A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 weeks in Combination with Methotrexate to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON45740

Source
ToetsingOnline

Brief title
GS-US-417-0301

Condition

- 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:

Safety will be assessed by documentation of AEs, clinical laboratory tests,

physical examinations, vital signs, and 12-lead ECGs during the study.

Efficacy:

The primary endpoint is the proportion of subjects who achieve an ACR20

response at Week 12.

Pharmacokinetics:

Plasma concentrations of filgotinib and its metabolite (GS-829845) will be

analyzed.

Secondary outcome

Efficacy:

The key secondary endpoints are:

* The proportion of subjects who achieve DAS28 (CRP)*3.2 at Week 12

* Change from Baseline in the HAQ-DI score at Week 12

* The proportion of subjects who achieve DAS28 (CRP)<2.6 at Week 24

* Change from Baseline in mTSS at Week 24

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 B-cell activation, T-cell co-stimulation, 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 anti-rheumatic 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 co-morbidities 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 pre-clinical and clinical development programs demonstrated its mechanisms of action via anti-inflammatory 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 anti-rheumatic 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 long-term efficacy in RA as mono therapy and in combination with background conventional synthetic disease modifying anti-rheumatic 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 effects of filgotinib versus placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement response (ACR20) at Week 12

The secondary objectives of this study include:

* To evaluate the effects of filgotinib versus placebo as measured by the proportion of subjects achieving Disease Activity Score for 28 joint count using c-reactive protein (DAS28[CRP]) *3.2 at Week 12
* To evaluate the effect of filgotinib versus placebo on physical function as measured by change from Baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) score at Week 12
* Toevaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of RA as measured by the proportion of subjects achieving DAS28 (CRP)<2.6 at Week 24
* To evaluate the effects of filgotinib versus placebo on preservation of joint structure as measured by change from Baseline in the van der Heijde modified Total Sharp Score (mTSS) at Week 24
* To evaluate the effects of filgotinib versus adalimumab for the treatment of

signs and symptoms of RA as measured by the proportion of subjects achieving DAS28 (CRP) * 3.2 at Week 12
* To evaluate the safety and tolerability of filgotinib
* To evaluate the effects of filgotinib on work productivity, fatigue, and general quality of life as measured by SF-36, FACIT-Fatigue, EQ-5D and WPAI-RA

The exploratory objectives of this study include:

* To characterize the pharmacokinetics (PK) of filgotinib and its metabolite (GS-829845, formerly G254445)
* To characterize the association of host genetics and other markers with disease severity, disease progression and treatment response to filgotinib in subjects with RA
* To evaluate the effects of filgotinib on healthcare resource utilization and other patient reported outcomes

Study design

This is a randomized, double-blind, placebo- and active-controlled, Phase 3 study in adult male and female subjects with active RA who have an inadequate response to MTX (MTX-IR). The study is designed to evaluate the efficacy, safety, and tolerability of filgotinib as well as its effect on work productivity, fatigue, and quality of life.

Approximately 1650 subjects will be randomized in a 3:3:2:3 ratio to filgotinib 200 mg, filgotinib 100 mg, active comparator (adalimumab), or placebo to match (PTM) administered for up to 52 weeks, all in the context of a weekly stable dose of MTX:

* Filgotinib 200 mg group: filgotinib (200 mg q.d.) + PTM filgotinib 100 mg (PTM q.d.) + PTM adalimumab (PTM s.c. injection q2w) (N=450)
* Filgotinib 100 mg group: filgotinib (100 mg q.d.) + PTM filgotinib 200 mg (PTM q.d.) + PTM adalimumab (PTM s.c. injection q2w) (N=450)
* Active comparator group: PTM filgotinib 200 mg (PTM q.d.) + PTM filgotinib 100 mg (PTM q.d.) + adalimumab (40 mg s.c. injection q2w) (N=300)
* Placebo control group: PTM filgotinib 200 mg (PTM q.d.) + PTM filgotinib 100 mg (PTM q.d.) + PTM adalimumab (PTM s.c. injection q2w) (N=450)

At Week 14, subjects who have not achieved at least 20% improvement from Day 1 in both swollen joint count (SJC) and tender joint count (TJC) will discontinue investigational study drug dosing but will continue with study visits and assessments per protocol. All subjects meeting this criterion who discontinue from investigational therapy are to receive standard of care treatment for their RA as determined by the investigator.

At Week 24, all subjects assigned to placebo + MTX will be reassigned 1:1 to either filgotinib 100 mg q.d. or 200 mg q.d. in addition to MTX in a blinded

fashion and will continue in the study per protocol up to Week 52.

