A Multicenter, Randomized, Double-Blind, Placebo-Controlled 16 Week Study Followed by Long Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in TNFi-Experienced Patients with Radiographic Axial Spondyloarthritis

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PrimaryThe primary objective is to compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) versus placebo in patients with active rad-axSpA at Week 16.SecondaryThe major secondary objective is:To compare both ixekizumab regimens (80 mg Q2W or 80...

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

Summary

ID

NL-OMON43396

Source
ToetsingOnline

Brief title
I1F-MC-RHBW

Condition

- Joint disorders

Synonym
Radiographic Axial Spondyloarthritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ixekizumab (LY2439821), TNFi-Experienced Patients Radiographic Axial Spondyloarthritis

Outcome measures

Primary outcome

Proportion of patients achieving an Assessment of Spondyloarthritis

International Society 40 (ASAS40) response

Secondary outcome

- Proportion of patients achieving an ASAS20 response

- Change from baseline in Ankylosing SpondylitisDisease Activity Score (ASDAS)

- Proportion of patients achieving Bath Ankylosing Spondylitis Disease Activity

Index 50 (BASDAI50) response

- Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)

- Proportion of patients achieving ASDAS inactive disease

- Change from baseline in Short Form 36 (SF-36) physical component score (PCS)

- Change from baseline in ASAS Health Index (ASAS HI)

- Change from baseline in magnetic resonance imaging (MRI) of the spine

(Ankylosing Spondylitis Spinal Magnetic Resonance Imaging [ASSpiMRI] - Berlin

score). (This endpoint applies to MRI addendum only).

- Proportion of patients who achieve ASAS20, ASAS40, ASAS 5/6, and partial

remission by ASAS criteria

- Change from baseline in the individual components of the ASAS criteria

- Change from baseline in BASDAI

- Proportion of patients reaching BASDAI50

- Change from baseline in ASDAS

- Proportion of patients who experience clinically-important improvement (change of ASDAS from baseline >=1.1), major improvement (change of ASDAS from baseline >=2.0), or inactive disease (ASDAS score <1.3)

- Change from baseline in the measure of high sensitivity C-reactive protein (CRP)

- Change from baseline in BASFI

- Change from baseline in mobility

o Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear) and individual components

o Chest expansion

o Change from baseline in occiput to wall distance

- Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)

- Change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Score

- Incidence and severity of peripheral arthritis by tender (TJC) and swollen joint count (SJC) scores of 46/44 joints

- Incidence rate of anterior uveitis or uveitis flares

- Change from baseline in the following health outcomes measures: Fatigue

Numeric Rating Scale (NRS) score, ASAS HI score, Jenkins Sleep Evaluation Questionnaire (JSEQ), Work Productivity Activity Impairment-Spondyloarthritis (WPAI-SpA) scores, and SF-36 (both PCS and mental component scores [MCS])

All endpoints assessed at Week 16 (above) and during the 16-week placebo-controlled period (above) will continue to be assessed through Week 52 (with the exception of MRI-related endpoints).

In addition, the following endpoint is added:

- NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs)
- Onset of action and treatment response (ASAS, ASDAS, CRP, BASFI) during the placebo-controlled period
- Efficacy response rates listed below at Weeks 16 and 52 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status:
  o Proportion of patients achieving ASAS40
  o Proportion of patients achieving ASAS20
  o Proportion of patients achieving ASDAS inactive disease
- Serum trough concentrations of ixekizumab
- Model parameters for the exposure-response relationship between ixekizumab serum trough concentrations and efficacy endpoints (for example, ASAS20, ASAS40) at Weeks 16 and/or 52
- Ixekizumab serum trough concentrations associated with ADA titer sub groups

Exploratory:

Biomarkers contained in blood (including mRNA and DNA), serum, plasma, and

urine samples

Note: Other exploratory objectives and endpoints will be specified in the

statistical analysis plan (SAP).

Study description

Background summary

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton (sacroiliac joints [SIJ] and spine) (Poddubnyy 2013). AxSpA is now recognized as a single disease entity, with a subset defined by the presence of radiographically defined structural damage of the SIJ (rad-axSpA) and a subset without clear structural damage defined radiographically (nonrad-axSpA). When comparing axSpA with rheumatoid arthritis (RA), it can be noted that while RA can be divided into erosive and nonerosive or seropositive and seronegative subsets, it is well accepted that it is still one disease. AxSpA, in a similar fashion, also has subsets, and thus can be considered a single disease (Deodhar et al. 2014).

