Filgotinib in Active Non-Infectious Uveitis: HUMBOLDT, a Randomized, Double-Masked Trial

A Randomized Clinical Trial

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Key Points

Question: What is the efficacy and safety of filgotinib in patients with active non-infectious uveitis?

Findings: Among 74 participants in a randomized, double-masked, placebo-controlled, clinical trial that was prematurely halted for business reasons ahead of meeting enrollment targets, the filgotinib group had fewer treatment failures by week 24 (the primary efficacy endpoint) than the placebo group, while differences in safety between groups were not detected.

Meaning: While the HUMBOLDT trial provided evidence supporting the efficacy of filgotinib in patients with active non-infectious uveitis, the termination of the trial prevented collection of additional safety or efficacy information of this Janus kinase 1 preferential inhibitor.

Abstract

Importance: Non-infectious uveitis is a leading cause of visual impairment with an unmet need for additional treatment options.

Objective: We assessed the efficacy and safety of filgotinib, a Janus kinase 1 (JAK1) preferential inhibitor, for the treatment of non-infectious uveitis.

Design and Setting: HUMBOLDT was a randomized, double-masked, placebo-controlled, phase 2 trial conducted at 26 centers in 7 countries.

Participants: Eligible participants (aged ≥18 years) had active non-infectious intermediate, posterior, or pan-uveitis despite ≥2 weeks of treatment with oral prednisone (10-60 mg/day).

Interventions: Participants were randomized 1:1 to receive filgotinib 200 mg or placebo orally once daily for up to 52 weeks.

Main Outcomes and Measures: The primary endpoint was the proportion of participants experiencing treatment failure by week 24. Treatment failure was a composite endpoint represented by assessment of the presence of chorioretinal and/or retinal vascular lesions, best corrected visual acuity, and anterior chamber cell and vitreous haze grades. Safety was assessed in participants who received at least one dose of study drug or placebo.

Results: Between July 26, 2017, and April 22, 2021, 116 participants were screened and 74 were randomized to receive filgotinib (n=38) or placebo (n=36). Despite early termination of the trial for business reasons ahead of meeting enrollment targets, a significantly reduced proportion of participants who received filgotinib experienced treatment failure by week 24 versus placebo (n=12/32 [37·5%] *vs* n=23/34 [67·6%]; difference *vs* placebo −30·1%, 95% confidence interval −56·2% to −4·1%; p=·006). Business reasons were unrelated to efficacy or safety. Adverse events were reported in 30/37 participants (81·1%) who received filgotinib and in 24/35 participants (68·6%) who received placebo. Serious adverse events were reported in 5/37 participants (13·5%) in the filgotinib group and in 2/35 participants (5·7%) in the placebo group. No deaths were reported during the trial.

Conclusions and Relevance: Filgotinib lowered the risk of treatment failure in participants with active non-infectious intermediate, posterior, or pan-uveitis versus placebo. While the HUMBOLDT trial provided evidence supporting the efficacy of filgotinib in patients with active non-infectious uveitis, the premature termination of the trial prevented collection of additional safety or efficacy information of this JAK1 preferential inhibitor.

Trial Registration: ClinicalTrials.gov ID: NCT03207815.

Introduction

Uveitis is characterized by intraocular inflammation of the uvea and adjacent structures,[1] and is one of the leading causes of blindness in the USA and Europe.[2-4] Diagnosis of uveitis can be challenging, with approximately half of cases being idiopathic.[1,5] In these patients, uveitis is presumed to be immune-mediated, with associated disorders including inflammatory bowel disease (IBD) and sarcoidosis.[1,5,6] These conditions have been associated with activation of signaling pathways involving Janus kinase (JAK) and signal transduction and activation of transcription (STAT) signaling proteins.[7]

Anterior uveitis, the most common form, can often be managed acutely with topical corticosteroid (CS) therapy.[5] Non-infectious intermediate, posterior, and pan-uveitis subtypes are more challenging to control,[5,8] requiring systemic or intravitreal CS therapies such as prednisone and triamcinolone acetonide, respectively.[1,5] Long-term use of CS is associated with potentially serious adverse events (AEs) such as diabetes, glaucoma, and cataracts.[1,8-10] Immunosuppressants such as azathioprine and methotrexate are recommended as a CS-sparing approach for patients with non-infectious uveitis, though these are not currently licensed for this indication.[1,5]

Adalimumab, (a subcutaneous anti-tumor necrosis factor [TNF] therapy), is the only non-CS treatment approved in the USA and Europe for non-infectious intermediate uveitis, posterior uveitis, and pan-uveitis.[11,12] Despite this, treatment with adalimumab has been associated with high treatment failure rates.[13,14] As such, uveitis is still associated with substantial morbidity and significant unmet therapeutic need.

Filgotinib, an oral preferential JAK1 inhibitor is indicated for the treatment of rheumatoid arthritis (RA) and ulcerative colitis (UC) in the EU, UK, Japan, South Korea and Taiwan;[15-17] it is not approved for use in the USA. Despite the role of the JAK–STAT pathway in inflammation,[7,17] there have been no randomized clinical studies of JAK inhibitors in uveitis, to our knowledge, published to date. The phase 2 HUMBOLDT trial was designed to assess a JAK inhibitor for this indication, assessing the efficacy and safety of filgotinib in participants with active, non-infectious intermediate, posterior, or pan-uveitis.

Methods

Study Design

HUMBOLDT (NCT03207815) was a randomized, double-masked, placebo-controlled, phase 2 trial conducted at 26 centers (clinics, research centers, and academic hospitals) in 7 countries (Australia, Canada, Germany, Israel, New Zealand, the UK, and the USA) between July 26, 2017 and April 22, 2021. The final protocol and the 4 amendments were reviewed and approved by the Independent Ethics Committee and/or Institutional Review Board at each trial site. All participants provided written informed consent and were reimbursed for inconveniences related to study participation, such as travel expenses. No financial incentives were offered for study participation. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The trial design is shown in **figure s1**.

Participants

Eligible participants were aged ≥18 years with a history of non-infectious intermediate, posterior, or pan-uveitis. At day 1/baseline, participants had active non-infectious intermediate, posterior, or pan-uveitis in at least 1 eye despite ≥2 weeks of maintenance therapy with oral prednisone (from ≥10 mg/day to ≤60 mg/day) or oral CS equivalent. Active uveitis was defined as the presence of at least 1 of: an active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion; ≥2+ anterior chamber cell (ACC) grade (Standardization of Uveitis Nomenclature [SUN] criteria); ≥2+ vitreous haze (VH) grade (National Eye Institute [NEI]/SUN criteria). Both of the participants' eyes were clinically evaluable for the purpose of determining eligibility and for assessment throughout the study.

Participants were excluded from the trial if they had: clinically significant (in the opinion of the investigator) active or chronic recurring infection, opportunistic infection, or immunodeficiency syndromes; intraocular pressure of >25 mmHg if they were receiving ≤1 glaucoma medication or intraocular pressure of >21 mmHg if they were receiving ≥2 glaucoma medications; evidence of glaucomatous optic nerve injury or glaucomatous field loss involving, encroaching upon, or having the potential to split fixation or cause visual acuity loss during the trial, regardless of intraocular

pressure or number of glaucoma medications. Full inclusion and exclusion criteria are listed in the supplementary material.

