A Multicenter, Double-blind, Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Subjects with Rheumatoid Arthritis

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The primary objective of this study is:* To evaluate the long-term safety and tolerability of filgotinib in subjects who have completed one of the parent studies of filgotinib in RA.The secondary objectives of this study are:* To evaluate the long-...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON47791

Source
ToetsingOnline

Brief title
GS-US-417-0304 / FINCH 304

Condition

- Autoimmune disorders
- Joint disorders

Synonym
rheumatism, Rheumatoid Arthritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Rheumatism, Rheumatoid arthritis

Outcome measures

Primary outcome

Safety will be assessed by the reporting of AEs, clinical laboratory tests,

physical examination, vital signs, and 12-lead ECGs.

Efficacy will be evaluated by ACR-N responses in each arm.

Secondary outcome

Exploratory Endpoints will include subject achievement of ACR20/50/70 and EULAR

responses.

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects approximately 1.3 million adults in the United States (US) {Helmick et al 2008}. Rheumatoid arthritis manifests principally as an attack on peripheral joints and may lead to marked destruction and deformity of joints, with considerable disability and impact on quality of life. It is characterized by the production of autoantibodies, synovial inflammation with formation of pannus tissue, and erosion of underlying cartilage and bone. Although people of any age can be affected, the onset of RA is most frequent between the ages of 40 and 50 years, and women are affected 3 times more often than men. While the cause of RA is still not completely understood, aberrant Bcell activation, Tcell costimulation, osteoclast differentiation, and cytokine release all have been implicated in its pathogenesis.

Treatment of RA is dependent on severity, the patient*s co*morbidities and initial response to therapy. Methotrexate (MTX) is a conventional disease modifying antirheumatic drug (DMARD) and continues to be the cornerstone of RA therapy {Singh et al 2012}. Patients with an inadequate response to conventional DMARD(s) are often treated with biologic therapies such as tumor necrosis factor inhibitors (TNFi) as an initial second line therapy. However, approximately 28% to 58% of RA patients with inadequate response to MTX fail TNFi as reviewed in {Redlich et al 2003}. In this setting, treatment guidelines recommend either switching to another TNFi, alternate biologic, or to a small molecule drug {Singh et al 2012}. Despite significant advances in disease management in recent years, there remains a need for new treatments, since not all patients respond adequately to current therapies, have comorbidities and some patients experience toxicities and/or intolerance that limit the use of approved therapies.

In November 2012, tofacitinib (Xeljanz®) became the first Janus kinase (JAK) inhibitor to receive Food and Drug Administration (FDA) approval for the treatment of adult patients with RA. Tofacitinib is a small molecule, has strong binding affinity for JAK1 and JAK3, and weaker affinity for JAK2. The extensive preclinical and clinical development programs demonstrated its mechanisms of action via antiinflammatory and immunosuppressive effects. The drug proved to be efficacious in treating the signs and symptoms of RA. However, the observed side effects and risk profile of tofacitinib are similar to those of several existing antirheumatic agents with cytopenias, elevated levels of liver function enzymes, increased total cholesterol levels, with increase in LDL typically exceeding those for HDL, and increased risk for infections including serious and opportunistic infections. At higher doses, tofacitinib treatment was associated with anemia, which is thought to be linked to inhibition of JAK2.

While the pan JAK inhibitor tofacitinib has shown an early onset of action and longterm efficacy in RA as mono therapy and in combination with background conventional synthetic disease modifying antirheumatic drugs (csDMARDs) therapy, dose levels were limited by side effects potentially mediated by its effect on JAK 2 and JAK 3. This highlights the need for more selective and targeted therapies with improved immunomodulatory and hematologic effects.

JAK1 is thought to be an integral part of RA pathogenesis due its role in transmitting inflammatory cytokine signaling. Hence, targeted inhibition of JAK1 has great potential for the treatment of RA with an improved safety and side effect profile.

Study objective

The primary objective of this study is:
* To evaluate the long-term safety and tolerability of filgotinib in subjects who have completed one of the parent studies of filgotinib in RA.

