Combined Phase 2b/3, Double-blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects with Moderately to Severely Active Ulcerative Colitis

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The overall objective of the study is to evaluate the effect of treatment with filgotinib on the induction and maintenance of remission in subjects with moderately to severely active Ulcerative Colitis (UC). Subjects who are biologic-naïve and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON47588

Source
ToetsingOnline

Brief title
GS-US-418-3898

Condition

- Gastrointestinal inflammatory conditions

Synonym
ulceration of the colon, Ulcerative Collitis

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences Inc.

Intervention

Keyword: Filgotinib, Ulcerative Collitis

Outcome measures

Primary outcome

Primary efficacy will be assessed by EBS remission, defined as an endoscopic subscore (based on central reading) of 0 or 1 (referencing the Mayo Score), rectal bleeding subscore of 0, and at least a 1 point decrease in stool frequency from baseline to achieve a subscore of 0 or 1.

Secondary outcome

Efficacy will also be assessed using the full MCS composed of 4 subscores (stool frequency, rectal bleeding, endoscopic findings, and PGA), ranging from 0 to 12. Assessments during non-endoscopic visits may use the partial MCS, which includes all components except flexible sigmoidoscopy/colonoscopy.
Geboes histologic remission will be assessed using the Geboes histologic scores composed of 6 different grades for evaluation of disease severity in UC.

Study description

Background summary

Ulcerative colitis (UC) is a chronic, intermittent, relapsing disease characterized by inflammation

of the colonic mucosa, which is limited to the colon and rectum. The disease characteristically
commences in the rectum and may extend proximally in an uninterrupted pattern into the colon.
It can involve the entire colon (pan-colitis), the left colon, or isolated recto-sigmoid disease with
patients being equally distributed in those 3 phenotypes. In the United States (US), the
prevalence of UC has been estimated to be 238 per 100,000 adults {Kappelman et al 2007}.
Europe has the highest reported prevalence values for inflammatory bowel disease (IBD; 505 per 100,000 persons for UC and 322 for Crohn*s Disease [CD]). The incidence and prevalence of inflammatory bowel disease (IBD) appear to be increasing over time globally. The hallmark symptoms of the disease are bloody diarrhea, rectal urgency, and tenesmus. The clinical coursetends to wax and wane with periods of remission interspersed with periods of active disease.
Ulcerative colitis may also be associated with extra-intestinal manifestations including ocular
lesions, skin lesions, arthritis, and primary sclerosing cholangitis. The exact pathophysiology is
not known, but a combination of genetic predisposition and environmental factors appear to
contribute to a disordered immune response in these patients {Rutgeerts et al 2005}.
In addition to the abdominal pain and frequent passage of bloody stools that impact activities of
daily living and quality of life for patients with UC, the disease also carries with it an increased
risk of colorectal cancer due to the chronic inflammation associated with the disease {Velayos et
al 2006}. With poorly controlled
disease, the rate of developing colorectal cancer increases with time. Ten years after diagnosis,
the cumulative probability of developing colorectal cancer is 2% and increases to 18% after
30 years. Overall, the risk of a UC patient developing colorectal cancer may be as high as
23-fold compared to the general population {Triantafillidis et al 2009}. Thus, UC represents a
serious, life-threatening disease for which new therapies are needed to interrupt the inflammatory
process to prevent disease progression and risk of colorectal cancer.
Treatment of UC is dependent on the severity and the location of disease. Goals of treatment
include improved quality of life, reduction in long-term corticosteroid use, and minimization of
cancer risk. Mild to moderate distal colitis may be treated with oral

aminosalicylates, topical
mesalamine, or topical steroids {Kornbluth et al 2010}. For moderate disease, oral
corticosteroids, and immunomodulators such as azathioprine and 6-mercaptopurine (6-MP) may
be utilized {Danese et al 2011}. For more moderate to severe disease, patients are commonly
treated with a tumor necrosis factor-alpha (TNF*) antagonist infusion or injection such as
infliximab (Remicade®), adalimumab (Humira®), and golimumab (Simponi®). Vedolizumab
(Entyvio®), an injectable integrin *4*7 monoclonal antibody, is also approved for moderately to
severely active disease. Ustekinumab (Stelara®, CNTO 1275; an IL-12 and IL-23 monoclonal.
antibody), tofacitinb (CP-690,550; JAK1 and JAK3 inhibitor), etrolizumab (PRO145223;
monoclonal antibody targeting the *7 subunit of the heterodimeric integrins *4*7 and *E*7), and
ozanimod (RPC1063; selective S1P1 and S1P5 receptor agonist) are currently being tested in
Phase 3 clinical trials. Despite several classes of treatment options for patients with UC, there remains an unmet
medical need, particularly in the treatment of moderately to severely active disease. Agents with
novel mechanisms of action that target the inflammatory cascade, with oral dosing and
acceptable immunomodulatory and hematologic effects, remain the most promising option to
address these unmet needs.