Eligible participants were enrolled and randomized in a 1:1 ratio to receive filgotinib 200 mg daily or placebo. Participants, site investigators, and all personnel directly involved in the conduct of the trial were masked to treatment assignment. Details of randomization and permitted concomitant medications are provided in the supplementary material. All participants received 60 mg/day of oral prednisone at day 1/baseline, followed by a mandatory protocol-defined taper requiring prednisone discontinuation by week 15 (**table s1**). Those who entered the trial while receiving topical ocular CS underwent a standardized taper schedule until discontinuation by week 9.

Procedures

Participants received filgotinib 200 mg (Rottendorf Pharma, Ennigerloh, Germany) or placebo, orally once daily for up to 52 weeks. Beginning at week 6, and at all subsequent visits, participants were examined for evidence of treatment failure (**table s2**). Participants were considered in treatment failure if they fulfilled at least 1 of the composite criteria in at least 1 eye. Those with evidence of treatment failure on or after week 6 discontinued the trial and were treated at the discretion of the investigator.

Participants were considered to have completed the trial if they completed the week 52 visit, or met the criteria for treatment failure, or discontinued for any other reason prior to week 52. Participants were considered to have completed treatment if they completed the protocol-specified study drug regimen. End of treatment (EOT) visits were conducted at week 52 for participants who completed the study or at the time of trial discontinuation for those with treatment failure. Early termination (ET) visits were conducted at the time of trial discontinuation for those who discontinued for any reason other than treatment failure before week 52. All participants were required to complete a follow-up visit 4 weeks after the last dose of study drug.

Outcomes

Definitions of efficacy endpoints are given in **table s2**. The primary objective was to evaluate the efficacy of filgotinib versus placebo for the treatment of active non-infectious uveitis, as measured by the proportion of participants with treatment failure by week 24.

A key secondary objective was to evaluate the efficacy of filgotinib in terms of time to treatment failure on or after week 6. Other secondary objectives were to evaluate changes from best state in VH grade, ACC grade, logarithm of the minimum angle of resolution (logMAR) best corrected visual acuity (BCVA), and central retinal thickness, as well as time to development of macular edema on or after week 6. Central retinal thickness was defined as the thickness of the retina in microns in the center of the foveal pit (1 mm subfield). Macular edema was determined by central reader evaluation of optical coherence tomography (OCT) images and defined as central retinal thickness >300 microns or >315 microns (as measured by Cirrus HD-OCT [Carl Zeiss Meditec] or Spectralis [Heidelberg Engineering] systems, respectively). Exploratory efficacy endpoints were to evaluate the efficacy of filgotinib on time to treatment failure that was due to: presence of a new active lesion, increased VH grade, increased ACC grade, and worsening of BCVA.

The safety and tolerability of filgotinib were assessed by comparing the incidence of AEs between treatment groups (coded according to MedDRA Version 24·0). The severity of AEs was graded and defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4·03.

Statistical Analyses

Sample size calculations were based on published data from the VISUAL I trial.[13] Assuming the observed proportion of participants with treatment failure by week 24 was 70% in the placebo group, 107 participants per treatment group would provide at least 85% power to detect a 20% reduction in the proportion of participants with treatment failure by week 24 in the filgotinib group using a two-sided significance level of 0·05. Given an expected attrition rate of 15%, a total of 248 participants would need to be randomized into the trial. By the time of study termination, 74 participants were enrolled; because this was fewer than planned, all hypothesis testing was exploratory, and all p values reported are nominal, two-sided and not adjusted for multiple analyses. All confidence intervals (CIs)

were calculated based on the nominal level of 95%. Two data monitoring committee safety data review meetings took place before early termination of the trial; no interim analyses of efficacy and futility had been performed at this point.

Efficacy endpoints were analyzed using the evaluable analysis set (all randomized participants who received at least 1 dose of study drug and did not permanently discontinue the trial before week 6). Safety endpoints were analyzed using the safety analysis set (all participants who received at least 1 dose of study drug).

Full details of statistical analyses are given in the supplementary material; in brief, the Cochran–Mantel–Haenszel approach, adjusting for the stratification factors, was used for the hypothesis testing of the primary endpoint, and the repeated measures analyses of covariance were used for continuous endpoints. A stratified log-rank test was used to compare time to treatment failure or development of macular edema on or after week 6 between treatment groups. Safety data were summarized using descriptive statistics. Statistical analyses were performed using SAS version 9·4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Flow and Baseline Characteristics

Between July 26, 2017 and April 22, 2021, 116 participants were screened. Of a planned 248 participants, 74 were enrolled and randomized to either filgotinib 200 mg (n=38) or placebo (n=36) (**figure 1**). On December 15, 2020, the trial was halted ahead of meeting its enrollment target, due to reasons related to a business decision to discontinue development efforts across all disease indications in the USA. Business reasons were unrelated to the efficacy or safety of filgotinib. Participants enrolled in the trial at time of termination were allowed to continue participation through all protocol-specified safety and efficacy evaluations.

In total, 72 participants (filgotinib, n=37; placebo, n=35) received at least 1 dose of study drug. Of these, 55 participants completed treatment (filgotinib, n=29; placebo, n=26) and 17 participants prematurely discontinued the study drug. The most common reasons for discontinuation were AEs

(filgotinib, n=2 [5·4%]; placebo, n=4 [11·4%]) and loss to follow-up (filgotinib, n=1 [2·7%]; placebo, n=2 [5·7%]).

Of the 72 participants treated, 66 participants (filgotinib, n=32; placebo, n=34) did not permanently discontinue the trial before week 6 and 59 participants completed the trial (filgotinib, n=30; placebo, n=29). Thirteen participants discontinued the trial; the most common reasons for premature discontinuation were AEs (filgotinib, n=1 [2·7%]; placebo, n=2 [5·7%]) and loss to follow-up (filgotinib, n=1 [2·7%]; placebo, n=2 [5·7%]). Each treatment group had 1 participant who discontinued the trial before administration of the study drug owing to protocol violations.

Baseline characteristics were generally similar across treatment groups (**table 1**). Most cases of uveitis were idiopathic in etiology, observed in (56·8% [n=21] filgotinib and 57·1% [n=20] placebo). At random, baseline immunosuppressant use was more frequent in participants treated with filgotinib than placebo (n=9 [24·3%] *vs* n=4 [11·4%], respectively). Other characteristics were similar between groups (**table 1**).

Efficacy

Primary Endpoint

A significantly lower proportion of participants who received filgotinib than placebo experienced treatment failure by week 24 (n=12/32 [37·5%] *vs* n=23/34 [67·6%]; treatment difference *vs* placebo −30·1%, 95% CI −56·2% to −4·1%; p=·006). This corresponded to an absolute risk reduction of 30·1% (95% CI 4·1% to 56·2%). Three participants (25·0%) who received filgotinib and 6 participants (26·1%) who received placebo had missing values for the primary efficacy endpoint (and were therefore considered as having treatment failure by week 24). A consistent result was obtained using a logistic regression analysis adjusted for stratification factors (odds ratio [OR] 0·234, 95% CI 0·079 to 0·689; p=·008).