Radiographic axSpA (rad-axSpA), formerly called ankylosing spondylitis (AS), represents a disease in which there is evidence of disease features on radiographic imaging. It is a chronic inflammatory disease characterized by chronic inflammation of the axial and SIJ and variable involvement of the peripheral joints (Braun and Sieper 2007). As the disease progresses, it can lead to new bone formation in the form of syndesmophytes and joint ankylosis, primarily in the axial skeleton. Patients with rad-axSpA may also have extra-articular manifestations of the disease such as enthesitis, anterior uveitis, psoriasis, and inflammatory bowel disease, as well as comorbidities of aortitis or cardiac conduction abnormalities. Compared with the general population, patients with rad-axSpA have increased rates of work disability, unemployment, and mortality (Boonen and van der Linden 2006).

AxSpA affects up to 1.4% of the adult population worldwide (Braun and Sieper 2007; Reveille et al. 2012; Strand et al. 2013). Although the exact etiology is unknown, it has been indicated that genetic factors and several loci are likely to be involved in susceptibility to the disease (Reveille 2011). There is a strong association with the major histocompatibility complex, human leukocyte antigen (HLA)-B27. About 90% to 95% of patients with rad-axSpA

are positive for HLA-B27, and the risk of this disease developing is as high as about 5% in HLA-B27-positive individuals and substantially higher in HLA-B27-positive relatives of patients (Braun and Sieper 2007). Most of the other known genetic susceptibility comes from genes involved in cytokine production, specifically including genes in the T helper (Th)17 pathway (Maksymowych 2010; Reveille 2011).

Current standard of care for rad-axSpA includes regular exercise, physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and tumor necrosis factor (TNF) alpha inhibitors (Braun et al. 2011; Ward et al. 2015). 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 (Braun and Sieper 2009). In contrast to patients with RA, patients with axSpA do not respond well to conventional disease-modifying antirheumatic drugs (cDMARDs) including methotrexate (MTX) or systemic corticosteroids (Braun and Sieper 2009; Haibel and Specker 2009).

Tumor necrosis factor inhibitors are effective and frequently prescribed when NSAID treatment has failed or cannot be tolerated (Zochling et al. 2006). While TNF inhibitors have proven to be effective treatments for axSpA, an unmet need remains, as not all patients respond well to or tolerate TNF inhibitor treatments (van der Heijde et al. 2006; Heiberg et al. 2008; Inman et al. 2008; Glintborg et al. 2010). While TNF inhibitors have demonstrated significant impact on signs and symptoms, function, and quality of life, they have not been able to demonstrate significant effect on structural progression in prospective clinical studies. The use of these biologic therapies in various diseases also is associated with safety concerns, such as opportunistic infections, demyelinating disorders, blood dyscrasias, reactivation of tuberculosis (TB), and exacerbation of congestive heart failure (Moreland 2005; Smith et al. 2009). There remains, therefore, a significant unmet need for safer, more effective treatments for patients with axSpA (Dougados and Baeten 2011). Ixekizumab may offer an alternative treatment approach to TNF inhibitor therapy in patients with axSpA.

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). Ixekizumab treatment is administered by subcutaneous (SC) injections. Compelling scientific information exists to date suggesting an important role of the IL-23/IL-17 pathway in the pathogenesis of axSpA (Baeten et al. 2010, 2014a; Maksymowych 2010; Baraliakos et al. 2011; Reveille 2011; Yeremenko et al. 2014). The demonstration of increased IL-17 producing Th17 lymphocyte numbers and serum IL-17 levels in rad-axSpA is consistent with a direct role of Th17 lymphocytes in this disease (Wendling et al. 2007; Jandus et al. 2008; Mei et al. 2011). IL-17 secreting cells have also been detected in situ in the bone marrow of facet joints obtained from patients with rad-axSpA (Appel et al. 2008).

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 are candidates for initial systemic treatment as well as those patients who have lost response, failed to respond, or are intolerant to currently marketed drugs, and may also offer a more favorable safety profile compared to currently marketed therapies.

Study objective

Primary

The primary objective is to compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) versus placebo in patients with active rad-axSpA at Week 16.