Study objective

The overall objective of the study is to evaluate the effect of treatment with filgotinib on the induction and maintenance of remission in subjects with moderately to severely active Ulcerative Colitis (UC). Subjects who are biologic-naïve and biologic-experienced will be enrolled in Cohorts A and B respectively. Treatment assignments will be randomized within each Cohort.

Study design

These are combined Phase 2b/3, double-blind, randomized, placebo-controlled studies evaluating the efficacy and safety of filgotinib in the induction and maintenance of remission in subjects with moderately to severely active ulcerative colitis.

These studies include:
Screening (Days -30 to -1)
Randomization (Day 1)
Blinded Induction Studies (Day 1 to Week 11)
- Cohorts A and B Week 10 efficacy assessments:
- At Week 10, MCS to assess MCS response or EBS remission
- Blinded Bridge Phase (Week 10 to 11): Dosing will continue in a blinded fashion through the end of Week 10 until re-randomization at Week 11
Re-randomization (Week 11)
- Subjects in Cohorts A and B who complete the Induction Study and achieve either EBS remission or MCS response at Week 10 will be re-randomized into the Maintenance Study at Week 11
- Subjects who achieve neither EBS remission nor MCS response at Week 10 will have the option to enter a separate, Long-Term Extension (LTE) study (GS-US-418-3899)
Blinded Maintenance Study (Weeks 11 to 58)
Post-Treatment (PTx) safety assessments:* Subjects who opt out of the LTE study (GS-US-418-3899) will
return 30 days after the last dose of study drug for PTx safety assessments
- Subjects who complete all procedures per protocol, including the endoscopy, of the 58-week study will be offered the option to continue into the LTE study (GS-US-418-3899)
- Subjects who are eligible and opt to participate in the LTE study (GS-US-418-3899) can continue into the study without PTx safety assessments

Intervention

Treatment Regimen (Cohorts A and B Induction Studies)
Based on protocol eligibility criteria, subjects will be screened for enrollment in either Cohort A or Cohort B.

Subjects who meet protocol eligibility criteria will be assigned to the respective Cohort and subsequently randomized in a blinded fashion in a 2:2:1 ratio to 1 of 3 treatments as follows:
- Treatment Group 1 (n = 260): filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg, once daily
- Treatment Group 2 (n = 260): filgotinib 100 mg and PTM filgotinib 200 mg, once daily
- Treatment Group 3 (n = 130): PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Note: United States (US) males who have not failed at least two biologic therapies (any tumor necrosis factor-alpha [TNF*] antagonist and vedolizumab) will be randomized in a 2:1 ratio to either filgotinib 100 mg or matching placebo.

Study burden and risks

Please refer to the Risks section in the ICF for a full overview of the risks associated with Filgotinib.

Contacts

Public
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US
Scientific
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Main inclusion criteria (cohorts A and B):
Subjects must meet all of the following inclusion criteria to be eligible for participation in either
the Cohort A or B Induction Study.
* Males or non-pregnant, non-lactating females, ages 18 to 75 years, inclusive based on the

date of the screening visit
* Documented diagnosis of UC of at least 6 months AND with a minimum disease extent of 15 cm from the anal verge. Documentation should include endoscopic and histopathologic evidence of UC as follows:
a) The criteria for documentation of UC based on endoscopy will be medical record documentation of, or an ileocolonoscopy (full colonoscopy with the intubation of the terminal ileum) report dated * 6 months before enrollment, which shows features consistent with UC, determined by the procedure performing physician
b) The criteria for documentation of UC based on histopathology will be medical record documentation of or a histopathology report indicating features consistent with UC as determined by the pathologist
* A surveillance colonoscopy is required at screening in subjects with a history of UC for 8 or more years, if one was not performed in the prior 24 months
* Moderately to severely active UC as determined by a centrally read endoscopy score * 2, a rectal bleeding score * 1, a stool frequency score * 1 and PGA of * 2 as determined by the Mayo clinic scoring system with endoscopy occurring during screening; total score must be between 6 and 12, inclusive
* May be receiving the following drugs (subjects on these therapies must be willing to remain on stable doses for the noted times):
a) Oral 5-aminosalicylate (5-ASA) compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must be stable for first 10 weeks after randomization
b) Azathioprine, 6-MP or MTX provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must be stable for first 10 weeks after randomization
c) Oral corticosteroid therapy (prednisone prescribed at a stable dose * 30 mg/day or budesonide prescribed at a stable dose of * 9 mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomization; dose must be stable for first 14 weeks after randomization;Cohort A (Biologic-naïve) Induction Study
Inclusion Criteria, Cohort A ONLY
Subjects must meet all of the additional following inclusion criteria to be eligible for participation in Cohort A Induction Study.
1) Previously demonstrated an inadequate clinical response, loss of response to, or intolerance
of at least 1 of the following agents (depending on current country treatment recommendations/guidelines):
a) Corticosteroids
i. Active disease despite a history of at least an induction regimen of a dose equivalent to oral prednisone 30 mg daily for 2 weeks or intravenously (IV) for 1 week, OR
ii. Two failed attempts to taper steroids below a dose equivalent of 10 mg daily prednisone, OR
iii. History of steroid intolerance including, but not limited to, Cushing*s syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, serious infections, depression, allergic reactions, mood disturbances, or any other condition that contributed to discontinuation of the agent;b) Immunomodulators
i. Active disease despite a history of at least a 12-week regimen of oral azathioprine (* 2 mg/kg/day) or 6-MP (* 1 mg/kg/day), or MTX (25 mg subcutaneously [SC] or intramuscularly [IM] per week for induction and * 15mg IM per week for