Key Secondary Endpoints

In the time to event analysis, participants who received filgotinib were less likely to have treatment failure on or after week 6 compared with those who received placebo (stratified hazard ratio [HR]:

0·309, 95% CI 0·144 to 0·663; p=·003). The treatment failure Kaplan-Meier curve for the filgotinib group separated early from the placebo group, a change that persisted through the treatment period (**figure 2**). Median time to treatment failure was 22·0 weeks for the placebo group and was not calculable for the filgotinib group because fewer than 50% of participants (12 of 32) met treatment failure criteria by the time they completed the trial. The 25th percentile for time to treatment failure was 12·1 weeks for the placebo group and 24·1 weeks for the filgotinib group.

Reduced changes from best state to week 52/EOT/ET visits in ACC grade (per eye: filgotinib, n=32; placebo, n=34; treatment difference of LS mean −0·4, 95% CI −0·8 to −0·1; p=·01), BCVA (filgotinib, n=32; placebo, n=34; −0·05, 95% CI −0·10 to −0·00; p=·04) and central retinal thickness (filgotinib, n=32; placebo, n=32; −0·02, 95% CI −0·05 to −0·00; p=·03) were observed in participants who received filgotinib compared with placebo. There was no difference in change to VH grade between treatment groups (filgotinib, n=32; placebo, n=33; −0·1, 95% CI −0·4 to 0·2; p=·36). Best state and week 52/EOT/ET visit data are summarized in **table s3.** Of the treatment failure criteria, an increase in ACC grade was the main reason for treatment failure in the placebo group (n=13 [38·2%]) (**figure s2**). An increase in VH grade and a worsening of BCVA were the main reasons for treatment failure in the filgotinib group (n=5 [15·6%] each).

No difference was observed between treatment groups in time to the development of macular edema on or after week 6 (treatment difference *vs* placebo 6·8%, 95% CI −19·6% to 33·2%) (**figure s3**). A total of 21/32 participants (65·6%) who received filgotinib had macular edema on or after week 6, compared with 20/34 participants (58·8%) who received placebo (**table s4**). Most participants in the evaluable analysis set who had OCT evidence of macular edema at baseline (filgotinib, n=18; placebo, n=20) also had macular edema on or after week 6 (filgotinib, n=16/18 [88·9%]; placebo, n=19/20 [95·0%]).

Exploratory Endpoints

Time to treatment failure due to a new active lesion was improved in the filgotinib group compared with the placebo group (stratified HR: 0·313, 95% CI 0·093 to 1·050; p=·06) (**figure 3A**). Time to

treatment failure due to increased ACC grade was also improved (stratified HR: 0·195, 95% CI 0·055 to 0·691; p=·01) (**figure 3B**). No differences were observed between treatment groups in time to treatment failure due to increased VH grade (stratified HR: 0·418, 95% CI 0·109 to 1·611; p=·21) or worsening of BCVA (stratified HR: 0·334, 95% CI 0·079 to 1·421; p=·14) (**figure 3C and 3D**).

Safety

Mean (standard deviation [SD]) durations of exposure to filgotinib and placebo were 34·0 (19·61) weeks and 22·6 (16·06) weeks, respectively. AEs were reported in 30 participants (81·1%) who received filgotinib and 24 participants (68·6%) who received placebo (**table s5**). There were 369·1 and 361·8 AEs per 100 participant-years in the filgotinib and placebo group, respectively.

The majority of AEs were mild or moderate in severity (**table s5**). AEs reported in ≥10% participants in the filgotinib group were visual impairment (n=5 [13·5%]) and insomnia, urinary tract infection, nausea, and abdominal pain (n=4 [10·8%] each), and in the placebo group were headache (n=7 [20·0%]), and insomnia, urinary tract infection, and dry eye (n=4 [11·4%] each).

Study drug-related AEs (as determined by the investigator) were reported in 15 participants (40·5%) who received filgotinib and 6 participants (17·5%) who received placebo. Twelve participants experienced uveitis-related AEs in each treatment group (filgotinib, 32·4%; placebo, 34·3%). The proportion of participants with grade 3 or higher (severe) AEs is detailed in **table s5**.

Serious AEs (SAEs) were reported in 5 (13·5%) participants in the filgotinib group and 2 (5·7%) participants in the placebo group (**table 2**). There were 19·2 SAEs per 100 participant-years in the filgotinib group and 11·2 in the placebo group. Two participants in the filgotinib group each experienced two SAEs (spinal stenosis and suicidal ideation; epilepsy and IBD). Of these, only the SAE of IBD was considered related to the study drug. Other treatment-related SAEs reported in the filgotinib group were COVID-19 and uveitis (n=1 [2·7%] each), while 1 participant (2·9%) who was receiving placebo experienced a treatment-related SAE of urinary tract infection. All other reported SAEs occurred in up to 1 participant in each treatment group.

AEs of interest included infections, serious infections, herpes zoster infection, opportunistic infection, gastrointestinal (GI) perforation, thromboembolism, and malignancy. The proportion of participants with infections was 32·4% in the filgotinib group and 25·7% in the placebo group (**table s5**). The most common infection was urinary tract infection, which was reported in 4 participants in each treatment group (filgotinib, 10·8%; placebo, 11·4%). Serious infections were reported in 1 participant in each treatment group (filgotinib, 2·7%; placebo, 2·9%). No arterial or venous thromboembolic events, major adverse cardiovascular events (MACEs), GI perforations, nonmelanoma skin cancers, opportunistic infections, cases of tuberculosis, or cases of herpes zoster were reported in either treatment group. No deaths were reported during the trial.

Discussion

We report a randomized, controlled trial to investigate a JAK inhibitor in the treatment of active non-infectious intermediate, posterior, or pan-uveitis. Owing to early termination of this trial (due to business reasons, unrelated to the efficacy or safety of filgotinib), only 74 participants were randomized (29·8% of the planned enrollment). Despite this, a significantly lower proportion of participants treated with filgotinib experienced treatment failure compared with placebo (demonstrated by the primary efficacy endpoint of treatment failure at week 24). Filgotinib also lowered the risk of treatment failure and loss of visual acuity compared with placebo, suggesting potential efficacy of filgotinib in this indication. The premature termination of the trial prevented collection of additional safety or efficacy information of this JAK1 preferential inhibitor in this disease state.

Participants who received filgotinib had a reduced probability of treatment failure on or after week 6, as well as significantly reduced mean changes in ACC grade and BCVA compared with placebo, findings that are in line with those in participants with active non-infectious intermediate, posterior, or pan-uveitis who received adalimumab in the phase 3 VISUAL I trial.[13] VH grade was unchanged between treatment groups and there was no functional difference in visual acuity on or after week 6 in participants who received filgotinib compared with placebo (the endpoint that most patients would value). Deterioration in VH grade and BCVA were the main reasons for treatment failure on or after

week 6 in those who received filgotinib (31·2% of participants). In comparison, in the VISUAL I trial, 36% of participants in the adalimumab-treated population experienced treatment failure due to the same disease progression parameters, though these were reported over a maximum duration of 80 weeks.[13]

While the HUMBOLDT trial provided evidence supporting the efficacy of filgotinib in patients with active non-infectious uveitis, the premature termination of the trial prevented collection of additional safety or efficacy information on this JAK1 preferential inhibitor in this disease state. Nevertheless, there were no new safety concerns identified in the immunosuppressed uveitis population in this trial. When adjusted for participant-years of exposure, there was only a slightly higher incidence of AEs in the filgotinib group versus the placebo group in our trial, though this is consistent with the profile of other systemic immune modifying therapies versus their respective placebo groups.[14] Most AEs were either mild or moderate (grade 1 or 2) in severity, consistent with findings from the phase 2b/3 SELECTION trial in patients with moderately to severely active UC, as well as the phase 2b/3 DARWIN 1, DARWIN 2, FINCH 1, and FINCH 2 trials in patients with RA.[18-23] The incidences of uveitis-related AEs, AEs and SAEs were similar in the filgotinib group and placebo group. The incidence of serious infections was low across treatment groups, similar to findings reported in several previous phase 2b/3 trials of filgotinib in RA (DARWIN 1, DARWIN 2, and FINCH 1-3) and UC (SELECTION).[18-24]

Together these data suggest that the safety profile of filgotinib in uveitis is akin to that seen in other inflammatory conditions. Participants who received filgotinib in HUMBOLDT did not experience any AEs of special interest typically reported for JAK inhibitors (e.g., thromboembolism, MACEs, malignancies, and GI perforations),[18,22,25] though this could be due to the small sample size. Alternatively, it could be hypothesized that individuals with uveitis are less susceptible to these events owing to the pathophysiology of the condition, or the specific characteristics of this trial's population.

It is feasible that the observed activity of filgotinib in this trial occurred by dampening of intraocular inflammation associated with uveitis,[5] via inhibition of the JAK-STAT inflammatory pathway.[26] While filgotinib is a JAK1 preferential inhibitor, it is unclear which downstream cytokines might have

been impacted. Future studies could evaluate the underlying mechanism of action of filgotinib in uveitis.[7] The findings of these studies could also have implications for patients with other diseases that are complicated by uveitis, such as sarcoidosis, IBD, RA, and ankylosis spondylitis.[6] The main limitation of this trial was its termination ahead of meeting its prespecified enrollment target. It is also unclear whether filgotinib could offer significant anti-inflammatory control as a monotherapy during an active flare period owing to the protocol-defined prednisone taper, although this is a minor point considering that clinicians typically regard corticosteroids as a bridge to biologics. On the other hand, the potential advantages of a nonsteroidal oral therapy for uveitis control should be considered.

Conclusions

In conclusion, filgotinib lowered the risk of treatment failure upon CS withdrawal in participants with active non-infectious intermediate, posterior, or pan-uveitis versus placebo. On average, the regression in ACC grade, BCVA, and central retinal thickness was reduced in the filgotinib group compared with the placebo group, while there was no difference in VH grade between groups. No functional difference in visual acuity was observed on or after week 6 in participants who received filgotinib compared with placebo (the endpoint that most patients would value). Treatment with filgotinib was generally well tolerated, with no new safety concerns identified in the immunosuppressed uveitis population treated with filgotinib, compared with other previously studied populations.[18-24] Overall, results of this trial indicate that filgotinib could be efficacious in individuals with active non-infectious intermediate, posterior, or pan-uveitis, and may warrant further investigation.

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Role of the funder/sponsor

Gilead Sciences, Inc. was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of Interests

Sunil K Srivastava has received research grants from Regeneron, Eyepoint, Allergan, Gilead and has received consultancy fees from Adverum, Aura, Bausch, Gilead, jCyte, Novartis, Optos, Regeneron, and Zeiss.

Timothy R Watkins is an employee and shareholder of Gilead Sciences, Inc.

Quan Dong Nguyen serves on the Scientific Advisory Board for Genentech, Kriya, Novartis, Regeneron, and Santen, among others. He serves on the Data Safety and Monitoring Board for Alvotech, and Bellus Health.

Sumit Sharma is a consultant for AbbVie, Bausch and Lomb, Clearside, EyePoint, Regeneron, Regenxbio, and Roche/Genentech, and provides research support to institutions from Genentech/Roche, Gilead, Ionis, and Santen.

David K Scales has no disclosures.

Mark S Dacey is a consultant, member of the speaker’s bureau and has participated in advisory boards for Allergan, AbbVie, Bausch & Lomb, and EyePoint.

Rajiv E Shah has been a speaker for Allergan, Bausch and Lomb, Horizon Mallincrockdt, and Regeneron; has received consultancy fees from Kriya; and has received research grants from Bayer, Genentech, Gilead, Immnovant, Ophthea, Priovant, Sling Therapeutics, and Tarsier.

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Mark C Genovese was an employee and shareholder of Gilead Sciences, Inc at the time of trial conduct and read-out.

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Robin Besuyen was an employee and shareholder of Galapagos and a partner of Gilead in the development of filgotinib at the time of trial conduct and read-out.

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James T Rosenbaum is employed by Corvus Pharmaceuticals. He has received consulting fees from AbbVie, Affibody, Gilead, Horizon, Novartis, Revolo, Roivant, Santen, and UCB. He has received research funding from Horizon and Pfizer. He serves on a Data Monitoring Committee for Celgene-Bristol Myers and on an Outcome Resolution Committee for Lilly. He receives royalties from UpToDate.

Access to data and data analysis

William T Barchuk and Ying Guo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Anonymized individual patient data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and its intended use. The full data sharing policy for Gilead Sciences, Inc., can be found at https://www.gilead.com/about/ethics-and-code-of-conduct/policies.

Author Contributions

Sunil K Srivastava, Quan Dong Nguyen, Sumit Sharma, David K Scales, Mark S Dacey, Rajiv E Shah, David S Chu, Dilraj S Grewal, Lisa J Faia, Eric B Suhler, Andrew D Dick and James T Rosenbaum contributed to data collection.

All authors contributed to data interpretation.

All authors contributed to development of the manuscript and all authors approved the final version.

All authors agree to be accountable for all aspects of the work.

All authors had final responsibility for the decision to submit for publication.

Non-author contributions

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Figures and Tables

Figure 1: Participant disposition (CONSORT flow diagram)

*Participants were randomized but discontinued the trial before administration of the study drug owing to protocol violations.

†Safety analysis set included participants who received at least one dose of study drug.

‡Evaluable analysis set included all participants who received at least one dose of study drug and did not permanently discontinue the trial before week 6.

§Trial completion was defined as the participant completing the week 52 visit or having met the criteria for treatment failure.

Figure 2: Probability of Treatment Failure on or After Week 6[a]

[a]Treatment failures on or after week 6 were counted as events (+); participants who were not observed to have treatment failure by the time of trial completion or by the time of discontinuation from the trial were censored at the date of their last available assessment.

Figure 3: Probability of Treatment Failure Due to (A) Presence of a New Active Lesion, (B) Increased ACC Grade, (C) VH Grade, and (D) BCVA

ACC=anterior chamber cell. BCVA=best corrected visual acuity. VH=vitreous haze.

Treatment failures on or after week 6 were counted as events (+); participants who were not observed to have treatment failure by the time of trial completion or by the time of discontinuation from the trial were censored at the date of their last available assessment.

Table 1: Baseline Characteristics of Participants

	Filgotinib 200 mg (n=37)	**Placebo (n=35)**
Age (years), mean (SD)	48 (15·1)	43 (15·7)
Sex at birth, n (%)		
Male	14 (37·8)	15 (42·9)
Female	23 (62·2)	20 (57·1)
Etiology of uveitis, n (%)		
Birdshot chorioretinopathy	5 (13·5)	5 (14·3)
Idiopathic	21 (56·8)	20 (57·1)
Multifocal choroiditis and pan-uveitis	0 (0·0)	1 (2·9)
Rheumatoid arthritis	2 (5·4)	0 (0·0)
Sarcoidosis	5 (13·5)	5 (14·3)
Spondyloarthritis	1 (2·7)	0 (0·0)
Tubulointerstitial nephritis and uveitis syndrome	0 (0·0)	1 (2·9)
Vogt-Koyanagi-Harada disease	1 (2·7)	3 (8·6)
Other	2 (5·4)	0 (0·0)
Anatomic type of uveitis, n (%)		
Intermediate	5 (13·5)	5 (14·3)
Intermediate and Posterior	3 (8·1)	0 (0·0)
Posterior	7 (18·9)	9 (25·7)
Pan-uveitis	22 (59·5)	21 (60·0)
Eye affected by uveitis flare, n (%)		
Left	3 (8·1)	4 (11·4)
Right	4 (10·8)	3 (8·6)
Both	30 (81·1)	28 (80·0)
Duration of uveitis from first symptoms, months		
n	35	35
Mean (SD)	48·6 (60·1)	59·5 (74·0)
Time since last uveitis flare at baseline, months		
n	26	27
Mean (SD)	12·9 (22·5)	24·5 (50·3)
Number of uveitis flares in the past 12 months		
n	37	35
Mean (SD)	2 (2·0)	2 (0·8)

Uveitis attributed to sarcoidosis, n (%)	5 (13·5)	5 (14·3)
Baseline immunosuppressant use, n (%)	9 (24·3)	4 (11·4)
Prior immunosuppressant use during screening, n (%)		
Azathioprine	7 (18·9)	3 (8·6)
Methotrexate	2 (5·4)	1 (2·9)
Prior use of anti-TNF therapy, n (%)	2 (5·4)	1 (2·9)
OCT evidence of macular edema, n (%)	**21 (56·8)**	**20 (57·1)**

OCT=optical coherence tomography. SD=standard deviation. TNF=tumor necrosis factor.

Denominator for percentages was the number of patients in the safety analysis set. Safety analysis set included patients who received at least 1 dose of study drug.

Table 2: Summary of Serious AEs

	Filgotinib 200 mg (n=37)	**Placebo (n=35)**
Participants with any SAE, n (%)*	5 (13·5)	2 (5·7)
Bladder prolapse	1 (2·7)	0 (0·0)
COVID-19	1 (2·7)	0 (0·0)
Epilepsy	1 (2·7)	0 (0·0)
Inflammatory bowel disease	1 (2·7)	0 (0·0)
Spinal stenosis	1 (2·7)	0 (0·0)
Suicidal ideation	1 (2·7)	0 (0·0)
Uveitis	1 (2·7)	0 (0·0)
Retinal vasculitis	0 (0·0)	1 (2·9)
Urinary tract infection	0 (0·0)	1 (2·9)

AE=adverse event. SAE=serious adverse event.

*SAEs began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation. Multiple AEs were counted only once per participant for each term and AEs were presented by descending order of the total frequencies for filgotinib participants.

Efficacy and Safety of Filgotinib in Active Non-Infectious Uveitis: Results From HUMBOLDT, a Randomized, Double-Masked, Phase 2 Trial

Srivastava SK et al.

Contents

Supplementary Material M1: HUMBOLDT trial inclusion and exclusion criteria

Inclusion criteria

Participants must have met all of the following inclusion criteria to be eligible for participation in this trial.

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 participants of childbearing potential
3) Male participants and female participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception
4) Lactating females must agree to discontinue nursing before the study drug is administered
5) Male or female participants who are ≥18 years of age on the day of signing informed consent
6) Diagnosed with active non-infectious intermediate uveitis, posterior uveitis, or pan-uveitis
7) Active uveitic disease at the day 1/baseline visit as defined by the presence of at least one 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 (CS) equivalent:
    a. Active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion
    b. ≥2+ anterior chamber cells (ACC) (Standardization of Uveitis Nomenclature [SUN] criteria)
    c. ≥2+ vitreous haze (VH) (National Eye Institute/SUN criteria)
8) Receiving oral prednisone ≥10 mg/day to ≤60 mg/day (or oral CS equivalent) for two or more weeks immediately before and including day 1/baseline
9) Documented prior adequate response to oral CS (equivalent of oral prednisone up to 1 mg/kg/day)
10) Participants must meet one of the following three tuberculosis (TB) screening criteria:
    a. No evidence of active or latent TB:
        i. A negative QuantiFERON®-TB Gold In-Tube test at screening, or evidence of negative result within the 3 months before screening
        ii. A chest radiograph (views as per local guidelines) taken at screening or within the 3 months before screening (with the report or films available for investigator review) without evidence of active or latent TB infection
        iii. No history of either untreated or inadequately treated latent TB infection
    b. Previously treated for TB:
        i. A participant 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
        ii. A chest radiograph must be obtained, if not done within 3 months before screening (with the report or films available for investigator review)
        iii. 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:
        i. A participant 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 before the first administration of study drug
        ii. 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 before enrollment in the trial. No participant with currently active TB or untreated latent TB may be enrolled in the trial.

    Participants with an indeterminate QuantiFERON-TB Gold test result may undergo a repeat test. Participants with a repeat indeterminate test result (two indeterminate results in total) are, in this trial, 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 participant’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. Written consent must be provided before initiating any screening

evaluations. Participants must have read and understood the informed consent form (ICF), must fully understand the requirements of the trial, and must be willing to comply with all trial visits and assessments. Participants who cannot understand the ICF may not be enrolled by a guardian or any other individual

Exclusion criteria

Participants who met any of the following exclusion criteria were not enrolled in this trial.

