A Phase 3, Randomized, Double-blind, Placebo and Adalimumab-controlled Study to Evaluate the Efficacy and Safety of Filgotinib in Subjects with Active Psoriatic Arthritis Who Are Naïve to Biologic DMARD Therapy

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Tendon, ligament and cartilage disorders
Study type	Interventional

Summary

ID

NL-OMON49695

Source
ToetsingOnline

Brief title
PENGUIN-1

Condition

- Tendon, ligament and cartilage disorders

Synonym
PsA, Psoriatic Arthritis

Research involving

Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: PsA, Psoriatic Arthritis

Outcome measures

Primary outcome

Safety:

Safety will be assessed by the documentation of AEs, physical examinations,

vital signs, and clinical laboratory parameters at specified time points during

the study.

Efficacy:

The primary endpoint is the ACR20 response at Week 12.

Pharmacokinetics:

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

be analyzed.

Secondary outcome

Efficacy:

The key secondary endpoints include:

* ACR50 response at Week 12

* Change from Baseline in HAQ DI at Week 12

* Change from Baseline in SF 36v2 physical component summary (PCS) at Week 16

* Change from Baseline in LEI at Week 16, in subjects with enthesitis at

Baseline

* Psoriasis Area and Severity Index 75% improvement (PASI75) response at Week

16, in subjects with psoriasis covering *3% of the BSA at Baseline

* MDA response at Week 16

* Change from Baseline in FACIT Fatigue at Week 16

* Change from Baseline in LDI at Week 16, in subjects with dactylitis at

Baseline

Study description

Background summary

This study will test an experimental drug named filgotinib for the treatment of PsA. PsA is a disease where the body*s immune system attacks its own joints causing joint pain, swelling and skin inflammation or lesions.
Filgotinib is currently not approved for treatment of any condition. It is being studied in people with rheumatoid arthritis (RA), inflammatory bowel disease including ulcerative colitis (UC) and Crohn*s disease (CD) and other inflammatory diseases involving joints, spine, eye, and kidney.

Study objective

The primary objective of this study is:
* To evaluate the effect of filgotinib compared to placebo in active psoriatic arthritis (PsA) as assessed by the American College of Rheumatology 20% improvement (ACR20) response at Week 12

Secondary objectives of this study are:
* To evaluate the effect of filgotinib on core domains of PsA as assessed by Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA), ACR responses, Psoriasis Area and Severity Index including Body Surface Area (PASI including BSA) responses, Spondyloarthritis Research Consortium of Canada Enthesitis Index and Leeds Enthesitis Index (SPARCC Enthesitis Index and LEI), Leeds Dactylitis Index (LDI), Psoriatic Arthritis Disease Activity Score

(PASDAS), Disease Activity Index for Psoriatic Arthritis (DAPSA), Modified Nail Psoriasis Severity Index (mNAPSI), and Physician*s Global Assessment of Psoriasis (PhGAP)
* To evaluate the effect of filgotinib on physical function in active PsA as assessed by Health Assessment Questionnaire * Disability Index (HAQ DI)
* To evaluate the effect of filgotinib on fatigue and quality of life in active PsA as assessed by Functional Assessment of Chronic Illness Therapy * Fatigue Scale (FACIT Fatigue), 36-item Short Form Health Survey Version 2 (SF 36v2), and 12 item Psoriatic Arthritis Impact of Disease (PsAID 12)
* To evaluate the efficacy of filgotinib versus adalimumab in active PsA as assessed by ACR20 response
* To evaluate the safety and tolerability of filgotinib

See Section 2 of the protocol for full list of study objectives

Study design

The study consists of two parts, the Main Study: Screening through Week 16 (inclusive) and the Long Term Extension (LTE): after Week 16 for 2 years.

After all subjects have completed the Week 16 Visit or have permanently discontinued the study prior to Week 16, the treatment assignments will be unblinded to the Sponsor only. The subjects and investigators will remain blinded to individual level treatment assignment.
Part 1 * Main Study (Screening through Week 16):
Approximately 854 subjects will be randomized in a 2:2:1:2 ratio to one of 4 dosing groups as outlined under Intervention below.
Randomization will be stratified by geographic region and concurrent use of csDMARD(s) and / or apremilast at randomization (yes or no).
Subjects will be permitted, but are not required, to continue stable doses of background csDMARD(s), apremilast, and / or NSAIDs. Every effort should be made to maintain stable background therapy for PsA treatment through the completion of the Week 16 Visit. Instructions for rescue therapy are detailed in Section 5.4 of the protocol.

