ISRCTN53678960 https://doi.org/10.1186/ISRCTN53678960

Phase II proof of concept study of baricitinib in individuals who are considered at risk of developing inflammatory arthritis: ExIST

Submission date
25/06/2022

Recruitment status
Recruiting

Registration date
26/08/2022

Overall study status
Ongoing

Last Edited
12/08/2024

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
This trial is an open-label randomised control trial (RCT) comparing the effect of the investigational medicinal product Baricitinib versus standard care in a population of individuals at moderate to high risk of developing inflammatory arthritis (IA). Such individuals can be identified by the presence of CCP antibodies in the blood and other clinical features. At present, there are no effective treatments in this pathway until individuals' develop IA, which is associated with inflammation, swelling, long-term joint pain and disability. Baricitinib may be effective at preventing the development of IA by inhibiting specific enzymes involved in the development of the disease.

The purpose of this trial is therefore to understand if baricitinib can delay the onset of IA in individuals who are deemed to be at-risk of developing IA.

Who can participate?
Adults patients with a moderate to high risk of developing IA. Participants will be primarily recruited from the CCP - Next Generation study, a large existing observational study of individuals considered at risk of developing IA. All participants that consent to ExIST will be withdrawn from the CCP - Next Generation study. Participants that did not participate in the CCP Next Generation study may also be recruited.

What does the study involve?
Eligible individuals will be randomly allocated to receive either a daily 2mg oral dose of baricitinib (Arm A) or to continue with the standard of care treatment (Arm B) for 48 weeks, with a 48 week period of follow-up. This study design (i.e. an RCT) provides the best chance of establishing whether differences observed between the two groups are due to the treatment. To understand whether Baricitinib is effective, clinical measurements, blood tests, and detailed scans will be taken every 12 weeks for the entire study duration (96 weeks) in both Arm A and Arm B, and the proportion of individuals developing IA at 48 and 96 weeks will be compared.

What are the possible benefits and risks of participating?
As part of the trial, additional study visits are required over and above what would occur with standard care alone. It is also possible that additional unscheduled hospital visits will be required to enable all of the relevant safety testing to be carried out and to check the participants' progress and possible side effects. Though this may be burdensome to the participant, there is the benefit of increased supervision and disease monitoring. Visits have been kept to a minimum where possible, and investigations grouped to reduce the frequency of visits.

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
From November 2020 to October 2027

Who is funding the study?
Eli Lilly (USA)

Who is the main contact?
Prof Paul Emery, P.Emery@leeds.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Kulveer Mankia

Contact details
Leeds Institute of Rheumatic and Musculoskeletal Medicine
Chapel Allerton Hospital
Chapeltown Road
Leeds
United Kingdom
LS7 4SA
+44 113 392 ext 4884
K.S.Mankia@leeds.ac.uk

Type(s)
Public

Contact name
Dr Tim Hardy

Contact details
Leeds Institute of Rheumatic and Musculoskeletal Medicine
Chapel Allerton Hospital
Chapeltown Road
Leeds
United Kingdom
LS7 4SA

+44 113 3924396
T.Hardy@leeds.ac.uk

Type(s)
Principal investigator

Contact name
Prof Paul Emery

Contact details
Level 2, Leeds Institute of Rheumatic and Musculoskeletal Medicine
Chapel Allerton Hospital
Chapeltown Road
Leeds
United Kingdom
LS7 4SA
+44 113 392 ext 4884
P.Emery@leeds.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2017-001248-36

Integrated Research Application System (IRAS)
1004563

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RR17/93192, IRAS 1004563, CPMS 53573

Study information

Scientific Title
Phase II proof of concept study of baricitinib in individuals who are considered at risk of developing inflammatory arthritis: ExIST

Acronym
ExIST

Study objectives
1. To evaluate the ability of baricitinib to reduce the incidence of inflammatory arthritis in individuals at risk of progressing to IA.
2. To obtain proof of concept that baricitinib may improve multiple immune, clinical and imaging biomarkers in those at risk of progressing to IA, and;
3. To obtain data to inform design of trials to investigate whether T-cell subsets are valid surrogate markers for progression to disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/08/2022, East Midlands - Nottingham 2 Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA; +44 (0) 207 104 816; nottingham2.rec@hra.nhs.uk), ref: 22/EM/0154