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 CS (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, Whipple's disease, Herpes Zoster virus, Lyme disease, toxoplasmosis, and herpes simplex virus
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 visualisation of the fundus or that likely requires cataract surgery during the duration of the trial
9) Participant with elevated intraocular pressures and/or severe glaucoma who is unable to meet the following criteria within the screening period:
    a. Intraocular pressure of <25 mmHg (in at least two consecutive measurements) in the absence of therapy or if receiving a single glaucoma medication
    b. Intraocular pressure of <21 mmHg (in at least two consecutive measurements) if receiving two or more glaucoma medications
    c. Participant 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
    d. Participant 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 trial, regardless of intraocular pressure or number of glaucoma medications
10) Exposure to a systemic carbonic anhydrase inhibitor within 1 week before screening
11) Best corrected visual acuity (BCVA) fewer 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 (either eye can satisfy active uveitis criteria for eligibility and either eye may meet treatment failure criteria)
14) Exposure to anti-tumor necrosis factor therapy or any biologic therapy within 4 weeks of day 1/baseline
15) Received intravitreal anti-vascular endothelial growth factor (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 one accepted immunosuppressive therapy (not counting CS) at day 1/baseline
17) Using concomitant immunosuppressive therapy at day 1/baseline other than methotrexate or azathioprine
18) If entering the trial on one concomitant immunosuppressive therapy, dose has been increased within 28 days before day 1/baseline visit or is not within the following allowable doses:
    a. Methotrexate ≤25 mg per week
    b. Azathioprine ≤175 mg per day
19) Systemic inflammatory disease requiring continued therapy with oral CS or a prohibited immunosuppressive agent at screening or day 1/baseline
20) Received Retisert® (glucocorticosteroid implant) within 3 years before the day 1/baseline visit or has had complications related to the device
21) Received intraocular or periocular CS in the 30 days before 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 (ie, vitreomacular traction, epiretinal membranes) with the potential for macular structural damage independent of the inflammatory process
25) Presence of severe VH that precludes visualisation of the fundus at the day 1/baseline visit
26) Received Ozurdex® (dexamethasone implant) within 3 months before the day 1/baseline visit
27) Received intravitreal methotrexate within 90 days before the day 1/baseline visit
28) Use of cyclophosphamide within 30 days before the day 1/baseline visit
29) Evidence of any clinically significant (as per the judgment 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 before 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 aluminum garnet posterior capsulotomy. These three 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 hospitalisation 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
38) Evidence of active hepatitis C virus (HCV) infection. Participants with positive HCV antibody (Ab) at screening, require reflex testing for HCV RNA. Participants with positive HCV RNA at screening will be excluded. Participants with positive HCV Ab, but negative HCV RNA are eligible per investigator judgment. Participants with active HCV during the trial, as evidenced by HCV RNA positivity will be discontinued from study drug as outlined in the protocol
39) Evidence of active hepatitis B virus (HBV) infection. Participants with positive Hepatitis B surface antigen (HBsAg) at screening are excluded from the trial. Participants with positive HBV core Ab and negative HBsAg, require reflex testing for HBV DNA. Participants with positive HBV DNA at screening will be excluded. Participants 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. Participants with evidence of active Hepatitis B during the trial, 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 immunoglobulin G)
41) History of malignancy within the last 5 years before 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 before screening
46) Use of any prohibited concomitant medications
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 participant at increased risk during trial 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 trial 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, 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 participant unlikely or unable to complete the trial or comply with trial procedures and requirements
55) Participation in any clinical trial of an investigational drug/device within 4 weeks or 5 half-lives (whichever is longer) of the drug before 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 participant 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 109^9cells/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 or aspartate aminotransferase ≥1·5 x upper limit of normal (ULN)
    g. Total bilirubin level ≥2 x ULN unless the participant 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[1]

Supplementary Material M2: HUMBOLDT trial design details

Concomitant medications

Concomitant medications permitted during the trial included inhaled (nasal or oral) CS and therapies for chronic medical conditions (e.g., well-controlled diabetes or hypertension). Either one of the immunosuppressants methotrexate (≤25 mg per week) or azathioprine (≤175 mg per day) were permitted, as long as the dose had not increased in the 28 days before day 1/baseline. Mycophenolate mofetil and cyclophosphamide were not permitted, as they had not been previously trialed in combination with filgotinib.

Randomisation and masking

Randomisation was achieved via an interactive web response system using a stratified randomisation schedule, with stratification based on uveitis attributed to sarcoidosis, baseline use of any immunosuppressant, and prior use of anti-tumor necrosis factor (TNF) therapy. Participants, site investigators, and all personnel directly involved in the conduct of the trial were masked to treatment assignment. Masking was maintained using study drugs that were identical in appearance.

Statistical analyses

For the primary efficacy endpoint, a superiority test was used to compare treatment groups based on the proportion of participants with treatment failure by week 24. The Cochran–Mantel–Haenszel approach, adjusting for the stratification factors, was used for the hypothesis testing of the primary endpoint. A non-responder imputation method was used, such that participants with missing values were considered as having treatment failure. The non-stratified point estimate for treatment differences along with its 95% confidence interval (CI) were provided, based on the normal approximation with a continuity correction. A logistic regression analysis was used to assess the odds ratio (OR) between treatment groups, adjusting for stratification factors. The point estimate of OR, as well as the corresponding 95% CI and p value, were presented.

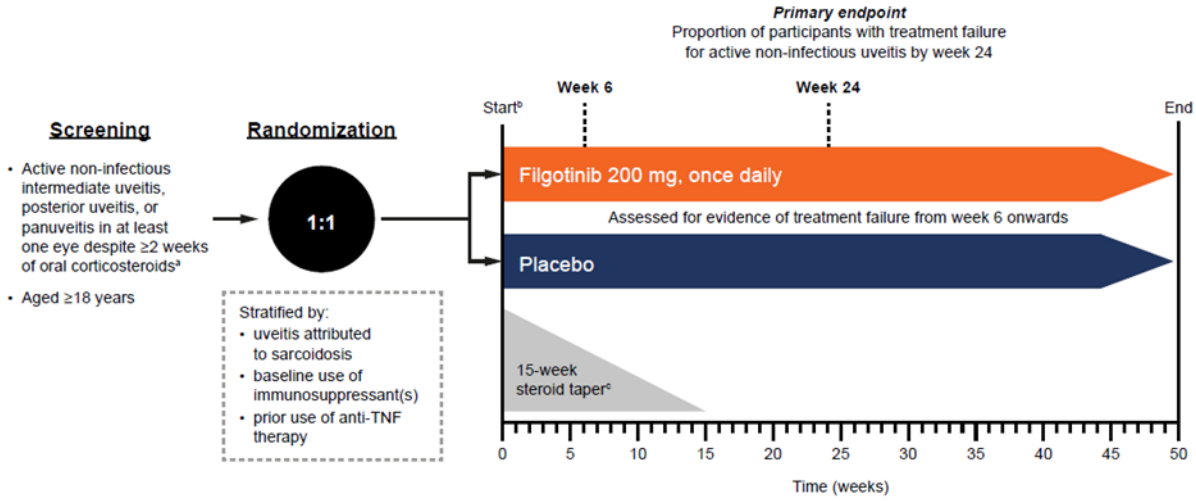
A stratified log-rank test was used to compare time to treatment failure on or after week 6, and time to development of macular edema on or after week 6, between treatment groups. A proportional hazards model with the trial group as a factor and stratification factors as covariates was fitted to estimate the hazard ratio (HR) and its 95% CI. Treatment failures on or after week 6 were counted as events; participants who completed the trial and did not have any events, or who permanently discontinued the trial owing to reasons other than treatment failure at any time, were censored. Participants not observed to have the specified events by trial completion or by the time of discontinuation from the trial were censored at the date of their last available assessment.

