A Phase 3, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Rheumatoid Arthritis.

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

Summary

ID

NL-OMON47671

Source
ToetsingOnline

Brief title
RA-BEYOND /219-709

Condition

- Joint disorders

Synonym
chronic inflammation of the joints and, 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: Long-Term, Phase 3, Rheumatoid Arthritis

Outcome measures

Primary outcome

Safety:

The following safety measures will be assessed in this study:

* adverse events (AEs)

* AESI

* SAEs

* suspected unexpected serious adverse reactions (SUSARs)

* concomitant medications

* physical examinations

* vital signs (blood pressure and pulse) and physical characteristics

* standard laboratory tests (including hematology, clinical chemistry,

urinalysis, lipid profile, eGFR, iron studies, hsCRP, and ESR)

AESIs or laboratory results of special interest will include:

* severe or opportunistic infections

* venous thromboembolism (DVT/PE)

* myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, or

thrombocytopenia

* thrombocytosis

* elevations in alanine aminotransferase or aspartate aminotransferase (>3

times the upper limit of normal [ULN]) with total bilirubin (>2 times the ULN)

Patients with these laboratory-value-specified events will be identified using the same criteria for the interruption of investigational product with the exception of anemia, which will be identified using the same criteria for the discontinuation of investigational product, and thrombocytosis, which will be defined as a platelet count >600,000/*L.

Health Outcomes:

The following health outcome measures will be administered in this study:

* duration of morning joint stiffness

* EQ-5D-5L

* Quick Inventory of Depressive Symptomatology Self-Rated-16 (QIDS-SR16)

* healthcare resource utilization

Secondary outcome

Efficacy:

The following efficacy measures will be assessed in this study:

* ACR20, ACR50, and ACR70 indices

* Hybrid ACR (bounded) response measure

* DAS28-ESR and DAS28-hsCRP

* EULAR28

* mTSS (includes joint space narrowing score and bone erosion score)

* HAQ-DI

* Simplified Disease Activity Index (SDAI)

* CDAI

Study description

Background summary

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 evaluate the safety profiles and durability of effect of 2 mg and 4 mg baricitinib doses when administered once daily (QD) over an extended time period to patients with RA who have completed a previous Phase 2 or Phase 3 study of baricitinib. 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 evaluate the long-term safety and tolerability of baricitinib in patients who have completed a previous baricitinib RA study. Safety and tolerability assessments will include:
* Treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
* Temporary investigational product interruptions and permanent investigational product discontinuations
* Vital signs and laboratory evaluations (including chemistry and hematology)

The secondary objective(s) of the study are:
To evaluate in patients initially randomized to receive baricitinib in the originating study, the effect of long-term administration of baricitinib as assessed by:
* Proportion of patients who maintain an improvement of 20, 50, or 70 percent, respectively, in the American College of Rheumatology criteria (ACR20, ACR50 and ACR70) from Month 6 (of the originating study) through Months 12, 24, 36, 48, and 54 of baricitinib treatment
* Proportion of patients who maintain a Disease Activity Score modified to include the 28 diathrodial joint count (DAS28)-high sensitivity C-reactive protein (hsCRP)/DAS28 erythrocyte sedimentation rate (ESR)*3.2 and Clinical Disease Activity Index (CDAI) *10, and Health Assessment Questionnaire Disability Index (HAQ-DI) improvement *0.22 and *0.3 from Month 6 (of the originating study) through Months 12, 24, 36, 48, and 54 of baricitinib treatment
* Change from baseline of originating study to Month 12 (Study JADX), Month 24 (Studies JADX, JADV and JADZ), Month 36 (Studies JADA, JADV, and JADZ), and Month 48 (Study JADA) in structural joint damage as measured by modified Total Sharp Score (mTSS) [van der Heijde method])

* Proportion of patients with mTSS change *0 from baseline of originating study to Month 12 (Study JADX), Month 24 (Studies JADX, JADV, and JADZ), Month 36 (Studies JADA, JADV, and JADZ), and Month 48 (Study JADA)
* Change from baseline of originating study to Month 12 (Study JADX), Month 24 (Studies JADX, JADV and JADZ), Month 36 (Studies JADA, JADV, and JADZ), and Month 48 (Study JADA) in joint space narrowing and bone erosion score
* Change from baseline of originating study in duration of morning stiffness at 12, 24, 36, 48, and 54 months of baricitinib treatment
* Change from baseline of originating study through Month 24 in European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) scores
* Evaluation of healthcare resource utilization through Month 24

Similar analyses will be conducted on patients who initiated treatment with baricitinib as rescue therapy at some time during the originating study.