Secondary

The major secondary objective is:
To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo at Week 16

Other secondary objectives are:
- To compare both ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo during the 16-week placebo-controlled period (Period 2)
- To determine if the effect of either ixekizumab regimen is maintained through Week 52
- To explore effect of starting dose (160 mg compared to 80 mg)
- To evaluate the incidence of anti-ixekizumab antibodies and their relationship to the efficacy of ixekizumab
- To measure ixekizumab exposure and assess the relationship between exposure and efficacy, and exposure and immunogenicity

Exploratory
* To explore biomarkers related to the disease or to the IL23/IL-17 pathway
* Note: Other exploratory objectives and endpoints will be specified in the statistical analysis plan (SAP).

Study design

Study I1F-MC-RHBW (RHBW) is a Phase 3, multicenter, randomized, double-blind, placebocontrolled, parallel-group, outpatient study examining the efficacy and safety of 2 ixekizumab treatment regimens (80 mg Q2W and 80 mg Q4W SC), as compared to placebo SC in patients with active rad-axSpA who are TNF inhibitor-experienced, during a double-blind, 16-week treatment period (Period 2). Starting doses of 80 mg and 160 mg (at Week 0) will be evaluated for each ixekizumab regimen.

Study RHBW will also evaluate long-term efficacy and safety of ixekizumab during the Extended Treatment Period (Period 3) for a total treatment duration of 1 year (52 weeks). Patients that complete Study RHBW may be eligible to enroll into a long-term study (Study I1FMC-RHBY [RHBY]) for up to 2 additional years. Patients that do not enroll into Study RHBY will complete the Post-Treatment Follow-Up Period (Period 4) in Study RHBW.

Intervention

Study RHBW has 3 treatment groups during the 16-week Blinded Treatment Dosing Period: ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, and placebo at 1:1:1 ratio. All patients randomized to an ixekizumab treatment group will receive a starting dose of ixekizumab 80 mg or 160 mg (1:1 ratio) at Week 0 followed by ixekizumab 80 mg Q4W or Q2W thereafter. All administrations are SC. Randomization will be stratified by country, baseline C-reactive protein (CRP) status (normal or elevated, elevated defined as >5.00 mg/L), and number of prior TNF inhibitors used (1 or 2). At Week 16, placebo patients will be rerandomized at a 1:1 ratio to ixekizumab 80 mg Q2W or Q4W with a 160 mg starting dose. All patients will be on an ixekizumab regimen for the Extended Treatment Period (Weeks 16 to 52). The study duration will be up to 1 year for ixekizumab administration, and up to 1 year and approximately 4 months for study participation over 4 periods ([1] Screening Period: up to 42 days; [2] Blinded Treatment Dosing Period: 16 weeks; [3] Extended Treatment Period: 36 weeks; [4] Post-Treatment Follow-Up Period: at least 12 weeks after the date of the patient*s early termination visit [ETV] or last regularly scheduled visit). Patients who complete Study RHBW may have the opportunity to continue into a long-term study instead of the Post-Treatment Follow-Up Period.

Study burden and risks

There are several risks involved with the study drug. 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 subject undergo a number of study procedures, such as filling out questionnaires, blood draws, subcutaneous Injections, x rays and genetic testing. These procedures may also be accompanied by certain risks. The procedures may also have other unknown risks.

Compelling scientific information exists to date suggesting an important role of the IL-23/IL-17 pathway in the pathogenesis of axSpA (Baeten et al. 2010, 2014a; Maksymowych 2010; Baraliakos et al. 2011; Reveille 2011; Yeremenko et al. 2014). The demonstration of increased IL-17 producing Th17 lymphocyte numbers and serum IL-17 levels in rad-axSpA is consistent with a direct role of

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from patients with rad-axSpA (Appel et al. 2008).

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 are candidates for initial systemic treatment as well as those patients who have lost
response, failed to respond, or are intolerant to currently marketed drugs, and may also offer a more favorable safety profile compared to currently marketed therapies. Wide range of dosing regimens were evaluated in Phase 2 psoriasis and RA studies and demonstrated efficacy.