Part 2 * LTE (After the Week 16 Visit for 2 years):
After completion of the Main Study, subjects who have not permanently discontinued study drug will continue on to the LTE as follows:
* Those who were assigned to the filgotinib groups will continue on the same study drug assignments
* Those who were assigned to the placebo or active comparator groups will be reassigned 1:1 in a blinded fashion to filgotinib 200 mg or 100 mg once daily

Discontinuation of Study Drug:
For the first 16 weeks of study participation, subjects who temporarily interrupt or permanently discontinue study drug for any reason are to continue with study visits and assessments through the Week 16 Visit, per Section 3.5 of

the protocol unless the subject withdraws consent, is lost to follow up, and / or continued participation in the study is medically contraindicated, per investigator*s judgment. Study drug interruption and discontinuation considerations are outlined in Section 3.5 of the protocol. All subjects who permanently discontinue study drug should continue to receive standard of care treatment for their PsA including additional therapies, if required.

Discontinuation of Study Participation:
If a subject is unable to complete the study through the Week 16 Visit, and has received at least one dose of study drug, the subject will complete an Early Termination (ET) Visit at the time of study discontinuation. Subjects will also complete a post study follow up visit approximately 4 weeks later (Safety Follow up Visit).
After the Week 16 Visit, subjects who permanently discontinue study drug for any reason are to discontinue the study. Subjects who exit the study early, regardless of dosing duration, are to complete an ET Visit and a Safety Follow up Visit.

Intervention

Dosing groups in the Main Study:
* Filgotinib 200 mg group: filgotinib 200 mg once daily + placebo to match (PTM) filgotinib 100 mg once daily + PTM adalimumab subcutaneous (SC) injection once every two weeks (q2w)
* Filgotinib 100 mg group: PTM filgotinib 200 mg once daily + filgotinib 100 mg once daily + PTM adalimumab SC injection q2w
* Active comparator group: PTM filgotinib 200 mg once daily + PTM filgotinib 100 mg once daily + adalimumab 40 mg SC injection q2w
* Placebo control group: PTM filgotinib 200 mg once daily + PTM filgotinib 100 mg once daily + PTM adalimumab SC injection q2w
NOTE: All subjects will discontinue adalimumab / PTM injections by the Week 16 Visit (the last injections should be at approximately Week 14).

Dosing groups in the LTE:
* Filgotinib 200 mg group: filgotinib 200 mg once daily + PTM filgotinib 100 mg once daily
* Filgotinib 100 mg group: PTM filgotinib 200 mg once daily + filgotinib 100 mg once daily

Study burden and risks

Additional information on filgotinib
The following changes in blood test results were observed in people with rheumatoid arthritis (RA) taking filgotinib; however, it is currently unknown if they were caused by the drug:
* Increased creatinine. On average, the values remained within the normal range

even though they increased from when filgotinib was started.
* Increase of (good and bad) fat in the blood. The proportion between bad and good fat in the blood was generally unchanged. The changes in fat in the blood were seen within the first 12 weeks of taking filgotinib and did not change much after then.

In a Phase 2 study among subjects with psoriatic arthritis receiving filgotinib 200 mg once daily for up to 16 weeks, the most frequently reported adverse effects were common cold, increased level of fat in the blood, and increased level of an enzyme called gamma-glutamyl transferase in the blood. The enzyme is normally present in many organs throughout the body, with the highest level found in the liver. The body may release it in response to damage or disease mostly to the liver or bile ducts. In this study, one subject who received filgotinib had serious adverse effect of pneumonia and died.

Other possible risks while taking filgotinib:
- Infections, including serious infections (some with fatal outcome).
- Tuberculosis has more often been seen in people with weakened immune system.
- Certain types of vaccines should not be given prior to and during treatment with filgotinib. The study doctor will discuss this with the patient.
- Drugs that affect the immune system may increase the risk of cancer. It is currently not possible to know whether taking filgotinib increases your risk of getting cancer.

Some adverse effects were observed in animals and are summarized below:
Filgotinib treatment caused malformations (birth defects) of the bone and internal organs in the foetuses of pregnant rats and rabbits. These birth defects happened at doses producing blood levels of filgotinib comparable to blood levels produced by the planned doses in study participants in this study. Other effects were also seen, including increased pregnancy loss and decreased foetal body weights.

Based on these animal data, filgotinib may cause birth defects in humans. 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.