For the continuous endpoints (i.e., changes in VH grade, ACC grade, logarithm of the minimum angle of resolution [logMAR] BCVA, and logarithm change in central retinal thickness from best state before week 6 to week 52/end of treatment [EOT] or early termination [ET] visit), a repeated

measures analysis of covariance (ANCOVA) was used to control for the clustered observations, with treatment (ie, observations from each of the participant's eyes), participant's eyes, interaction of treatment and participant's eyes, stratification factors, and best state values as covariates. For the logarithm change in central retinal thickness, the analysis was additionally adjusted for the type of optical coherence tomography (OCT) system used. The treatment difference of least squares (LS) mean and 95% CI between filgotinib and placebo in change from best state before week 6 at week 52/EOT or ET visit and the corresponding p value from the ANCOVA model were provided.

The following were analyzed using data from each eye individually: change in ACC grade from best state achieved before week 6 to week 52/EOT or ET visit, change in VH grade from best state achieved before week 6 to week 52/EOT or ET, change in logMAR BCVA from best state achieved before week 6 to week 52/EOT or ET, and log change in central retinal thickness from best state achieved before week 6 to week 52/EOT or ET visit. The best state for the VH grade and ACC grade was defined as the minimum grade before week 6. The best state for BCVA was defined as the maximum score before week 6. The best state for central retinal thickness was the minimum value before week 6.

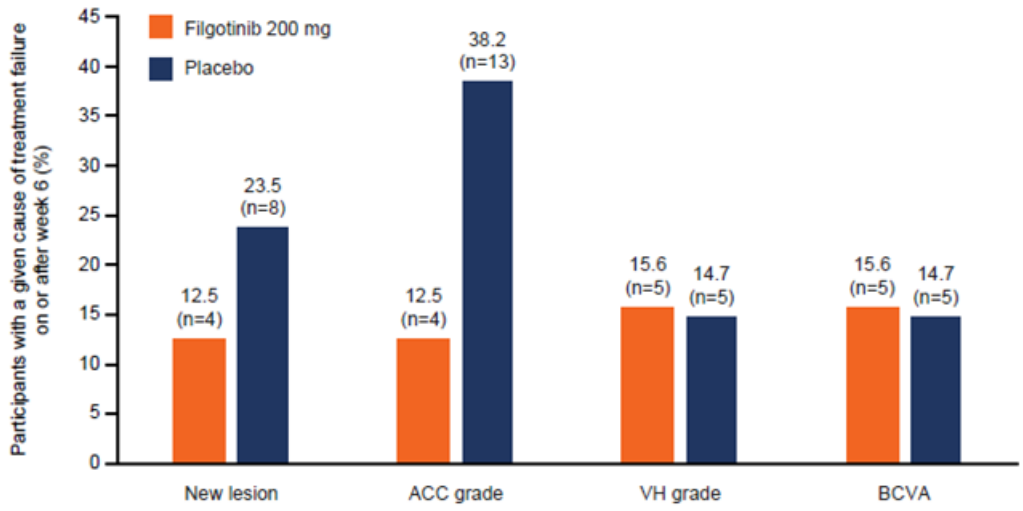
Figure s1: Trial design



CS=corticosteroids; TNF=tumor necrosis factor.

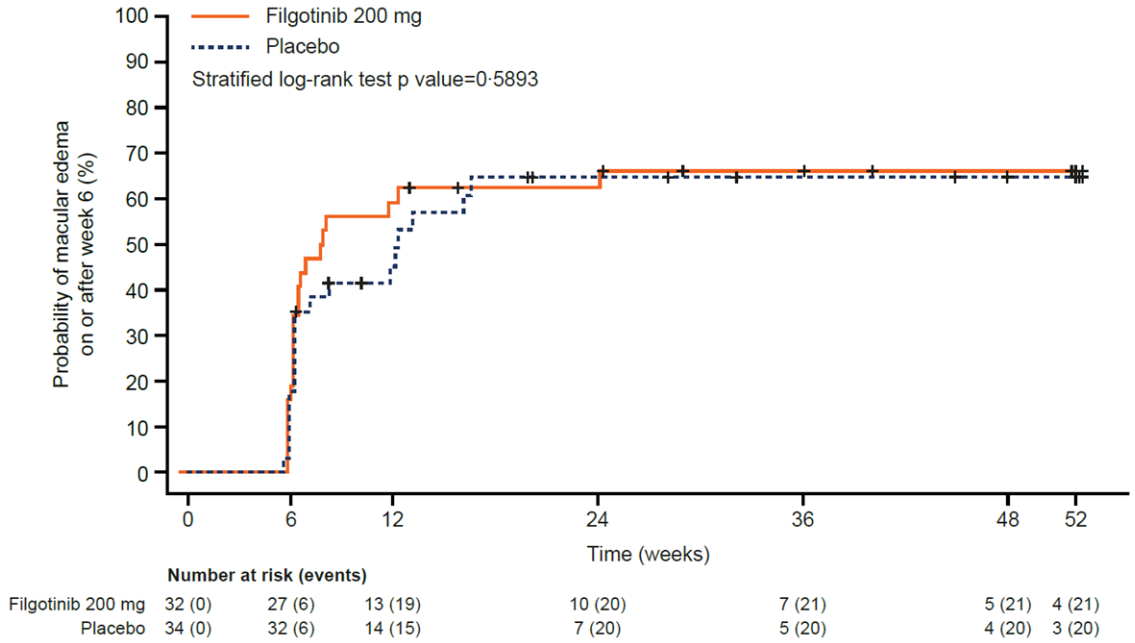
[a]Maintenance therapy with oral prednisone at a dose of ≥10 mg/day to ≤60 mg/day or oral CS equivalent.
[b]Participants were given 60 mg/day oral prednisone at day 1 followed by a mandatory taper, with all participants who continued in the trial having discontinued no later than week 15.
[c]Participants who entered the trial on topical ocular CS underwent a taper schedule until discontinuation no later than week 9.

Figure s2: Reasons for treatment failure on or after week 6*



*Treatment failures were considered on or after week 6 and up to week 48; participants who were not observed to have treatment failure by the time of trial completion or by the time of discontinuation from the trial were censored at the date of their last available assessment.

Figure s3: Probability of macular edema[*] development on or after week 6



OCT=optical coherence tomography.
[a]Macular edema was determined by central reader evaluation of OCT images and defined as central retinal thickness >300 microns or >315 microns (as measured by Cirrus HD-OCT [Carl Zeiss Meditec] or Spectralis [Heidelberg Engineering] systems, respectively).

Table s1: HUMBOLDT trial prednisone taper schedule

Trial 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

Table s2: Efficacy endpoint definitions

Criteria	Definition of treatment failure*	
	Week 6 visit	**All visits after week 6**
Inflammatory chorioretinal and/or inflammatory retinal vascular lesions†	New active, inflammatory lesions relative to baseline (day 1)	New active, inflammatory lesions relative to baseline (day 1)
ACC grade (SUN criteria)‡	Inability to achieve ≤grade 0·5+	Two-step increase relative to best state achieved§
VH grade (NEI/SUN criteria)†	Inability to achieve ≤grade 0·5+	Two-step increase relative to best state achieved§
Visual acuity ETDRS¶	Worsening of BCVA by ≥15 letters relative to best state achieved	Worsening of BCVA by ≥15 letters relative to best state achieved

ACC=anterior chamber cell. BCVA=best corrected visual acuity. ETDRS=Early Treatment Diabetic Retinopathy Study. logMAR=logarithm of the minimum angle of resolution. NEI=National Eye Institute. SUN=Standardization of Uveitis Nomenclature. VH=vitreous haze.

