A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 24 weeks in Combination with Conventional Synthetic Disease-modifying Anti-rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic DMARD(s) Treatment

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

Summary

ID

NL-OMON45679

Source
ToetsingOnline

Brief title
GS-US-417-0302

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 the documentation of AEs, clinical laboratory tests,

physical examination, 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 active 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

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 sideeffects 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 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 are:

* To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of RA 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 Questionaire Disability Index (HAQ-DI) 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 objective of this study is as follows:

* 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 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-controlled, add-on, Phase 3 study in adult male and female subjects with active RA despite csDMARD(s) therapy (ie, MTX, hydroxychloroquine, sulfasalazine, leflunomide) who have had an inadequate response or are intolerant to at least one biologic DMARD (bDMARD).

Approximately 423 subjects will be randomized in a 1:1:1 ratio to filgotinib 200 mg, filgotinib 100 mg, or placebo to match (PTM) administered for up to 24 weeks, all in the context of a stable dose of permitted csDMARD(s):

Filgotinib 200 mg group: filgotinib (200 mg once daily [q.d.]) + PTM filgotinib 100 mg (PTM q.d.) (N=141)
Filgotinib 100 mg group: filgotinib (100 mg q.d.) + PTM filgotinib 200 mg (PTM q.d.) (N=141)
Placebo control group: PTM filgotinib 200 mg (PTM q.d.) and PTM filgotinib 100 mg (PTM q.d.) (N=141)

Randomization will be stratified by geographic region, prior exposure to number of bDMARDs (<3 or >=3 bDMARDs) and presence of rheumatoid factor (RF) or anti-CCP (cyclic citrullinated peptide) antibody (Ab)) at screening.

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.

All subjects who attain responder status at Week 14 will continue on their assigned study drug, in a blinded fashion through Week 24. Placebo-responders at Week 14 will continue on placebo in a blinded fashion through Week 24.

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 visit Week 4), regardless of dosing duration.

At completion of the 24-week dosing period all subjects, regardless of response, who have not discontinued the study due to toxicity, 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 once daily [q.d.]) + PTM filgotinib 100 mg (PTM q.d.) (N=141)
Filgotinib 100 mg group: filgotinib (100 mg q.d.) + PTM filgotinib 200 mg (PTM q.d.) (N=141)

Placebo control group: PTM filgotinib 200 mg (PTM q.d.) and PTM filgotinib 100 mg (PTM q.d.) (N=141)

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

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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 and exclusion criteria, please refer to Sections 4.2.;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 for RA), and are ACR functional class I-III.;3) Have *6 swollen joints (from a SJC66) and *6 tender joints (from a TJC68) at Screening and Day 1;4) Have serum CRP * 4 mg/L based on central laboratory analysis at Screening;5) Ongoing treatment with a stable prescription of 1 or 2 csDMARD(s) as follows:;Permitted csDMARDs
a) Use of MTX for at least 12 weeks prior to Day 1. Subject is on a stably prescribed dose and route of administration of 7.5-25 mg/weekly for at least 4 weeks prior to Day 1. Stable weekly doses <7.5 mg are allowed only in the presence of intolerance to or toxicity from higher doses or where higher doses are prohibited by the local label or local clinical practice. Doses >25 mg weekly are not permitted.;b) Subjects on MTX should be receiving an adequate and 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. MTX is not permitted to be used in combination with leflunomide.;c) Oral hydroxychloroquine *400 mg/day or chloroquine *250 mg/day with prescription having been stable for at least 4 weeks prior to Day 1;d) Oral sulfasalazine 1 g to 3 g/day with prescription having been stable for at least 4 weeks prior to Day 1;e) Oral leflunomide 10-20 mg/day, with prescription having been stable for at least 4 weeks prior to Day 1;The treatment with csDMARD should be continued at a stable dose until the end of the study. Dose adjustments are only permitted for the management of toxicity. Prior treatment with additional csDMARDs is allowed, however, subject may only be on 1 or 2 csDMARDs at Day 1 and appropriate wash out needs to be satisfied according protocol (Section 5.3), in order to be eligible for the study.;6) Have received at least one bDMARD for the treatment of RA to which they have had an inadequate response or intolerance. An inadequate response is defined as documented continued or recurrent disease activity after at least 12 weeks of treatment with any investigational or licensed bDMARD, including biosimilars, for the treatment of RA. Intolerance is defined as treatment discontinuation due to any documented adverse effect associated with a bDMARD used according to its respective label. There is no limit to the prior number of bDMARDs that may have been used by the subject, however the subject may not be on a bDMARD at Day 1 or during the study.

