A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Evaluating the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Tumor Necrosis Factor Inhibitors

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

Summary

ID

NL-OMON40024

Source
ToetsingOnline

Brief title
I4V-MC-JADW (219-428)

Condition

- Autoimmune disorders
- Joint disorders

Synonym

chronic inflammation of the joints and surrounding tissues., Rheumatoid Arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Double-Blind, Phase 3, Placebo-Controlled, Rheumatoid Arthritis

Outcome measures

Primary outcome

The primary objective of the study is to determine whether baricitinib 4 mg QD

is superior to

placebo in the treatment of patients with moderately to severely active RA who

have had an inadequate response to a TNF inhibitor, despite ongoing treatment

with cDMARDs, as assessed by the proportion of patients achieving a 20%

improvement in American College of Rheumatology Criteria (ACR20) at Week 12.

Secondary outcome

Secondary study parameters/outcome of the study:

The major secondary objectives of the study are:

• to evaluate the efficacy of baricitinib 4 mg QD versus placebo as assessed by:

1. change from baseline to Week 12 in Health Assessment

Questionnaire-Disability Index (HAQ-DI) score

2 change from baseline to Week 12 in Disease Activity Score 28 (DAS28)-high

sensitivity C-reactive protein (hsCRP)

• to evaluate the efficacy of baricitinib 2 mg QD versus placebo as assessed by:

1. proportion of patients achieving ACR20 at Week 12

2. change from baseline to Week 12 in HAQ-DI score

3. change from baseline to Week 12 in DAS28-hsCRP

Please refer to section 6.2 (Secondary Objectives) page 23 of the protocol for

the complete list.

Study description

Background summary

Management of RA has improved substantially in recent years. In addition to reduction of signs and symptoms, improvement of physical function, and inhibition of structural damage, better patient outcomes and clinical remission are now considered achievable goals. Therefore, the current recommended primary target for treatment of RA should be a state of clinical remission (Smolen et al. 2010; Felson et al. 2011).
Despite a variety of approved agents for RA, complete or sustained disease remission is unusual. Conventional disease-modifying anti-rheumatic drugs (cDMARDs) have been used with some success.
In addition to cDMARDs, biological agents that block or antagonize critical inflammatory mediators, T cells, or B cells can reduce pain and swelling and provide joint protection against structural damage. The efficacy of these biologics, particularly in combination with MTX, has been shown to have a clinically important effect on the signs and symptoms of RA (Fleischmann 2005). However, disease progression can still occur even for patients who achieve apparent adequate control of their signs and symptoms with cDMARDs and/or biologic therapies (Klareskog et al. 2009; Rubbert-Roth and Finckh 2009). Accordingly, a significant unmet need remains for more effective and better tolerated treatments for RA.

Baricitinib (LY3009104) is an oral Janus kinase 1 (JAK1)/Janus kinase 2 (JAK2) selective inhibitor representing a potentially effective therapy for treatment of patients with moderately to severely active rheumatoid arthritis (RA). The rationale for the current study is to confirm the efficacy and to continue to define the safety profile of 4 mg baricitinib and 2 mg baricitinib when administered once a day (QD) to patients with RA who have had an inadequate response to or are intolerant to at least 1 biologic tumor necrosis factor (TNF) inhibitor therapy (TNF-IR patients) and who are also taking background

conventional disease-modifying antirheumatic drugs (cDMARDs) (with or without methotrexate [MTX]). The safety and tolerability data from this study are intended to inform the current understanding of the benefit-risk relationship for baricitinib in patients with RA.

Study objective

The primary objective of the study is to determine whether baricitinib 4 mg QD is superior to
placebo in the treatment of patients with moderately to severely active RA who have had an inadequate response to a TNF inhibitor, despite ongoing treatment with cDMARDs, as assessed by the proportion of patients achieving a 20% improvement in American College of Rheumatology Criteria (ACR20) at Week 12.

Study design

Study JADW will be a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, outpatient study comparing the efficacy of 4-mg and 2-mg QD oral doses of baricitinib versus placebo on signs and symptoms of RA.

A total of 525 patients will be randomized in a 1:1:1 ratio to 1 of the following 3 treatment arms: baricitinib 4 mg QD (n=175), baricitinib 2 mg QD (n=175), or placebo (n=175). All patients will continue on a background of cDMARDs. Patients with renal impairment, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2, will receive 2 mg baricitinib QD if assigned to active treatment. Patients not assigned to receive active treatment will receive matching placebo. After the Week 24 study visit, eligible patients may proceed to a separate extension study (Study I4V-MC-JADY) or to the post-treatment follow-up period of this study (Part B).

Study JADW consists of 3 parts:
• Screening: A screening period lasting from 3 to 42 days prior to Visit 2 (Week 0)
• Part A: A double-blind, placebo-controlled period from Week 0 to Week 24
• Part B: A post-treatment follow-up period.

Planned Duration of Treatment: 24 weeks
Lead-in period: 3 to 42 days
Treatment period: 24 weeks
Follow-up period: 28 days

Intervention

Baricitinib will be administered orally as a 4-mg or 2-mg tablet QD. Patients not assigned to baricitinib treatment will receive either a 4-mg or 2-mg

matching placebo tablet.

Patients will continue to take their background cDMARD therapy during the course of the study.

Study burden and risks

There may be risks or side effects either related to the drugs or the study procedures.

As of 28 March 2012, 766 adults (188 healthy volunteers, 475 patients with rheumatoid arthritis (RA), 67 subjects with psoriasis (Ps), and 36 people with damaged kidneys) from 18 to 80 years of age, plus 2 children with rare diseases, have taken baricitinib.
Baricitini) is a molecule that blocks the effects of proteins in the body called Janus kinases. Blocking these proteins can affect the immune system. One effect may be a reduction in inflammatory and autoimmune diseases such as rheumatoid arthritis (RA), psoriasis (Ps), or diabetic nephropathy. Other drugs that affect the immune system can increase the risk of infection and cancer. Baricitinib may also increase these risks.

A complete overview of the risks and discomforts related to the study drugs and the study procedures can be found in the patient information brochure.

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. are at least 18 years of age
2. have a diagnosis of adult-onset RA as defined by the ACR/EULAR 2010 Criteria for the Classification of RA (Aletaha et al. 2010)
3. have moderately to severely active RA defined as the presence of at least 6/68 tender joints and at least 6/66 swollen joints
a. If surgical treatment of a joint has been performed, that joint cannot be counted in the TJC or SJC for entry or enrollment purposes.
4. have a C-reactive protein (or hsCRP) measurement >=1 times the upper limit of normal (ULN) based on the most recent data (if available)
5. have been treated at approved doses with at least 1 biologic TNF-α inhibitor (eg, infliximab, certolizumab, golimumab, etanercept, adalimumab) for at least 3 months and in the opinion of the investigator either:
a. experienced insufficient efficacy or loss of efficacy at a dose that, in accordance with local clinical practice, is considered acceptable to adequately assess clinical response or
b. experienced intolerance of such treatment
6. have had regular use of at least 1 cDMARD for at least the 12 weeks prior to study entry at a dose that, in accordance with local clinical practice, is considered acceptable to adequately assess clinical response, as specified below:
a. The dose of MTX must have been a stable, unchanging oral dose of 7.5 to 25 mg/week (or the equivalent injectable dose) for at least the 8 weeks prior to study entry. The dose of MTX is expected to remain stable throughout the study and may be adjusted only for safety reasons.
b. For patients entering the trial on MTX doses <15 mg/week, there must be clear documentation in the medical record that higher doses of MTX were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines.
c. Local standard of care should be followed for concomitant administration of folic acid.
d. For patients entering the trial while receiving the following DMARDs, the dose must be stable for at least 8 weeks prior to study entry and not exceed the dose listed: hydroxychloroquine up to 400 mg/day; sulfasalazine up to 3000 mg/day; leflunomide (Arava®, Sanofi-Aventis) up to 20 mg/day; and azathioprine up to 150 mg/day or 2 mg/kg/day.
7. are able to read, understand, and give written informed consent

Exclusion criteria

8. have received a biologic treatment for RA such as etanercept, anakinra, infliximab, tocilizumab, certolizumab, adalimumab, golimumab or abatacept within 28 days of planned randomization; have received rituximab within 6 months of planned randomization
9. are currently receiving corticosteroids at doses >10 mg per day of prednisone (or equivalent) or have been receiving an unstable dosing regimen of corticosteroids within 2 weeks of study entry or within 6 weeks of planned randomization
10. have started treatment with NSAIDs (for which the NSAID use is intended for treatment of signs and symptoms of RA) within 2 weeks of study entry or within 6 weeks of planned randomization or have been receiving an unstable dosing regimen of NSAIDs within 2 weeks of study entry or within 6 weeks of planned randomization
11. are currently receiving concomitant treatment with MTX, hydroxychloroquine, and sulfasalazine
12. have started a new physiotherapy treatment for RA in the 2 weeks prior to study entry
13. have received any parenteral corticosteroid administered by intramuscular or intravenous (IV) injection within 2 weeks prior to study entry or within 6 weeks prior to planned randomization or are anticipated to require parenteral injection of corticosteroids during the study
14. have had 3 or more joints injected with intraarticular corticosteroids within 2 weeks prior to study entry or within 6 weeks prior to planned randomization
a. Joints injected with intraarticular corticosteroids within 2 weeks prior to study entry or within 6 weeks prior to planned randomization cannot be counted in the TJC and SJC for entry or enrollment purposes.
15. have active fibromyalgia, that in the investigator*s opinion, would make it difficult to appropriately assess RA activity for the purposes of this study;Please refer to section 8.1.2 (Exclusion criteria) page 30 of the protocol for the complete list.

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):	16-05-2013
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Baricitinib

Ethics review

Approved WMO Date:	21-11-2012
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	17-01-2013
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	21-01-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	14-05-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO	

Date:	24-05-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	20-06-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	30-09-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	11-11-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	25-11-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO	

Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	13-10-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

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	EUCTR2012-002323-15-NL
CCMO	NL42146.048.12