# A Phase 3, Double-Blind, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Systemic Lupus Erythematosus (SLE)

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PrimaryTo evaluate the long-term safety and tolerability of baricitinib in patients with SLE.

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

## Summary

### ID

NL-OMON49425

**Source**
ToetsingOnline

**Brief title**
I4V-MC-JAIM

### Condition

- Autoimmune disorders

**Synonym**
Lupus, SLE

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** PPD
**Source(s) of monetary or material Support:** Farmaceutische industrie

## Intervention

**Keyword:** Baricitinib, JAK1 and JAK2 inhibitor, Long-term safety, Systemic lupus erythematosus (SLE)

## Outcome measures

### Primary outcome

Safety and tolerability assessments will include:

* Proportion of patients with treatment-emergent adverse events (TEAEs),

adverse events of special interest (AESIs), and serious adverse events (SAEs).

* Proportion of patients with temporary investigational product interruptions

and permanent discontinuations.ctivity (Section 9.1.1.4).

### Secondary outcome

Proportion of patients achieving SRI-4 response through Week 156, defined as:

o Reduction of *4 points from baseline in SLEDAI-2K score; and

o No new British Isles Lupus Assessment Group (BILAG) A or no more than 1 new

BILAG B disease activity score; and

o No worsening (defined as an increase of *0.3 points [10 mm] from baseline) in

the Physician*s Global Assessment of Disease Activity.

# Study description

### Background summary

3.2. Background
Systemic lupus erythematosus is a chronic, often debilitating, multisystem, autoimmune disease that is characterized by the presence of autoreactive B cells and elevated autoantibodies, which directly damage the body*s cells and tissues. Systemic lupus erythematosus can affect multiple organ systems simultaneously or sequentially, and follows a highly variable clinical course where periods of relatively stable disease are followed by flares and/or

periods of persistently
active disease; all of which can ultimately lead to irreversible damage to tissues and organ systems.

Systemic lupus erythematosus is predominately a disease affecting women (approximately 9:1 female to male ratio), which can begin at any age but most commonly begins in adolescence or early adulthood (Yu et al. 2017). It affects 20 to 150 people per 1,000,000 people in the US (UpToDate® 2018 [WWW]) and is more common in African-Americans (Lim et al. 2014; Somers et al. 2014), with as many as 1 in 537 African-American women afflicted with SLE (Somers et al. 2014). Additionally, SLE appears to be more severe in African-Americans, Asian-Americans, and Latinos compared to Caucasians (Kaslow 1982; Alarcón et al. 2001).

Clinically, SLE presents with varying signs and symptoms, including fever, arthralgia/arthritis, skin rash, alopecia, pleuritis, pericarditis, nephritis, vasculitis, stroke, seizure, leukopenia, thrombocytopenia, anemia, photosensitivity, and the presence of autoantibodies reactive with nuclear antigens. Fatigue is the most prevalent symptom reported among patients with SLE (Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue 2007). Pain that interferes with daily living activities is also commonly reported (Özel and Argon 2015). Skin and joint disease are also among the most prevalent features of the illness. Age, African-American race/ethnicity, SLEDAI-2K score, steroid use, and hypertension were associated with transition from no damage to damage, and increase(s) in preexisting damage (Bruce et al. 2015). Over 60% of patients with SLE will develop clinically detectable organ damage within 2 to 7 years of diagnosis, as measured by the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) damage index (Cooper et al. 2007).

Improvements in earlier diagnosis, treatment regimens, and medical care over the past several decades have reduced mortality in SLE. However, patients continue to experience premature death, with cardiovascular disease being the leading cause. A recent meta-analysis of published data involving over 27,000 patients with SLE observed a 3-fold increase in the risk of death in patients with SLE compared with the general population (Yurkovich et al. 2014). Morbidity remains substantial as measured by various tools for features, such as health-related quality of life, loss of work productivity, pain, and fatigue (Ad Hoc Committee on Systemic Lupus
Erythematosus Response Criteria for Fatigue 2007; Özel and Argon 2015). Thus, there remains substantial unmet medical need for individuals who have SLE.

Standard of care for SLE includes antimalarial agents, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressive agents, and cytotoxic agents; however, there are relatively few drugs approved for the treatment of SLE. For example, in the US, approved therapies for SLE include

aspirin, antimalarials, corticosteroids, and belimumab. In general, treatment regimens are broadly similar around the world and are tailored to the severity of disease and the specific organs involved. Mild disease is often treated with low-dose corticosteroids, NSAIDs, and antimalarials; while serious, organ-threatening or life-threatening disease is typically treated with high-dose corticosteroids and immunosuppressive agents. In addition to their direct impact on disease, immunosuppressive agents are also utilized as so called *corticosteroid-sparing agents* to reduce chronic exposure to corticosteroids.

The current SoC therapies have broad effects on immune and inflammatory pathways, including host defense, and have been associated with short- and long-term morbidity. For example, long-term use of corticosteroids is associated with cataracts, osteoporosis, avascular necrosis, increased infection, cardiovascular events, hyperglycemia, and weight gain, while cyclophosphamide increases the risk of premature ovarian failure, serious infection, and cancer.

Although recent improvements in treatment regimens and medical care have reduced overall morbidity and mortality, many patients still have incompletely controlled disease, which progresses to end-stage organ involvement. In addition, the disease increases mortality and negatively impacts health-related quality of life. New treatment options with an acceptable safety profile that reduce disease activity and flares, delay organ damage, and reduce the requirement for corticosteroids and cytotoxic agents are urgently needed for patients with SLE.

Accordingly, pharmacologic interventions that target specific pathways associated with the pathology of SLE may provide novel therapeutic approaches to disease management. One of the signaling pathways implicated in SLE disease activity is the type I IFN signaling pathway. Upregulation of genes associated with the activation of type I IFN signaling, referred to as a type I IFN signature, is observed in approximately 75% of patients with SLE (Hoffman et al. 2017).
In SLE, a high type I IFN signature was associated with increased disease severity, as measured by SLEDAI score, increased anti-double-stranded deoxyribonucleic acid (anti-dsDNA), decreased complement, and increased risk of severe flares (Hoffman et al. 2017). Another cytokine implicated in the pathogenesis of SLE is IL-6. Increased expression of IL-6 has been found in murine models of SLE and in patients with SLE, and inhibition of IL-6 signaling was associated with a decrease in disease activity (Linker-Israeli et al. 1999, Illei et al. 2010). Both type I IFNs and IL-6 signal through the JAK/STAT pathway; therefore, treatment of SLE with
baricitinib or other JAK inhibitors is an area of intense interest.

**Study objective**

Primary
To evaluate the long-term safety and tolerability of baricitinib in patients with SLE.

## Study design

Study I4V-MC-JAIM [JAIM] is a Phase 3, multicenter, randomized, outpatient, long term extension trial to evaluate the long-term safety and efficacy of baricitinib in eligible patients with SLE who have completed the treatment period in an originating study (such as, Study I4V-MC-JAHZ [JAHZ] or Study I4V-MC-JAIA [JAIA]).

## Intervention

Patients randomized to active treatment, baricitinib 4-mg daily or baricitinib 2-mg daily, during Study JAHZ or Study JAIA will continue on the same, blinded, dose of baricitinib in Study JAIM. Patients randomized to placebo during Study JAHZ or Study JAIA will be randomized 1:1 to receive baricitinib 4-mg or baricitinib 2-mg daily during Study JAIM. The treatment period will last up to 156 weeks (3 years) from enrollment into Study JAIM.

## Study burden and risks

Risks associated with baricitinib

Eli Lilly and Company (Lilly) regularly reviews all important safety information for their study drugs. As of 13 August 2019, a total of 8267 people have taken 1 or more doses of baricitinib in studies. This number includes healthy people and people with arthritis, lupus (autoimmune disease), dermatitis, diabetic kidney disease, psoriasis, alopecia areata (spot baldness), and primary biliary cholangitis (autoimmune disease of the liver). Baricitinib is also being provided to children and young adult people with very rare diseases. Baricitinib is being sold in many countries around the world. It is estimated that 95100 people have taken baricitinib worldwide as of 31 July 2019. Lilly looked at the most recent data from all of these people. The risks and discomforts found are described below.

