A Multicenter, Long-Term Extension Study of 104 Weeks, Including a Double-Blind, Placebo-Controlled 40-Week Randomized Withdrawal-Retreatment Period, to Evaluate the Maintenance of Treatment Effect of Ixekizumab (LY2439821) in Patients with Axial Spondyloarthritis

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Primary objective:-To evaluate in patients having achieved a state of sustained remission whether the ixekizumab treatment group is superior to the placebo group in maintaining response during the randomized-withdrawal periodSecondary objectives:-To…

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

Summary

ID

NL-OMON47213

Source
ToetsingOnline

Brief title
I1F-MC-RHBY

Condition

- Joint disorders

Synonym
Axial Spondyloarthritis, Chronic Inflammatory disease affecting the spine and sacroiliac joint.

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly

Intervention

Keyword: Axial spondyloarthritis, Inflammatory, Multicenter, Phase 3

Outcome measures

Primary outcome

The proportion of patients in the randomized withdrawal population who do not

experience a flare during the randomized withdrawal retreatment period

Secondary outcome

-Change in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS score)

-The proportion of patients in the randomized withdrawal population who do not

experience a flare during the randomized withdrawal-retreatment period

-Time to flare during the randomized withdrawal-retreatment period

-Time to flare during the randomized withdrawal-retreatment period

Study description

Background summary

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton (sacroiliac joints and spine) with onset of symptoms that typically appear in the second or third decade of life. AxSpA affects up to 1.4% of the Caucasian adult population worldwide. Current standard of care for nonrad-axSpA includes regular exercise, physical therapy,

and nonsteroidal anti-inflammatory drugs (NSAIDs). TNF inhibitors have also demonstrated efficacy in nonrad-axSpA; however, they are not yet approved globally for this indication, and approximately 40% of patients only obtain a partial response on TNF inhibitors. Corticosteroid injections may also be of some benefit. Though NSAIDs are the first line of drug treatment for axSpA, they are not effective or well tolerated in all patients. In contrast to patients with RA, patients with axSpA do not respond well to conventional disease-modifying antirheumatic drugs (cDMARDs) or systemic corticosteroids. Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine interleukin-17A (IL-17A, also known as IL-17). Compelling scientific evidence exists indicating an important role of the IL-23/IL-17 pathway in axSpA pathogenesis. Recently disclosed data from Phase 3 studies with secukinumab (Cosentyx®), a drug with a similar mechanism of action (MoA) as ixekizumab, have demonstrated the effectiveness of inhibiting IL-17A in patients with radiographic-axial spondyloarthritis (rad-axSpA, also called Ankylosing Spondylitis) who were biological disease modifying antirheumatic drug (bDMARD) naive or had previously received tumor necrosis factor (TNF) inhibitors. The present study evaluates the efficacy and safety of ixekizumab in nonradiographic-axSpA (nonrad-axSpA) patients who are bDMARD naive.

Study objective

Primary objective:
-To evaluate in patients having achieved a state of sustained remission whether the ixekizumab treatment group is superior to the placebo group in maintaining response during the randomized-withdrawal period

Secondary objectives:
-To compare the combined ixekizumab treatment group to historical control for 2-year radiographic progression in spine in patients with active radiographic axSpA
-To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg every 2 weeks (Q2W) treatment group or ixekizumab 80 mg every 4 weeks (Q4W) treatment group is superior to placebo in maintaining response
-To evaluate in patients having achieved a state of sustained remission whether the combined ixekizumab treatment group is superior to the placebo group in maintaining response after treatment withdrawal
-To evaluate in patients having achieved a state of sustained remission whether the ixekizumab 80 mg Q2W treatment group or ixekizumab 80 mg Q4W treatment group is superior to placebo in maintaining response after treatment withdrawal

Study design

Study I1F-MC-RHBY (RHBY) is a Phase 3, multicenter, long-term extension study

that provides patients who have completed any of the originating studies (RHBV, RHBW, and RHBX) an opportunity to continue ixekizumab (LY2439821) treatment for up to 2 additional years. Study RHBY includes 4 study periods:

-Lead-In [Period 1]: 24 weeks (Week 0 to Week 24)
-Extension Period including Double-Blind, Placebo-Controlled, Randomized Withdrawal-Retreatment [Period 2]: 40 weeks (Week 24 to Week 64)
-Long-Term Extension Period [Period 3]: 40 weeks (Week 64 to Week 104)
-Post-Treatment Follow-Up [Period 4]: at least 12 weeks and up to 24 weeks after the date of the patient*s early termination visit (ETV) or last regularly scheduled visit

Intervention

During the Lead-In Period (Period 1; 24 weeks), patients will receive active treatment in the form of ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W (open label or blinded depending on the previous originating study).

