr}\ (mL/min) \quad [140 - age\ (years)] \times BW(kg)}{72 \times Scr}$

Female: $\frac{CL_{cr}\ (mL/min) \quad [140 - age\ (years)] \times BW(kg) \times 0.85}{72 \times Scr}$

S_{cr} serum creatinine (mg/dL)

Appendix 7. Corticosteroid Conversion Table

Substance Names	Selection of Trade Names	Prednisone Equivalents 5 mg
Betamethasone	Alphatrex, Betacord, Betaderm, Betatrex, Beta-Val Betnelan, Betamethasone Dipropionate, Celestone/Alphatrex, Diprolene AF, Diprosone, Maxivate, Teladar/Diprolene, Celestan, Betnesol	0.75 mg
Cloprednole	Synthesan	2.5 mg
Cortisone	Cortison CIBA, Cortone Acetate	25 mg
Deflazacort	Calcort	6 mg
Dexamethasone	Aeroseb-Dex, Dalalone, Decadron Phosphate, Dexacen LA-8, Dexacen-4, Dexasone, Dexone, Hexadrol Phosphate, Solurex, Decadron, Fortecortin, Auxiloson, Milicorten	0.75 mg
Fluocortolone	Ultralan	5 mg
Hydrocortisone	Cortef, Cortenema, Hydrocortisone, Solu-Cortef, Hydrocortison Hoechst	20 mg
Methylprednisolone	Medrol/Depo-Medrol, Duralone, Medralone, Rep-Pred/ A-Methapred, Solu-Medrol, Medrate Urbason	4 mg
Paramethasone	Monocortin	2 mg
Prednisolone	Delta-Cortef, Hydeltrasol, Hydeltra-TBA, Key-Pred 25, Predalone 50, Predcor-25, Prelone, Solu Decortin-H, Detacortril, Hostacortin-H, Ultracorten-H, Scherisolon	5 mg
Prednisone	Apo-Prednisone, Deltasone, Meticorten, Orasone, Panasol-S, Prednicen-M, Sterapred, Winpred, Decortin, Hostacortin	5 mg
Prednylidene	Decortilen	6 mg
Triamcinolone	Amcort, Aristocort, Atolone, Azmacort, Cenocort A-40, Cenocort Forte, Kernocort, Kenalog, Tac-40, Triam-A, Triamcinolone, Triam Forte, Triamolone, Tri-kort, Trilog, Trilone, Delphicort, Extracort, Tram-oral, Volon	4 mg

Appendix 8. AREDS 2008 Clinical Lens Opacity Grading Procedures

AREDS Study Group

- Dilate pupils to at least 5 mm diameter
- Use slit lamp with ~10× magnification
- Use brightest beam intensity
- Nuclear opacity

  Orient beam at 45° to viewing axis

  Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width

  Compare opalescence of nucleus with that in standard photos
- Cortical and PSC opacities

  Select wide slit beam setting optimum for retro-illumination of lens

  Visualize lens opacities against red fundus reflex background

  Count only opacities definitely visible against red reflex

  Mentally combine all cortical opacities into one contiguous area

  Compare total opacity area with that in standard photos
- Classify each opacity with scale defined by 3 standard photos
- Select nearest half-step

  Similar to standard or between two standards

  Obviously less than mildest standard or greater than most severe