Baricitinib blocks the effects of proteins in the body called Janus kinases. Blocking these proteins can affect the immune system. Drugs that affect the immune system can increase the risk of infection and cancer. Baricitinib may also increase these risks and other risks as described below.

Infections
Upper respiratory tract infections include symptoms similar to the common cold (cough, stuffy or runny nose, scratchy or sore throat, sneezing). These have been very common during studies in people taking baricitinib. Infections that

were common include shingles and cold sores. Some people with atopic dermatitis had other rashes caused by the cold sore virus.

Serious infections requiring hospitalization have also occurred in people taking baricitinib. These were common during studies.
Unusual infections can occur in people with weakened immune systems. These infections include tuberculosis, invasive fungal infections, and some viruses. These have been uncommonly reported in people taking baricitinib.
Your doctor will decide what treatment, if any, you may need for an infection.

Cancers
Drugs that affect the immune system may increase the risk for cancer. Individual events of cancer have been reported in people taking baricitinib. The types of cancer that were most frequently reported were skin cancer, including melanoma and non-melanoma cancer types, lung cancer, and breast cancer.

Blood Clots in the Blood Vessels
Some people who received baricitinib developed blood clots in the blood vessels of their legs. These clots may then dislodge and travel to the lungs.
Baricitinib should be used with caution in people who are at high risk for blood clots in their blood vessels.
Tell your doctor if you have had blood clots in the veins of your legs or lungs in the past. The study drug will be stopped if signs or symptoms of blood clots develop.

Digestive System
Small increases in blood tests related to the liver were common in people taking baricitinib during trials. These increases were also seen when baricitinib was given along with another medicine (methotrexate) used to treat arthritis. This medicine (methotrexate) is known to be associated with effects on the liver.

Upset stomach has been commonly reported with baricitinib. This has usually been seen when first starting baricitinib. In most people, the upset stomach got better with continued baricitinib use.

Blood Tests
Higher amounts of cholesterol in the blood (good and bad cholesterol) were very common in people who took baricitinib. Higher amounts of fat in the blood were uncommon. Taking baricitinib did not increase the chance of having heart related problems such as heart disease, heart attack, heart failure, or stroke.
A higher number of parts of the blood that aid in clotting (blood platelets) were commonly reported in people taking baricitinib. These increases have not been associated with an increased risk of stroke, heart attack, or blood clots.
Small changes in blood tests related to muscle have been seen uncommonly in people treated with baricitinib. In most people with these changes, the changes

were temporary. Although there was no clear link with any muscle problems, symptoms such as muscle aches and pain were reported by some people. In people with atopic dermatitis, small changes in blood tests related to muscle were seen commonly.
Baricitinib affects your immune system. It may decrease the number of parts of the blood that aid in fighting infections (white blood cells). This decrease may increase your risk for infections. Decreases in white blood cells have been uncommon with baricitinib.

Weight Gain
People taking baricitinib gained on average 1 kg of weight over 16 weeks. Some people had weight gain greater than 1 kg.

Skin
Skin rash was commonly reported, while hives and swelling of the face or lips were uncommonly reported. Some of these reactions occurring in the first days after starting baricitinib could be due to an allergic reaction to baricitinib.

Acne has been seen uncommonly in people taking baricitinib. In people with atopic dermatitis, acne was seen commonly.

Headache
Headache was commonly reported during the first months of treatment.

Additional Information
Your doctor will frequently check your general health. Your doctor will also check your white blood cell count, platelet count, kidney function, liver function, blood tests related to muscles, and levels of blood cholesterol and fat during the study.
You should report any changes in your medical condition to your doctor. Make sure you tell your doctor about any medicine that you take, including prescription medicine, over-the-counter medicine, and herbal products.
Baricitinib is removed from the body by the kidneys. People with reduced kidney function do not remove baricitinib as quickly as those with normal kidney function. People with reduced kidney function may require a lower dose of baricitinib.

Elderly
Only a small number of people who are 75 years old or older have taken baricitinib. Based on the data in people 65 years old or older, unwanted effects appear to be the same as those seen in younger people.

Risks associated with study procedures

Risks of Blood Tests:

You may feel an uncomfortable needle prick when your blood is drawn.
For most people, needle punctures for blood draws do not cause any bad problems. However, sometimes they may cause bleeding, bruising, discomfort, infections, and/or pain where you had the blood drawn. You may also feel dizzy or faint. If you feel faint or dizzy, tell the study doctor or staff right away.

Questions on Your Well-Being:
You will be asked questions on how you feel during your treatment. You will also be asked about what you think the treatment is doing to your symptoms. Your answers, along with the answers of others in the study, will be collected to see if a new treatment will help patients in the future. The answers that you give are confidential, but there is always a risk that your answers will be read by people who should not read your personal information. You may also feel uncomfortable answering some of the questions. If you do not want to participate in answering these questions, this will not cause you to be taken off the trial.

Risks of a urine test:
You will be asked to urinate or *pee* into a small cup. The test involves only normal urination. There is usually no discomfort.
In addition to the risks named above, baricitinib and the study procedures may have other unknown risks.

## Contacts

**Public**
PPD

Bornweg 12C
Bennekom 6721 AH
NL
**Scientific**
PPD

Bornweg 12C
Bennekom 6721 AH
NL

## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

6.1. Inclusion Criteria
Patients are eligible to be included in the study only if they meet all of the following criteria at
screening:
Type of Patient and Disease Characteristics
[1] Have completed the final treatment study visit of an originating study, such as Study JAHZ or Study JAIA.
Patient Characteristics
[2] Male or nonpregnant, nonbreastfeeding female patient
a. Patients of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship
(as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with the opposite sex.
b. Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 1 week following the last dose of investigational
product. Periodic abstinence, such as calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal, are not acceptable methods of contraception.
c. Otherwise, patients of childbearing potential together with their partners must agree to use 2 effective methods of contraception, where at least 1 form is highly effective, for the entirety of the study and for at least 1 week following the last dose of investigational product.
d. The following contraception methods are considered acceptable (the patient should choose 2, and 1 must be highly effective [defined as less than 1% failure rate per year when used consistently and correctly]):
* Highly effective birth control methods:
* Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral,intravaginal, or transdermal
* Progestogen-only containing hormonal contraception associated with inhibition

of ovulation: oral, injectable, or implantable
* Intrauterine device (IUD)/intrauterine hormone-releasing system (IUS)
* Vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
* Effective birth control methods:
* Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
* Diaphragm with spermicide
* Cervical sponge
* Cervical cap with spermicide
Note: When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed. Patients of non*child-bearing potential are not required to use birth control andthey are defined as:
* Women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation)
* Post-menopausal * defined either as
* A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
* Cessation of menses for at least 1 year
* At least 6 months of spontaneous amenorrhea with folliclestimulating hormone >40 mIU/mL
* Women aged 55 years or older who are not on hormone therapy, and who have had at least 6 months of spontaneous amenorrhea
* Women aged 55 years or older who have a diagnosis of menopause
Informed Consent
[3] Must read and understand the informed consent approved by Eli Lilly and Company (Lilly), or its designee, and the institutional review board (IRB)/ethics review board (ERB) governing the site, and provide written informed consent.

## Exclusion criteria

6.2. Exclusion Criteria
Medical Conditions
[4] Have significant uncontrolled cerebro-cardiovascular (for example, myocardial infarction, unstable angina, unstable arterial hypertension, severe heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that, in the opinion of the investigator, pose an unacceptable risk to the patient if investigational product continues to be administered.
[5] Have a known hypersensitivity to baricitinib or any component of this investigational product.

[6] Had investigational product permanently discontinued at any time during a previous baricitinib study.
[7] 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.
[8] 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.
[9] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research, judged not to be scientifically or medically compatible with this study.

# Study design

## Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Masking: | Double blinded (masking used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 16-02-2021 |
| Enrollment: | 12 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Olumiant |
| Generic name: | Baricitinib |
| Registration: | Yes - NL outside intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 02-07-2020 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 23-09-2020 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 04-11-2020 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 04-12-2020 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 04-03-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 15-04-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 28-05-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 14-06-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# 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 | EUCTR2017-005028-11-NL |
| ClinicalTrials.gov | NCT03843125 |
| CCMO | NL71584.029.20 |