maintenance) OR
ii. History of intolerance to at least 1 immunomodulator including, but not limited to, serious infections, hepatotoxicity, cytopenia, pancreatitis, thiopurine methyltransferase (TPMT) genetic mutation, allergic reactions, or any other condition that contributed to discontinuation of the agent;Cohort B (Biologic-experienced) Induction Study
Inclusion Criteria, Cohort B ONLY
Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least one of the following agents (depending on current country treatment recommendations/guidelines):
a) TNF* Antagonists
i. Infliximab: Minimum induction regimen of 5 mg/kg at 0, 2, and 6 weeks (in the EU, duration of treatment of 14 weeks)
ii. Adalimumab: An 8-week induction regimen consisting of 160 mg (four 40-mg injections in 1 day or two 40-mg injections per day for 2 consecutive days) on Day 1, followed by a second dose 2 weeks later (Day 15) of 80 mg and a 40 mg dose 2 weeks later (Day 29), followed by a 40 mg dose every other week until Week 8 (Day 57).
iii. Golimumab: Minimum induction duration of 6 weeks (12 weeks in EU) is required for golimumab, which includes 200 mg SC injection at Week 0, followed by 100 mg at Week 2 and then 100 mg every 4 weeks. OR
iv. Recurrence of symptoms during maintenance therapy with the above agents, OR
v. History of intolerance to any TNF* antagonists including, but not limited to, serious infections, hepatotoxicity, heart failure, allergic reactions, or any other condition that contributed to discontinuation of the agent
b) Vedolizumab
i. Active disease despite a history of at least a 14 week (10 weeks in EU) induction regimen of vedolizumab consisting of 300 mg IV at weeks 0, two, and six OR
ii. History of intolerance to vedolizumab including, but not limited to, serious infections, hepatotoxicity, cytopenia, allergic reactions, or any other condition that contributed to discontinuation of the agent
2) Must not have used any TNF* antagonist or vedolizumab * 8 weeks prior to screening or any other biologic agent * 8 weeks prior to screening or within 5 times the half-life of the biologic agent prior to screening, whichever is longer;Maintenance Study
Main Inclusion Criteria
* Completion of Cohort A or B induction study with MCS response or EBS remission based on week 10 assessments

Exclusion criteria

Main exclusion criteria (Cohorts A and B):
* Should not have Crohn*s disease, undetermined colitis, Ischemic colitis, Fulminant colitis, ulcerative proctitis or toxic megacolon
* Should not have active tuberculosis (tb) or a history of latent tb that is untreated
* Should not use any prohibited co-medications such as described in the protocol

Cohort A (Biologic naïve) induction research
Main Exclusion criteria, ONLY for cohort A:
* No previous or current treatment with TNF-*-antagonists inclusive (but not limited to) infliximab, adalimumab, golimumab, certolizumab or biosimilar agents, at any moment
* No previous or current treatment with vedolizumab, at any moment;Cohort B (biologic previously treated) induction research
Main exclusion criteria, ONLY cohort B
* May not have been treated with TNF-*-antagonist or vedolizumab * 8 weeks before screening, or another biological * 8 weeks before screening or within 5 times the half-life of the biological before screening, whichever is the longest.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-07-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Filgotinib
Generic name:	Filgotinib

Ethics review

Approved WMO Date:	16-08-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-11-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-01-2019

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-001392-78-NL
ClinicalTrials.gov	NCT02914522
CCMO	NL58867.041.16