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Inflammatory arthritis

Interventions
This trial will compare the effect of a 48-week daily dose of Baricitinib (Arm A) vs. standard care (Arm B) in a population of individuals at moderate to high risk of developing inflammatory arthritis (IA). Participants in Arm A will be given a 2 mg daily oral dose of Baricitinib for 48 weeks. Participants in Arm B will undergo standard care, which is follow-up without treatment. Participants will be randomised 1:1 to Arm A and Arm B by the Medicines Management and Pharmacy Services team at Leeds General Infirmary using a randomisation list.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
baricitinib

Primary outcome(s)
1. Proportion of individuals developing inflammatory arthritis (IA) measured according to clinical diagnosis at, or before, 48 weeks

Key secondary outcome(s))
1. Proportion of participants developing IA measured according to clinical diagnosis at, or before, 96 weeks
2. Time to develop IA measured according to clinical status between baseline and 96 weeks
3. Joint tenderness measured using mean 53 tender joint count at 48 and 96 weeks
4. CRP levels measured using blood tests at 48 and 96 weeks
5. Physician assessment of disease activity measured using median physician assessment of global disease activity visual analogue scale (VAS) at 48 and 96 weeks
6. Early morning stiffness measured using median early morning stiffness duration at 48 and 96 weeks

7. Ultrasound synovitis measured using median total ultrasound synovitis (grey scale & power Doppler) and erosion scores at 48 and 96 weeks
8. Joint erosion and joint space narrowing measured using mean van der Heijde modified Sharp score at 48 and 96 weeks
9. Median participant-reported measures measured using the following at 48 and 96 weeks:
9.2. Functional impairment (Health Assessment Questionnaire Disability Index)
9.3. Quality of life index value and general health VAS (EQ-5D-3L)
9.4. Joint symptom VAS
9.5. Pain VAS
9.6. Fatigue VAS
9.7. Work Instability (Rheumatoid Arthritis Work Instability Scale)
10. Mean T cell subset levels measured using blood tests at 48 and 96 weeks

Completion date
12/10/2027

Eligibility

Key inclusion criteria
1. Musculoskeletal symptoms and have tested positive for anti-CCP antibodies (CCP2 test)
2. Aged >18 years
3. Are able to read, understand, and give written informed consent
4. Consents to be randomised to either Baricitinib treatment or continued usual care
5. At moderate to high risk of progression to IA as calculated using a prediction model to risk stratify individuals based on the following predictors:
5.1. Tenderness of ≥1 small joint of the hands or feet defined by the physician (1 point)
5.2. Early morning stiffness duration ≥30 min (1 point)
5.3. RF and/or anti-CCP Ab concentration >3x upper limit of normal. (2 points)
Those with a score of ≥3 will be eligible to participate.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Previous diagnosis of RA or other form of inflammatory arthritis including, but not limited to SLE, psoriatic arthritis, ankylosing spondylitis, gout or pyrophosphate arthropathy and including current treatment with DMARDs or biological therapy, or a history of DMARD or biological therapy that in the opinion of the investigator constitutes a therapeutic dose

