A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of Baricitinib in Patients with Systemic Lupus Erythematosus.

Published: 13-05-2019
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To evaluate the effect of baricitinib 4-mg QD and background standard-of-care therapy compared with placebo and background standard-of-care therapy on SLE disease activity.

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

Summary

ID

NL-OMON49315

Source
ToetsingOnline

Brief title
I4V-MC-JAHZ

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, Plus standard-of-care therapy, Systemic lupus erythematosus (SLE)

Outcome measures

Primary outcome

Proportion of patients achieving an SRI-4 response at Week 52, defined as:

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

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

BILAG B disease activity score; and

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

the Physician*s Global Assessment of Disease Activity.

Secondary outcome

* Proportion of patients achieving an SRI-4 response at Week 24.

* Proportion of patients achieving a lupus low disease activity state (LLDAS)

response at Week 52

* Proportion of patients receiving >7.5 mg prednisone (or equivalent) at

baseline able to decrease dose by >=25% to a prednisone equivalent dose of <=7.5

mg/day maintained between Week 40 and Week 52.

* Time to first severe flare over 52 weeks.

* Change from baseline in Worst Pain NRS at Week 52.

* Change from baseline in FACIT-Fatigue total score at Week 52.

* Proportion of patients achieving an SRI-4 response at Week 52.

* Proportion of patients achieving an SRI-4 response at Week 24.

* Proportion of patients achieving a lupus low disease activity state (LLDAS)

response at Week 52

* Proportion of patients receiving >7.5 mg prednisone (or equivalent) at

baseline able to decrease dose by >=25% to a prednisone equivalent dose of <=7.5

mg/day maintained between Week 40 and Week 52.

* Time to first severe flare over 52 weeks.

* Change from baseline in Worst Pain NRS at Week 52.

* Change from baseline in FACIT-Fatigue total score at Week 52

Study description

Background summary

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.

Baricitinib is an oral, reversible, selective inhibitor of Janus kinase (JAK)1 and JAK2 (Fridman et al. 2010). This activity profile suggests that baricitinib may inhibit cytokines implicated in SLE, most notably type I interferon (IFN; JAK1/tyrosine kinase [TYK]2), interleukin (IL-6; JAK1/JAK2/TYK2), and type II IFNγ, as well as other cytokines that may have a role in SLE, including IL-23 (JAK2/TYK2), granulocyte--macrophage colony stimulating factor (JAK2/JAK2) and IL-12 (JAK2/TYK2). In a recently completed Phase 2 study (I4V-MC-JAHH [JAHH]), baricitinib demonstrated clinical efficacy in patients with SLE. Baricitinib plus standard of care was superior to placebo plus standard of care in the proportion of patients achieving remission of rash and/or arthritis as defined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), as well as the proportion of patients achieving a Systemic Lupus Erythematosus Responder Index-4 (SRI-4) response at Week 24.

Given the efficacy of baricitinib demonstrated in clinical trials for treating autoimmune/autoinflammatory diseases involving joints, skin, and kidney

(including SLE), the acceptable safety profile of baricitinib observed through the current stage of development, and a continuing unmet medical need in patients with SLE, there is a compelling rationale for the initiation of a Phase 3 program to evaluate baricitinib in treatment of SLE.

Study objective

To evaluate the effect of baricitinib 4-mg QD and background standard-of-care therapy compared with placebo and background standard-of-care therapy on SLE disease activity.

Study design

Study I4V-MC-JAHZ (JAHZ) is a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled, outpatient, 52-week study evaluating the efficacy and safety of baricitinib 4-mg and 2-mg in patients with SLE receiving standard therapy. Background standard therapies for SLE include corticosteroids, antimalarials, and immunosuppressants.

Intervention

- The investigator will do a physical examination - at 2 visits;
- The investigator will make an ECG - at 1 visit;
- The investigator will take a chest X-ray - at 1 visit;
- The investigator will take urine samples and draw blood - at all 17 visits. Between 1 to 5 tubes of blood are taken each time. This is to monitor your response to the study drug and also to measure the amount of study drug that is in your body and how your body breaks it down.
- The investigator will ask you to complete a questionnaire about the symptoms of your disease at all 17 visits.