During the Extension Period, including blinded, randomized withdrawal-retreatment (Period 2; 40 weeks):
(Group A): Patients who do not meet entry criteria for participation in the randomized withdrawal-retreatment period will continue to receive uninterrupted ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W.
(Group B): For patients having achieved a state of sustained remission who do meet the criteria for participation in the 40-week double-blind placebo-controlled randomized withdrawal-retreatment period
o Patients in the ixekizumab 80 mg Q2W treatment group will be re-randomized to either ixekizumab 80 mg Q2W or placebo. Patients who experience a flare will receive ixekizumab 80 mg Q2W.
o Patients in the ixekizumab 80 mg Q4W treatment group will be re-randomized to either ixekizumab 80 mg Q4W or placebo. Patients who experience a flare will receive ixekizumab 80 mg Q4W.

During the Long-Term Extension Period (Period 3; 40 weeks),
o (Group A): Patients in Group A will continue their assigned treatment regimen uninterrupted. Patients in Group A receiving ixekizumab 80 mg Q4W may have their dose escalated to ixekizumab 80 mg Q2W if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control.
o (Group B): Patients in Group B will continue the same treatment that they were receiving at the end of Period 2. However, if a patient experiences a flare and meets criteria for retreatment, the patient will be retreated with the ixekizumab treatment regimen (ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W) that he or she was receiving prior to withdrawal to evaluate whether the patient can regain his or her original response.
During the Long-Term Extension Period, patients in Group B receiving ixekizumab 80 mg Q4W may also have their dose escalated to ixekizumab

80 mg Q2W if the investigator determines that the patient may benefit from an increase in frequency of dosing to achieve adequate disease control.

All patients receiving at least 1 dose of investigational product will enter the Post-Treatment Follow-Up (Period 4) for a minimum of 12 weeks and up to 24 weeks after their last regularly scheduled visit (or the date of their ETV).

Study burden and risks

The Investigational Product and other medication required by Protocol and the study procedures are associated with certain risks and discomforts, as described in the patient information leaflet. The combination of experimental medicine and study procedures may be associated with additional risks or discomforts that at this point are not fully known. The most common side effects associated with lxekizumab are: Runny nose and sore throat; cold symptoms; Upper respiratory tract infection; injection site reaction; Headache; Worsening of rheumatoid arthritis; Urinary tract Infection; Sinus irritation; Injection site pain; Injection site redness; Diarrhea; Back pain; Bronchitis; High blood pressure; Dizziness; Joint pain; Cough; Nausea; Vertigo. The subjects undergo an number of study procedures such as SC injections, blood collections, TB skin test, x-rays, MRI, and ECG tests. These procedures may also be accompanied by certain risks. The procedures may also have other unknown risks. These risks are described in the Informed consent form. Selectively targeting IL-17A with ixekizumab is hypothesized to provide therapeutic benefit without unduly impacting host defenses. As such, ixekizumab may offer a therapeutic option for patients who have failed NSAIDs and for patients who have lost response, failed to respond, or are intolerant to current marketed drugs. Ixekizumab may offer a more favorable safety profile compared to currently marketed therapies.

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.Have completed the final study visit in Study RHBV, RHBW, or RHBX. (Note: Patients from Study RHBX are not eligible if they permanently discontinued ixekizumab and were receiving a TNF inhibitor).
2.Must agree to use a reliable method of birth control.
3.Have given written informed consent.

Exclusion criteria

-Have significant uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that developed during a previous ixekizumab study that, in the opinion of the investigator, pose an unacceptable risk to the patient if investigational product continues to be administered.
-Have a known hypersensitivity to ixekizumab or any component of this investigational product.
-Had investigational product permanently discontinued during a previous ixekizumab study.
-Had temporary investigational product interruption at any time during or at the final study visit of a previous ixekizumab study and, in the opinion of the investigator, restarting ixekizumab poses an unacceptable risk for the patient*s participation in the study.
-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
-Are currently enrolled in any other clinical trial 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
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):	08-03-2018
Enrollment:	7
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	07-12-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-03-2017
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-09-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-04-2018
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2016-002634-69-NL
CCMO	NL59346.048.16