2. Clinical synovitis on clinical examination by a rheumatologist
3. Palindromic rheumatism
4. Individuals who are largely or wholly incapacitated permitting little or no self-care, such as being bedridden or confined to wheelchair
5. Presence of concomitant illness likely to require systemic steroid therapy during the study, in the opinion of the investigator
6. Co-morbidities requiring chronic treatment with immunosuppressive or immune modulating therapy
7. Treatment with an oral, intravenous, intramuscular, intrabursal or intraarticular corticosteroid within 12 weeks prior to randomization
8. Have had any major surgery within 12 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator, would pose an unacceptable risk to the screenee
9. Scheduled for or anticipating joint replacement surgery
10. History of acute allergic reactions to biologic therapies or immunoglobulins
11. Have experienced any of the following within 12 weeks of screening: myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage IV heart failure
12. Uncontrolled hypertension (≥160/95 mmHg), uncontrolled diabetes, cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia, or any other cardiovascular condition in the past 24 weeks prior to Screening, which, in the opinion of the investigator, would put the screenee at risk by participating in the study
13. Have a history or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders or any other serious and /or unstable illness that, in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data
14. Have a history of lymphoproliferative disease; or have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; or have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years
15. Have a current or recent (<4 weeks prior to baseline) viral, bacterial, fungal, or parasitic infection that is clinically serious in the opinion of the investigator
16. History of disseminated Staphylococcus aureus infection
17. History of invasive or opportunistic infection (e.g. listeriosis, pneumocystis or histoplasmosis) or immunodeficiency syndrome
18. Have symptomatic herpes simplex or have had symptomatic herpes zoster infection within 12 weeks prior to baseline
19. Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, CNS involvement, or post-herpetic neuralgia)
20. Currently on any therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex, herpes zoster and atypical mycobacteria)
21. Screenees who are ≥50 years old will be advised to have herpes zoster vaccination. Vaccination must occur >4 weeks prior to baseline. Screenees will be excluded if they are exposed to herpes zoster vaccination within 4 weeks of planned baseline.
22. In the opinion of the investigator, are at an unacceptable risk for participating in the study
23. Positive test for hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV)
24. Screenees with tuberculosis (TB), including those at high risk of TB
25. Women with positive urine pregnancy test within 48 h prior to start of investigational product. Women of childbearing potential are defined as women who have had any menstrual bleeding in the last 24 months and who have not had a hysterectomy or surgical sterilisation.
26. Mothers who are breast feeding

27. Female screenees with reproductive potential unwilling to use an acceptable method of contraception to avoid pregnancy during treatment and for at least 4 weeks after the last dose of trial medication, in the event that they are randomised to the treatment arm
28. Male screenees with a female partner of reproductive potential unwilling to use an acceptable form of contraception during treatment and for at least 4 weeks after the final dose of trial medication, in the event that they are randomised to the treatment arm
29. Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study
30. History of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within the 2 years prior to screening
31. Have previously been in another study investigating baricitinib
32. Unable or unwilling to make themselves available for the duration of the study and/or unwilling to follow study restrictions/procedures
33. Currently enrolled in, or discontinued within 4 weeks prior to screening from any other clinical trial involving an investigational product or non-approved use of a drug or device or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
34. Are investigator site personnel directly affiliated with this study and/or are their immediate families. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted
35. Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the screenee's participation in the study
36. Have been exposed to a live vaccine within 12 weeks of the anticipated first dose of study medication or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination)
37. Have screening laboratory test values, including thyroid-stimulating hormone (TSH; where clinically indicated), outside the reference range for the population or investigative site that, in the opinion of the investigator, pose an unacceptable risk for the screenee's participation in the study. TSH is routinely reviewed in patients that have received stable thyroxine replacement therapy for ≥12 weeks. This investigation and any subsequent management will be in accordance with routine clinical care and outside the context of this trial.
38. Have a hypersensitivity to the active substance or any of the excipients listed in section 6.1 of the current, approved, Summary of Product Characteristics for baricitinib
39. Have any of the following specific abnormalities on screening laboratory tests:
39.1. Haemoglobin <8·5 g/dl International System of Units [SI]: <85 g/l
39.2. White blood cells <3·0 × 103 cells/mm3 (SI: <3·0 × 109 cells/l)
39.3. Neutrophils <1·5 × 103 cells/mm3 (SI: <1·5 × 109 cells/l)
39.4. Lymphocytes <0·5 × 103 cells/mm3 (SI: <0·5 × 109 cells/l)
39.5. Platelets <100 × 103 cells/mm3 (SI: <100 × 109 cells/l)
39.6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 × ULN
39.7. Total bilirubin level ≥2 × ULN, unless the screenee has been diagnosed with Gilbert's disease and this is clearly documented
39.8. eGFR of <40 ml/min/1.73 m2

Date of first enrolment
12/12/2022

Date of final enrolment
09/12/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Industry

Funder Name
Eli Lilly and Company

Alternative Name(s)
Lilly, Eli Lilly & Company, Eli Lilly & Co., Eli Lilly And Co, Eli Lilly & Co

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study will be included in the subsequent results publication

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes