A Randomized, Double-Blind, Placebo- and Active Controlled, Phase 3 Study Evaluating the Efficacy and Safety of Baricitinib in Patients with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate Therapy.

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

Summary

ID

NL-OMON40030

Source
ToetsingOnline

Brief title
I4V-MC-JADV (219-427)

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- and Active Controlled, Rheumatoid Arthritis

Outcome measures

Primary outcome

The primary objective of the study is to determine whether baricitinib is superior to placebo in the treatment of patients with moderately to severely active RA despite MTX treatment (ie, MTX IR), as assessed by the proportion of patients achieving ACR20 at Week 12.

Secondary outcome

The major secondary objectives of the study are to evaluate the efficacy of baricitinib versus placebo or adalimumab as assessed by:

• change from baseline to Week 24 in structural joint damage as measured by modified Total Sharp Score (mTSS [van der Heijde method]) compared to placebo

• change from baseline to Week 12 in Health Assessment Questionnaire-Disability Index (HAQ-DI) score compared to placebo

• change from baseline to Week 12 in DAS28-high-sensitivity C-reactive protein (hsCRP) compared to placebo

Please refer to section 6.2 (Secondary Objectives) page 29 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 when administered once daily (QD) to patients with RA who have had an inadequate response to methotrexate (MTX) therapy. 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 is superior to placebo in the treatment of patients with moderately to severely active rheumatoid arthritis (RA) despite methotrexate treatment (ie, inadequate response to methotrexate [MTX-IR]), as assessed by the proportion of patients achieving a 20% improvement in American College of Rheumatology criteria

(ACR20) at Week 12.

Study design

Study I4V-MC-JADV (JADV) will be a 52-week, Phase 3, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group, outpatient study comparing the efficacy of baricitinib versus placebo on signs and symptoms, function, remission, and structural progression in patients with moderately to severely active RA who have had an insufficient response to methotrexate (MTX) and who have never been treated with a biologic disease-modifying antirheumatic drug (DMARD) (ie, MTX-IR patients). The study will include a noninferiority comparison of baricitinib versus adalimumab on signs and symptoms.

A total of 1280 patients are planned for enrollment in this study (480 to receive baricitinib, 480 to receive placebo, and 320 to receive adalimumab). After the Week 52 study visit, eligible patients may proceed to a separate extension study (Study I4V-MC-JADY) lasting for up to 2 years or to the posttreatment follow-up period of this study (Part C).

Study JADV will consist of 4 parts:
• Screening: Screening period lasting from 3 to 42 days prior to Visit 2 (Week 0)
• Part A: double-blind, placebo- and active-controlled period from Week 0 through Week 24
• Part B: double-blind, active-controlled period from Week 24 through Week 52
• Part C: posttreatment follow-up period

Planned Duration of Treatment: 52 weeks.
Screening period: 3 to 42 days
Treatment period: 52 weeks
Follow-up period: 28 days

Intervention

Baricitinib will be administered as a 4-mg tablet once daily (QD). The dose for patients with renal impairment, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2, will be 2 mg baricitinib QD.

Patients not assigned to the baricitinib treatment arm will receive either a 4-mg or 2-mg matching placebo tablet. Adalimumab (40 mg) will be administered by subcutaneous (SC) injection biweekly (ie, every 2 weeks). Patients not assigned to adalimumab will receive a matching placebo SC injection biweekly.

Patients will continue to take their background MTX 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.
Baricitinib 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 and SJC for entry or enrollment purposes.
4. have a C-reactive protein (CRP) (or hsCRP) measurement >=6 mg/L based on the most recent data (if available)
5. have had regular use of MTX 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. 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
a. 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.
b. Local standard of care should be followed for concomitant administration of folic acid.
6. are able to read, understand, and give written informed consent

Exclusion criteria

7. are currently receiving corticosteroids at doses >10 mg of prednisone per day (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
8. 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
9. are currently receiving concomitant treatment with MTX, hydroxychloroquine, and sulfasalazine
10. are currently receiving or have received cDMARDs (eg, gold salts, cyclosporine, azathioprine, or any other immunosuppressives) other than MTX, hydroxychloroquine (up to 400 mg/day), or sulfasalazine (up to 3000 mg/day) within 8 weeks prior to study entry
a. Doses of hydroxychloroquine or sulfasalazine should be stable for at least 8 weeks prior to

study entry.
b. Immunosuppression related to organ transplantation is not permitted.
11. have received leflunomide in the 12 weeks prior to study entry (or within 4 weeks prior to study entry if the standard 11 days of cholestyramine is used to washout leflunomide)
12. have started a new physiotherapy treatment for RA in the 2 weeks prior to study entry;Please refer to section 8.1.2 (Exclusion criteria) page 37 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):	04-07-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Humira
Generic name:	Adalimumab
Registration:	Yes - NL intended use
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:	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:	12-11-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	26-11-2013
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Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	28-11-2013
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	EUCTR2012-002322-73-NL
CCMO	NL42145.048.12