Exclusion criteria

For a complete list of study exclusion criteria, please refer to study protocol (Sections 4.3):;1)

Prior treatments for RA as defined in Section 4.3 of the protocol;2) Known hypersensitivity or allergy to the study drug(s), its metabolites, or formulation excipients.;3) Oral steroids at a dose >10 mg/day of prednisone equivalent or a prescription for oral steroids which has changed within 4 weeks of Day 1.;4) Receipt of an intra-articular or parenteral corticosteroid injection within 4 weeks prior to Day 1.;5) Use of nonsteroidal anti-inflammatory drugs (NSAID(s) which have not been at a stable dose (defined as no change in prescription) for at least 2 weeks prior to Day 1. ;6) Administration of a live/ attenuated vaccine within 30 days prior to Day 1, or planned during the study.;7) Participation in any clinical study of an investigational drug/device within 4 weeks or 5 half-lives prior to Screening, whichever is longer. Exposure to investigational biologics should be discussed with the sponsor.;8) Have undergone surgical treatments for RA including synovectomy or arthroplasty in >4 joints and/or within the last 12 weeks prior to Screening;9) Have any chronic, uncontrolled medical condition, which would put the subject at increased risk during study participation, such as uncontrolled: diabetes, hypertension, morbid obesity, thyroid, adrenal, pulmonary, hepatic, renal, neurologic or psychiatric disease, or other disease of concern, as per judgment of investigator;10) Have a history of major surgery (requiring regional block or general anaesthesia) within the last 12 weeks prior to Screening or planned major surgery during the study.;11) Have a moderately to severely active, generalized musculoskeletal disorder that would interfere with assessment of study parameters or increase risk to the subject by participating in the study;12) Active autoimmune disease other than those listed above, that would interfere with assessment of study parameters or increase risk to the subject by participating in the study, eg, inflammatory bowel disease, uncontrolled thyroiditis, systemic vasculitis, transverse myelitis or uveitis.;13) History of or current moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia or new or significant ECG finding at Screening, or any other cardiovascular condition which, in the opinion of the investigator, would put the subject at risk by participation in the study. ;14) History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ with no evidence of recurrence). ;15) History of lymphoproliferative disease or current lymphoproliferative disease.;16) History of gastrointestinal perforation.;17) History of organ or bone marrow transplant. ;18) Positive serology for human immunodeficiency virus (HIV) 1 or 2;19) Evidence of active Hepatitis C Virus (HCV) infection;20) Evidence of active Hepatitis B Virus (HBV) infection. ;21) History of opportunistic infection or immunodeficiency syndrome which would put the subject at risk, as per investigator judgment.;22) Active infection that is clinically significant, as per judgment of the investigator, or any infection requiring hospitalization or treatment with intravenous anti-infectives within 60 days of Screening; or any infection requiring oral anti-infective therapy within 30 days of Screening.;23) Currently on any therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, and atypical mycobacteria). Past history of disseminated Staphylococcus aureus or disseminated Herpes simplex infection.;24) History of symptomatic herpes zoster infection within 12 weeks prior to Screening or have history of disseminated/complicated herpes zoster infection (multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement or postherpetic neuralgia).;25) History of an infected joint prosthesis or other implanted device with retention of the prosthesis or device in situ.;26) Current drug, tobacco or alcohol abuse per investigator judgment.;27) Any condition including active fibromyalgia that based on the investigator*s

opinion would make it difficult to appropriately assess RA activity for the purposes of this study.;28) 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.;29) Significant blood loss (>450 mL) or transfusion of any blood product within 12 weeks prior to Day 1.;30) Use of prohibited medication as outlined in the study protocol (Section 5.3);31) Tests performed at the central laboratory at Screening as defined in study protocol (Section 4.3)

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:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

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

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:	21-09-2017
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	EUCTR2016-000569-21-NL
ClinicalTrials.gov	NCT02873936
CCMO	NL58693.044.16