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

†Evaluated by dilated indirect ophthalmoscopy. VH grades are 0, 0.5+, 1+, 2+, 3+ and 4+, with higher scores indicating increased severity of uveitis.

‡Evaluated by slit lamp examination. ACC grades are 0, 0.5+, 1+, 2+, 3+ and 4+, with higher scores indicating more cells visible in the 1 mm x 1 mm slit beam (anterior chamber) and increased severity of uveitis.

§A two-step increase is represented by a change of grade 0 to grade 2+ or by grade 0·5+ to grade 3+.

¶Evaluated using ETDRS chart. BCVA data were expressed as logMAR units.

Table s3: Summary of best state and week 52/EOT/ET data for ACC grade, VH grade, logMAR BCVA and central retinal thickness

	Filgotinib 200 mg (n=32)		Placebo (n=34)	
	Left eye	**Right eye**	**Left eye**	**Right eye**
ACC grade				
Best state, n	32	32	34	34
Mean (SD)	0·0 (0·1)	0·0 (0·1)	0·1 (0·2)	0·1 (0·3)
Week 52/EOT/ET, n	32	32	34	34
Mean (SD)	0·2 (0·6)	0·2 (0·5)	0·7 (0·9)	0·8 (1·1)
VH grade				
Best state, n	32	32	33	34
Mean (SD)	0·3 (0·4)	0·3 (0·4)	0·2 (0·3)	0·3 (0·5)
Week 52/EOT/ET, n	32	32	33	33
Mean (SD)	0·5 (0·8)	0·3 (0·7)	0·5 (0·7)	0·5 (0·7)
logMAR BCVA				
Best state, n	32	32	34	34
Mean (SD)	0·1 (0·2)	0·1 (0·2)	0·1 (0·2)	0·1 (0·3)
Week 52/EOT/ET, n	32	32	34	34
Mean (SD)	0·1 (0·2)	0·1 (0·2)	0·1 (0·3)	0·2 (0·4)
Central retinal thickness (logarithm scale)*				
Best state, n	32	32	34	34
Mean (SD)	2·5 (0·1)	2·5 (0·1)	2·5 (0·1)	2·4 (0·1)
Week 52/EOT/ET, n	32	32	32	32
Mean (SD)	2·5 (0·1)	2·5 (0·1)	2·5 (0·1)	2·5 (0·1)

ACC=anterior chamber cell. ANCOVA=repeated measures analysis of covariance. BCVA=best corrected visual acuity. EOT=end of treatment. ET=early termination. logMAR=logarithm of the minimum angle of resolution. OCT= optical coherence tomography. SD=standard deviation. VH=vitreous haze.

296 *A repeated measure ANCOVA model was used to control for the clustered observations, with treatment (i.e., observations
297 from each of the participant's eyes), participant's eyes, interaction of treatment and participant's eyes, stratification factors,
298 and best state values as covariates.

Table s4: Participants with macular edema[*] on or after week 6

	Filgotinib 200 mg (n=32)	**Placebo (n=34)**
Participants with macular edema on or after week 6, n (%)	21 (65·6)	20 (58·8)
KM estimate of median time to macular edema (weeks)[†]	7·8	12·3
Difference in rate of macular edema versus placebo, % (95% CI)	6·8 (−19·6 to 33·2)	

CI, confidence interval. KM=Kaplan–Meier. OCT=optical coherence tomography.
[*]Macular edema was determined by central reader evaluation of OCT images and defined as central retinal thickness >300 microns or >315 microns (as measured by Cirrus HD-OCT [Carl Zeiss Meditec] or Spectralis [Heidelberg Engineering] systems, respectively).
[†]Time to macular edema was the time from first dosing date to the first occurrence of macular edema. Participants who discontinued from the trial or completed the trial without macular edema were censored on the date of the last assessment visit.

309 ***Table s5: Summary of AEs***

	Filgotinib 200 mg (n=37)	**Placebo (n=35)**
Participants with any AE, n (%)	30 (81·1)	24 (68·6)
AE	30 (81·1)	24 (68·6)
AE of grade 2 or higher	21 (56·8)	15 (42·9)
AE of grade 3 or higher	6 (16·2)	1 (2·9)
AE related to study drug	15 (40·5)	6 (17·1)
Uveitis-related AE	12 (32·4)	12 (34·3)
Infection	12 (32·4)	9 (25·7)
Serious AE	5 (13·5)	2 (5·7)
Serious AE related to study drug	3 (8·1)	1 (2·9)
Serious infection	1 (2·7)	1 (2·9)
AE leading to death	0 (0·0)	0 (0·0)
AEs in ≥10% participants, n (%)*		
Visual impairment	5 (13·5)	1 (2·9)
Insomnia	4 (10·8)	4 (11·4)
Urinary tract infection	4 (10·8)	4 (11·4)
Nausea	4 (10·8)	1 (2·9)
Abdominal pain	4 (10·8)	0 (0·0)
Headache	3 (8·1)	7 (20·0)
Dry eye	2 (5·4)	4 (11·4)
Uveitis-related AEs, n (%)*		
Uveitis	3 (8·1)	0 (0·0)
Chorioretinal disorder	2 (5·4)	2 (5·7)
Intraocular pressure increased	2 (5·4)	2 (5·7)

Macular edema	2 (5·4)	1 (2·9)
Vitreous haze	2 (5·4)	0 (0·0)
Anterior chamber cell	1 (2·7)	1 (2·9)
Anterior chamber inflammation	1 (2·7)	2 (5·7)
Eye irritation	1 (2·7)	0 (0·0)
Eye pain	1 (2·7)	0 (0·0)
Ocular discomfort	1 (2·7)	0 (0·0)
Visual impairment	1 (2·7)	0 (0·0)
Cataract	0 (0·0)	1 (2·9)
Cataract subcapsular	0 (0·0)	1 (2·9)
Cystoid macular edema	0 (0·0)	1 (2·9)
Dry eye	0 (0·0)	1 (2·9)
Halo vision	0 (0·0)	1 (2·9)
Iris bombe	0 (0·0)	1 (2·9)
Keratic precipitates	0 (0·0)	1 (2·9)
Keratitis interstitial	0 (0·0)	1 (2·9)
Persistent pupillary membrane	0 (0·0)	1 (2·9)
Retinal vascular disorder	0 (0·0)	1 (2·9)
Retinal vasculitis	0 (0·0)	1 (2·9)
Vision blurred	0 (0·0)	1 (2·9)
Visual acuity reduced	0 (0·0)	1 (2·9)

AE=adverse event. CTCAE=Common Terminology Criteria for Adverse Events.

*Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation. Multiple AEs were counted only once per participant for each term and terms were presented by descending order of the total frequencies for filgotinib participants.

Severity grades were defined by CTCAE Version 4·03. Death included any death that occurred during the trial.

References

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**:31–41.