All subjects who continue on study drug will be evaluated for loss of therapeutic response from Week 30 through Week 52. Subjects failing to maintain at least a 20% improvement from Day 1 in TJC and SJC, (which is confirmed at 2 consecutive visits), will discontinue from investigational study drug therapy but will continue with study visits and assessments per protocol. All subjects meeting this criterion who discontinue from investigational study drug dosing are to receive standard of care treatment for their RA as determined by the investigator.

All subjects who have received at least one dose of study drug and exit the study early will complete an early termination (ET) visit at the time of study discontinuation, with a follow up visit four weeks after the last dose of study drug (Post Treatment Week 4), regardless of dosing duration.

At completion of the 52-week dosing period, subjects who have not discontinued assigned study drug dosing, will be provided the option to enroll into a separate Long Term Extension (LTE) study
(GS-US-417-0304).

Intervention

* Filgotinib 200 mg group: filgotinib (200 mg q.d.) + PTM filgotinib 100 mg (PTM q.d.) + PTM adalimumab (PTM s.c. injection q2w) (N=450)
* Filgotinib 100 mg group: filgotinib (100 mg q.d.) + PTM filgotinib 200 mg (PTM q.d.) + PTM adalimumab (PTM s.c. injection q2w) (N=450)
* Active comparator group: PTM filgotinib 200 mg (PTM q.d.) + PTM filgotinib 100 mg (PTM q.d.) + adalimumab (40 mg s.c. injection q2w) (N=300)
* Placebo control group: PTM filgotinib 200 mg (PTM q.d.) + PTM filgotinib 100 mg (PTM q.d.) + PTM adalimumab (PTM s.c. injection q2w) (N=450)

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. If you or your partner becomes pregnant during the study, you should let your study doctor know right away. If you have any changes in your health or if you have any health problems, you should let your study doctor know right away.

Contacts

Public
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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For a complete list of study inclusion criteria, please refer to Section 4.2 of the study protocol.;Main Eligibility Criteria
1) Male or female subjects who are *18 years of age, on the day of signing informed consent.
2) Have a diagnosis of RA (2010 ACR/EULAR criteria) , and are ACR functional class I-III.
3) Have *6 swollen joints (from a SJC66) and *6 tender joints (from a TJC68) at both Screening and Day 1.
4) Must meet at least one of the following parameters at Screening:
a) *1 documented joint erosion on radiographs of the hands, wrists or feet by central reading AND a positive result for anti-CCP or RF at the central laboratory,
OR b) *3 documented erosions on radiographs of the hands, wrists or feet by central reading if both antibodies (ie, RF, anti-CCP) are negative (based on central laboratory),
OR c) Serum CRP * 6 mg/L based on central laboratory value
5) Ongoing treatment with a stable dose of MTX as described below:
a) Use of oral MTX on a continuous basis for at least 12 weeks prior to Day 1 and on a stably prescribed dose of 7.5-25 mg/weekly for at least 4 weeks prior to Day 1. Stable doses of <7.5 mg/week are allowed only in the presence of intolerance or toxicity to higher doses or where higher doses are prohibited by the local label or local clinical practice. Doses >25 mg weekly are not permitted during the study.
b) Subjects should be receiving an adequate and prescribed stable dose of folic acid (*5 mg/week total dose or as per local clinical practice) which should be confirmed or initiated at Screening,
and continued throughout the study.
c) Subjects may use concomitant hydroxychloroquine (HCQ) *400 mg/day or chloroquine *250 mg/day during the study with the prescription having been stable for at least 4 weeks prior to Day 1.

Exclusion criteria

For a complete list of study exclusion criteria, please refer to section 4.3 of the study protocol:

Subjects that have failed prior therapy with a bDMARD are not eligible to participate. Subjects with prior exposure to one bDMARD may be enrolled (approximately 20% of total study population) if there is documented evidence of limited exposure (ie, less than 3 months) to the bDMARD

Study design

Design

Study phase:	3
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):	21-12-2017
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adalimumab (Humira)
Generic name:	Adalimumab (Humira)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Filgotinib
Generic name:	Filgotinib
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Methotrexate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-06-2017
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	18-07-2017
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	15-12-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	25-01-2018
Application type:	Amendment
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)
Approved WMO Date:	24-10-2018

Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	13-03-2019
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	EUCTR2016-000568-41-NL
ClinicalTrials.gov	NCT02889796
CCMO	NL58689.044.16