The patient will receive baricitinib tablets (either 4 mg or 2 mg), or placebo. The chance that the patient will receive baricitinib is 2 in 3.

Study burden and risks

17 times visits in 62 weeks, or 14 months. A visit will take 2 to about 4 hours
- Physical examination - at 1 visit;
- ECG - at 1 visit;
- Chest X-ray - at 1 visit;
- Draw blood - at all 17 visits;
- Questionnaires at all 17 visits

The study drug 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. The study drug

may also increase these risks and other risks as described below.

Possible side effects of the study drug:
Very Common (occur in 1 in 10 people)
• higher amounts of cholesterol in the blood
• upper respiratory tract infections

Common (1 to less than 10%)
• small increases in blood tests related to the liver
• higher number of blood platelets (parts of the blood that aid in clotting)
• cold sores and shingles
• upset stomach
• rash
• headache

Uncommon (0.1 to less than 1%)
• changes in blood tests related to muscle
• acne
• lower number of white blood cells, including special types of white blood cells (blood cells that fight infections)
• higher amounts of fat in the blood
• blood clots in veins
• shingles
• swelling of the face
• weight gain

The study drug may also have side effects that are still unknown.

Contacts

Public
PPD

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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

[1] Are at least 18 years of age., [2] Have a clinical diagnosis of SLE at least 24 weeks prior to screening., [3] Have documentation of having met at least 4 of 11 Revised Criteria for Classification of Systemic Lupus Erythematosus according to the 1997 Update of the 1982 ACR criteria for classification of SLE (Tan et al. 1982; Hochberg et al. 1997) prior to randomization., [4] Have 1 or more of the following as assessed by the central lab during screening: a positive antinuclear antibody (ANA; titer >=1:80), and/or a positive anti-dsDNA, and/or a positive anti-Smith (anti-Sm). Patients with an ANA <1:80 at screening with documentation of a historical ANA >=1:80 may be eligible, as assessed by the eligibility review committee., Note: The ANA, anti-dsDNA, and anti-Smith measurements may be repeated by the central lab once during the screening period, and the value resulting from repeat testing may be accepted for enrollment eligibility if it meets the eligibility criterion., [5] Have a total SLEDAI-2K score >=6 during screening, with at least 4 points attributed to clinical items (not including items requiring laboratory value assessment). SLEDAI-2K items requiring laboratory values should be assessed based on the results from the labs drawn during the screening period., [6] Have a clinical SLEDAI-2K score >=4 at Baseline (Visit 2); not including any items requiring laboratory value assessment., [7] Have at least 1 BILAG A score or 2 BILAG B scores during the screening period. BILAG items requiring laboratory values should be assessed based on the results from the labs drawn during the screening period., Prior/Concomitant Therapy
[8] Are receiving at least one of the following SoC medications for SLE:, a. A single antimalarial (such as hydroxychloroquine, chloroquine, quinacrine) at a stable therapeutic dose for at least 8 weeks prior to screening (Visit 1)., b. A single immunosuppressant (such as methotrexate [MTX], azathioprine, mycophenolate, tacrolimus) at a stable therapeutic dose for at least 8 weeks prior to screening (Visit 1)., c. An oral corticosteroid, initiated at least 4

weeks prior to screening (Visit 1), at a stable dose <= 40 mg/day prednisone (or equivalent) for at least 2 weeks prior to screening (Visit 1) and through baseline (Visit 2). If the patient is not receiving an antimalarial or immunosuppressant, the dose of corticosteroid must be >= 7.5 mg/day prednisone (or equivalent)., Patient Characteristics
[9] 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 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, intravaginal, or transdermal
* 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 spermacide
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 and they are defined as:
* women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation who has had either
* Cessation of menses for at least 1 year
* At least 6 months of spontaneous amenorrhea with follicle-stimulating 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
[10] 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

Medical Conditions
[1] Have severe active lupus nephritis defined clinically and/or by histologic evidence of proliferative glomerulonephritis on renal biopsy (if available) within the 24 weeks prior to screening, or urine protein/creatinine ratio >200 mg/mmol (as an estimate of approximate proteinuria >2 g/day) or eGFR (Modification of Diet in Renal Disease [MDRD]) <40 mL/min/1.73 m2 at screening, or as determined by
the eligibility review committee., Note: The lab measurements related to lupus nephritis may be repeated once by the central lab during the screening period, and the values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.,
[2] Have active CNS lupus as defined by ACR nomenclature for neuropsychiatric lupus syndromes and as captured by SLEDAI-2K (seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, and cerebrovascular accident).,
[3] Have active fibromyalgia that, in the investigator*s opinion, would make it difficult to appropriately assess SLE activity for the purposes of this study.,
[4] Have been treated for or had an active occurrence of a systemic inflammatory condition other than SLE such as, but not limited to, RA, juvenile chronic arthritis, spondyloarthropathy, Crohn*s disease, ulcerative colitis, or psoriatic arthritis within the 12 weeks prior to screening. Patients with secondary Sjögren*s syndrome are not excluded.,
[5] Have had any major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator in
consultation with Lilly or its designee, would pose an unacceptable risk to the patient.,
[6] Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the patient*s participation in the study.,
[7] Have experienced any of the following within 12 weeks of screening: VTE (DVT/pulmonary embolism [PE]), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure.,

[8] Have a history of recurrent (>= 2) VTE (DVT/PE).,
[9] 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.,
[10] Have a history of lymphoproliferative disease; have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly (other than primarily due to SLE); have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years prior to randomization. The following may be exempted:
a. Patients with cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease for at least 3 years may participate in the study.
b. Patients with basal cell or squamous epithelial skin cancers that have been completely resected with no evidence of recurrence for at least 3 years may participate in the study., [11] Have a current or recent (<4 weeks prior to randomization) clinically serious viral, bacterial, fungal, or parasitic infection or any other active or recent infection that in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study. Note: For example, a recent viral upper respiratory tract infection or uncomplicated urinary tract infection need not be considered clinically serious., [12] Have symptomatic herpes simplex at the time of randomization., [13] Have had symptomatic herpes zoster infection within 12 weeks prior to randomization., [14] Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, CNS involvement, or
post-herpetic neuralgia)., [15] Have a positive test for hepatitis B virus (HBV) defined as:
a. positive for hepatitis B surface antigen (HBsAg), or
b. positive for hepatitis B core antibody (HBcAb) and positive for hepatitis B virus deoxyribonucleic acid (HBV DNA)
Note: Patients who are HBcAb-positive and HBV DNA-negative may be enrolled in the study but will require additional HBV DNA monitoring during the study., [16] Have hepatitis C virus (HCV) infection (hepatitis C antibody-positive and HCV ribonucleic acid [RNA]-positive).
Note: Patients who have documented anti-HCV treatment for a past HCV infection AND are HCV RNA-negative may be enrolled in the study., [17] Have evidence of HIV infection and/or positive HIV antibodies., [18] Have had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB., [19] Have evidence of active TB or latent TB
a. Have evidence of active TB, defined in this study as the following:
* Positive purified protein derivative (PPD) test (>=5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, clinical features, and abnormal chest x-ray at screening.

* QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB.
Exception: patients with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray at screening (i.e., a chest x-ray performed within the past 6 months will not be accepted)., b. Have evidence of untreated/inadequately or inappropriately treated latent TB, defined in this study as the following:
* Positive PPD test, no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening; or
* If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines). If the test results are not negative, the patient will be considered to have latent TB (for purposes of this study); or
* QuantiFERON®-TB Gold test or T- SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test.
If the test results are positive, the patient will be considered to have latent TB. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study).
Exception: Patients who have evidence of latent TB may be enrolled if he or she completes at least 4 weeks of appropriate treatment prior to randomization and agrees to complete the remainder of treatment while in the trial.
Exception: Patients with a history of latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray

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:	Completed
Start date (anticipated):	14-11-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	13-05-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2021
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:	24-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2021
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	EUCTR2017-005026-37-NL
CCMO	NL69210.029.19

Study results

Date completed: 25-08-2021

Results posted: 17-01-2023

First publication
13-04-2022