The exploratory objective(s) of the study are:
* To determine if treatment with baricitinib 2 mg QD maintains the low disease activity level or remission achieved with the 4 mg QD dose (ie, step-down dosing) on the following outcomes:
o Proportion of patients who maintain a CDAI score of *10 (or *2.8 if from Study JADZ) after 3 months of treatment with baricitinib 2 mg QD and with patients continuing treatment with the 4 mg QD dose
o Time to relapse (where relapse is defined as a CDAI score >10 or >2.8 if from Study JADZ) after randomization to the baricitinib 2 mg and 4 mg QD doses
* To describe the clinical course of patients initiating baricitinib at the time of enrollment in Study JADY as assessed by DAS28-hsCRP, DAS28-ESR, and CDAI at 3,6, 12, 18, and 24 months of baricitinib treatment by initial treatment allocation in the originating study.
o From placebo in Studies JADW or JADX to baricitinib in Study JADY
o From methotrexate (MTX) in Study JADZ to baricitinib in Study JADY
o From adalimumab in Study JADV to baricitinib in Study JADY
* To describe the clinical course of patients switching from MTX + baricitinib in Study JADZ to baricitinib monotherapy in Study JADY as assessed by DAS28-hsCRP, DAS28-ESR, and CDAI at 3, 6, 12, 18 and 24 months of baricitinib monotherapy

Study design

Study I4V-MC-JADY (JADY) is a Phase 3, multicenter, long term extension study evaluating the safety and efficacy of baricitinib (2 mg QD and 4 mg QD) in patients with rheumatoid arthritis for up to 2 years. Based upon longer term acceptability of the safety profile, the JADY study may be extended to allow for continued baricitinib treatment for up to 5 years. Patients who completed an originating study (Study JADA, JADZ, JADV, JADX, or JADW) may be eligible for enrollment into Study JADY. Patients from future baricitinib RA studies may also be enrolled into Study JADY. Planned enrollment will be approximately 2400 (if only the above mentioned studies are included) to 3000 patients (if

patients from future baricitinib studies are enrolled).
This study will consist of 3 parts: a screening period that will occur during the last visit of the originating study; Part A: treatment period lasting up to 2 years from enrollment into Study JADY; and Part B: posttreatment follow-up period.
Patients will receive baricitinib 4 mg QD or baricitinib 2 mg QD.

Intervention

Patients who have completed Study JADV, JADZ, JADX, or JADW will be assigned to blinded baricitinib treatment (2 mg QD or 4 mg QD), and all patients who have completed Study JADA will be assigned to receive open-label baricitinib 4 mg QD. Patients with renal impairment at baseline of the originating study (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m2) will only be eligible for dosing with baricitinib 2 mg QD. Baricitinib tablets will be administered orally.

Patients originating from Studies JADV, JADZ, JADX, or JADW and who were not previously rescued will receive either a 4 mg or 2 mg matching placebo tablet to maintain the blind of the step-down.

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

Public
Eli Lilly

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Indianapolis IN 46285
IE
Scientific
Eli Lilly

Lilly Corporate Center 1
Indianapolis IN 46285
IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. have completed the final active treatment study visit in Study I4V-MC-JADV, I4V-MC-JADZ, I4V-MC-JADX, JADW, or I4V-MC-JADA.

Exclusion criteria

1. have significant uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that developed during a previous baricitinib study that, in the opinion of the investigator, pose an unacceptable risk to the patient if investigational product continues to be administered
2. have a known hypersensitivity to baricitinib or any component of this investigational

product.
3. had investigational product permanently discontinued at any time during a previous baricitinib study
4. had temporary investigational product interruption at the final study visit of a previous baricitinib study and, in the opinion of the investigator, this poses an unacceptable risk for the patient*s participation in the study
5. have any other condition that, in the opinion of the investigator, renders the patient unable to understand the nature, scope, and possible consequences of the study or precludes the patient from following and completing the protocol
6. are females of childbearing potential who do not agree to use 2 forms of highly effective birth control when engaging in sexual intercourse while enrolled in the study and for at least 28 days following the last dose of investigational product (see protocol page 33 for definition fertile age and approved contraception)
7. are males who do not agree to use 2 forms of highly effective birth control while engaging in sexual intercourse with female partners of childbearing potential while enrolled in the study and for at least 28 days following the last dose of investigational product

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-02-2014
Enrollment:	19
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	13-06-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-06-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-09-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	24-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-02-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2018

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2012-003686-17-NL
CCMO	NL43523.048.13