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.

Damage to the testes in rats and dogs was observed at doses producing blood levels of filgotinib slightly higher than blood levels produced by the planned doses in study participants 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 adverse effects did not go away. These adverse effects were not seen in the testes of rats and dogs when these animals were given a dose that produces blood levels of filgotinib similar to blood levels produced by 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. Two additional separate studies are ongoing in men 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.

As with any drug, there are unknown risks involved, since only a limited number of people have taken this drug and not all adverse effects or risks of taking this drug are known. In the future, more serious and/or long-term adverse 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.

Additional information on adalimumab (HUMIRA®)
Some uncommon, but potentially serious or life-threatening events seen in patients taking adalimumab include:
* Infections of the brain and the protective membranes covering the brain
* Opportunistic infections (rare infections that only occur in individuals with a weakened immune system)
* Tuberculosis
* Cancer
* Stroke
* Myocardial infarction (heart attack)
* Arrhythmia (irregular heartbeat)
* Heart failure
* Aortic aneurism (abnormal blood vessel enlargement)
* Pulmonary embolism (blood clot in the lung)
* Reaction at the site of injection (e.g. swelling, itching, stinging, tenderness)

Contacts

Public
Gilead Sciences

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US

Scientific
Gilead Sciences

Lakeside Drive 333
Foster City CA94404
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Male or female subjects who are 18 75 years of age (19-75 years of age at sites in Republic of Korea, 20 75 years of age at sites in Japan and Taiwan) on the day of signing initial informed consent
* Meet Classification Criteria for Psoriatic Arthritis (CASPAR) and have a history consistent with PsA *6 months at Screening
* Have active PsA defined as *3 swollen joints (from a 66 swollen joint count [SJC]) and *3 tender joints (from a 68 tender joint count [TJC]) at Screening and Day 1; these may or may not be the same joints at Screening and Day 1
* Must have a documented history or active signs of at least one of the following at Screening:
a) Plaque psoriasis
b) Nail changes attributed to psoriasis
* Have had inadequate response or intolerance to *1 csDMARD, apremilast and / or NSAID, administered over the course of *12 weeks for the treatment of PsA, as per local guidelines / standard of care
* If continuing csDMARD(s) during the study, subjects are permitted to use only a maximum of 2 of the drugs as outlined in Section 4.2 and must have been on this treatment for *12 consecutive weeks prior to Screening, with a stable dose and route of administration (defined as no change in prescription) for *4 weeks prior to Day 1
* Concomitant NSAIDs or corticosteroids are permitted as specified in Sections

4.2 and 4.3 of the protocol.

For a complete list of study inclusion criteria, please refer to Section 4.2 of the protocol.

Exclusion criteria

* Prior PsA or psoriasis treatment with a bioDMARD
* Prior exposure to a JAK inhibitor >2 doses
* Any active / recent infection, as specified in Section 4.3 in the protocol
* Any chronic and / or uncontrolled medical condition that would put the subject at increased risk during study participation or circumstances which may make a subject unlikely or unable to complete or comply with study procedures and requirements, per investigator judgement
* Any moderately to severely active musculoskeletal or skin disorder other than PsA or plaque psoriasis that would interfere with assessment of study parameters, as per judgement of investigator

NOTE: Prior history of reactive arthritis or axial spondyloarthritis is permitted if there is documentation of change in diagnosis to PsA or additional diagnosis of PsA

* Any history of an inflammatory arthropathy with onset before age 16 years old
* Active autoimmune disease that would interfere with assessment of study parameters or increase risk to the subject by participating in the study (e.g. uveitis, inflammatory bowel disease, uncontrolled thyroiditis, systemic vasculitis, transverse myelitis), per judgement of investigator
* Presence of any extra articular manifestations typically associated with rheumatoid arthritis (RA), such as rheumatoid nodules, rheumatoid lung, or other signs / symptoms, as per judgement of investigator
* Pregnancy or nursing females
* Active drug or alcohol abuse, as per judgement of investigator
* Unwilling or unable to follow protocol requirements

For a complete list of study exclusion criteria, please refer to Section 4.3 of the protocol.

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:	7
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Adalimumab
Generic name:	Humira 40 mg s.c. injection
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Filgotinib
Generic name:	Filgotinib

Ethics review

Approved WMO Date:	01-10-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-11-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-11-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2019-001996-35-NL
ClinicalTrials.gov	NCT04115748
CCMO	NL70851.028.20