The secondary objectives of this study are:
* To evaluate the long-term efficacy of filgotinib in subjects with RA
* To evaluate the long-term effects of filgotinib on subject-reported outcomes, such as disability, fatigue, and quality of life.

The exploratory objective of this study is:
* To characterize the association of host genetics and other markers with disease severity, disease progression and treatment response to filgotinib in subjects with RA

Study design

This will be a dose-blinded, long term extension (LTE) study of safety and efficacy of filgotinib in subjects with RA. Subjects may be enrolled in the study after they have completed one of the 2 parent RA studies (GS US 417 0301 and GS-US-417-0302).

The Day -1 visit for this study will be performed at either the last visit for the parent protocol (week 52 visit for GS-US-417-0301, week 24 visit for GS-US-417-0302) or within 4 weeks after the final study visit for the parent protocol.

The subject*s first dose of LTE study drug defines the first day of participation on the LTE, and should not occur sooner than the day after the final visit for the parent protocol. However, the subject may be consented and eligibility confirmed on Day -1 (the same day as the last visit for the parent protocol), with study drug dispensed to start on Day 1 of the LTE study.

Subjects will review and sign the consent for the LTE study prior to any procedures or tests being performed. After eligibility for the study has been confirmed, the subject will be assigned to one of the two filgotinib dosing arms in a blinded fashion.

Subjects who were on blinded filgotinib at the final visit of the parent study will continue on their same dose of filgotinib in a blinded fashion (100 mg or 200 mg QD). Subjects who were receiving adalimumab (GS-US-417-0301) or placebo (GS-US-417-0302) at their final visit of the parent study, will be re-randomized on Day -1 of the LTE in a 1:1 ratio to either 100 mg or 200 mg filgotinib QD in a blinded fashion.

Subjects from study GS-US-417-0301, who completed the study after being transitioned to standard of care therapy, are not eligible for the LTE study.

Subjects from study GS-US-417-0302, who discontinued blinded study drug due to inadequate response of their RA, but completed all study visits are eligible for the LTE, and will be re-randomized on Day 1 of the LTE in a 1:1 ratio to either 100 mg or 200 mg filgotinib QD in a blinded fashion.

* Subjects will be provided filgotinib for up to 3 years, or until filgotinib becomes commercially available, or until Gilead Sciences terminates clinical development of filgotinib; whichever comes first.
* All subjects may continue their stable dose of permitted csDMARD(s) as indicated in the parent protocol.

All subjects who are re-randomized on Day -1 of the LTE will be stratified by geographic region and parent study.

Intervention

200 mg filgotinib orally once daily (QD)
100 mg filgotinib orally once daily (QD)

Study burden and risks

FILGOTINIB COMMON ADVERSE EVENTS

INFECTIONS
Drugs that affect your immune system can lower your body*s ability to fight off infections. There is a possibility that your ability to fight off infections will be weakened while taking filgotinib. In studies of patients with RA and CD, there have been more infections in people who took filgotinib compared to those who took a placebo. Pneumonia (lung infection) has been identified as a side effect of filgotinib based on studies in people with RA and CD. Serious infections leading to hospitalization and, in 3 cases, death have been reported. Overall, less than 3% of patients taking filgotinib developed a serious infection of any type.

Neutrophils are a type of blood cell that helps to fight infections. The number of neutrophils was lower in the blood of patients with RA who were given filgotinib, but only approximately 1.5% of these patients had a severe decrease in neutrophils. Other types of infection fighting cells in the blood were not affected.

MALE INFERTILITY
Filgotinib caused damage to the testes (testicles) of male rats and dogs. In these animals, filgotinib caused deterioration and loss of cells that make sperm, resulting in less sperm, or no sperm being produced. As a result, filgotinib caused male rats to be infertile (unable to get a female rat pregnant).

Damage to the testes in rats and dogs was observed at doses slightly higher than the doses that are planned to be given to people in this study. At these doses, while sperm counts in rats and dogs increased after filgotinib was stopped, they stayed low overall and did not return to normal. At the highest

doses tested in male rats and dogs, these side effects did not go away. These side effects were not seen in the testes of rats and dogs when a dose was given that was similar to the 200 mg daily dose in humans.

Based on the results in male rats and dogs, there is a risk that men treated with filgotinib may have reduced sperm production, and may become temporarily or permanently infertile (unable to get a woman pregnant). An additional study will be done in men with RA to measure the effect of filgotinib on sperm production. Until results from that study are available, the long term effect of filgotinib on sperm production in humans is unknown. Do not enroll in this study unless you understand and accept the risk that you may have reduced fertility (a lower chance of getting a woman pregnant) or infertility (unable to get a woman pregnant), and that this side effect may not go away after you leave the study; it could be permanent.

BIRTH DEFECTS
Filgotinib treatment caused malformations (birth defects) of the bone and internal organs in the fetuses (unborn babies) of pregnant rats and rabbits. These birth defects happened at doses of filgotinib similar to those planned to be given to humans. Other effects were also seen, including increased pregnancy loss and decreased fetal body weights.

Based on this animal data, filgotinib may cause birth defects in humans. Do not enroll in this study unless you understand and accept this risk and are willing to take appropriate measures to avoid pregnancy. To be in this study, highly effective birth control is required for both men and women. Birth control should also be considered for female partners of male participants; your study doctor can provide details on recommended types of birth control. If you are planning to become pregnant in the future, you should discuss this with your study doctor before entering the study.

OTHER EFFECTS Increases in cholesterol, including certain types of both good and bad cholesterols, have been seen in people taking filgotinib, but the importance of these findings is not yet known. A small increase in creatinine (which is a measure of how well the kidney is working) was seen in studies with RA patients. The creatinine levels overall, however, stayed within normal limits.

As with any drug, there are unknown risks involved, since only a limited number of people have taken this drug and not all side effects and risks of taking this drug are known. In the future, more serious and/or long term side effects could happen, including allergic reactions. Also, the risks or discomforts described here could happen more often or be more severe than what has been seen before. Your health will be checked at each visit during the study by your Study Doctor, and you will be asked to report any changes or problems you may have noticed.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Male or female subjects who may benefit from filgotinib as judged by the investigator AND who completed a Gilead sponsored filgotinib parent study for RA as outlined below:
a) Subjects who completed GS-US-417-0301 or GS-US-417-0302 on study drug OR
b) Subjects who completed GS-US-417-0302 on standard of care therapy due to RA non-responder status
2) Females of childbearing potential must have a negative pregnancy test prior to first dose of study drug in the LTE;
3) Lactating female subjects must agree to discontinue nursing at Day -1 for the duration of the study
4) Male and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception, during the study and through 35 days (female) or 90 days (male) after their last dose of study drug or longer as

indicated by the product label of the subject*s concurrent csDMARD therapy.
5) Subjects receiving protocol permitted RA medications should be on a stable dose (defined as no change in prescription) within 7 days or 5 half lives (whichever is longer) prior to the first administration of LTE study drug on Day 1, as much as possible.
6) Subjects, who meet study drug interruption criteria at Day 1, are eligible to enter into the LTE, but should not start study drug until deemed medically appropriate.

Exclusion criteria

1) Diagnosis of an autoimmune or inflammatory joint disease other than RA, which would put the subject at risk by participating in the study or would interfere with study assessments/data interpretation, per judgment of the investigator
2) Known hypersensitivity to the study drug or its excipients.
3) Any medical condition (including, but not limited to, cardiac or pulmonary disease, alcohol or drug abuse) which would put the subject at risk by participating in the study or would interfere with study assessments/data interpretation, per judgment of the investigator.
4) History of an infected joint prosthesis or other implanted device with retention of the prosthesis or device in situ.
5) Administration of a live/ attenuated vaccine within 30 days prior to Day 1
6) Currently on any therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, and atypical mycobacteria)
7) History of disseminated/complicated herpes zoster infection (multi dermatomal involvement, ophthalmic zoster, central nervous system involvement or postherpetic neuralgia)
8) 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
9) Use of prohibited medication as outlined in the protocol
10) Subjects who meet discontinuation criteria as outlined in the protocol

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	06-09-2017
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	08-02-2018
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	04-05-2018
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	METC Twente (Enschede)

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	EUCTR2016-003630-25-NL
ClinicalTrials.gov	NCT03025308
CCMO	NL61321.044.17