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

Patients are eligible to be included in the study only if they meet all of the following criteria at screening or as specified:;Type of Patient and Disease Characteristics;[1] Have an established diagnosis of rad-axSpA with sacroiliitis defined radiographically according to the mNY criteria (van der Linden et al. 1984) based on central reading: sacroiliitis grade >=2 bilaterally or grades 3 to 4 unilaterally.;AND;At least 1 SpA feature, according to ASAS criteria (Rudwaleit et al. 2009; Sieper et al. 2009), listed in Appendix 5.;[2] Patients have a history of back pain >=3 months with age at onset <45 years.;[3] Have active rad-axSpA defined as BASDAI >=4 and total back pain >=4 (Sieper et al. 2009, Box 25 Spinal Pain) on an NRS at screening and baseline.;[4] Have had prior treatment with at least 1 and not more than 2 TNF inhibitors. The patient must have discontinued at least 1 TNF inhibitor due to either intolerance or an inadequate response (defined as: In the opinion of the investigator, the patient had an inadequate response to at least 12 weeks of treatment with a TNF inhibitor at an adequate dose). Note: The following washout periods prior to baseline randomization must be followed: etanercept >=28 days; infliximab, adalimumab, or certolizumab pegol >=60 days; golimumab >=90 days.;[5] Must have had an inadequate response, as determined by the investigator, to 2 or more NSAIDs at the therapeutic dose range for a total duration of at least 4 weeks OR have a history of intolerance to NSAIDs.;[6] Patients must have a history of prior therapy for axSpA of at least 12 weeks prior to screening. Examples of prior therapy may include but are not limited to physical therapy, NSAID, and TNF inhibitor treatment.;[7] If taking NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, the dose must be stable for at least 2 weeks prior to baseline randomization.;Patient Characteristics;[8] Are ambulatory male or female patients >=18 years of age at time of screening.;[9] Must agree to use a reliable method of birth control:
-* If a male patient, patient agrees to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of birth control include, but are not limited to, condoms with spermicide and male
sterilization.;OR
-* If a female patient is a woman of childbearing potential who tests negative for pregnancy and agrees to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of
contraception include, but are not limited to: oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive foam.;OR;- If a female patient is a woman of nonchildbearing potential, she must test negative for pregnancy and is not required to use any method of birth control. Non childbearing potential is defined as:
- Women who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation)
or
- women who are >=60 years of age
or
- Women >=40 and <60 years of age who have had a cessation of menses for >=12 months and a follicle stimulating hormone (FSH) test confirming nonchildbearing potential (>=40

mIU/mL or
>=40 IU/L).;Informed Consent;[10] Have given written informed consent approved by Lilly, or its designee, and the Investigational Review Board (IRB)/Ethical Review Board (ERB) governing the site.

Exclusion criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening or as specified:;Medical Conditions;[11] Have total ankylosis of the spine, as assessed locally, based on lateral radiographs of the cervical and lumbar spine.;[12] Have a history of other systemic inflammatory diseases that might confound the evaluations of benefit from ixekizumab therapy (such as, but not limited to, lupus, vasculitis, or RA), or other chronic pain conditions (such as, but not limited to, fibromyalgia). Note: Patients with psoriasis that do not require systemic treatment, such as, but not limited to, oral agents or biologic therapies, can be included provided these patients fulfill the entry criteria.;[13] Have active Crohn*s disease (CD) or active ulcerative colitis (UC). Note: Patients may be enrolled if they have had a history of inflammatory bowel disease, including CD and UC, but have had no exacerbation for >=6 months prior to baseline randomization and, if currently on treatment, must be on stable treatment for >=6 months prior to baseline randomization.;[14] Have evidence of active anterior uveitis (an acute episode) within the last 42 days prior to baseline randomization.;[15] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease, within 5 years prior to baseline randomization; or have active or history of malignant disease within 5 years prior to baseline randomization.;[16] Have a history of fluid overload, myocardial infarction (MI), uncompensated heart failure, or evidence of new-onset ischemic heart disease, or in the opinion of the investigator, other serious cardiac disease, within 12 weeks prior to baseline randomization.;[17] Presence of significant uncontrolled cerebrocardiovascular events (for example, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association class III/IV], or cerebrovascular accident) at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering
with the interpretation of data.;[18] Presence of any comorbid respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic disorders, at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.;[19] Presence of any neurologic or neuropsychiatric disorders at screening that, in the opinion of the investigator, poses an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.;[20] Presence of significant uncontrolled neuropsychiatric disorder; have recent history (30 days within screening visit [Visit 1] and any time between screening visit [Visit 1] and baseline randomization [Visit 2]) of a suicide attempt; or have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology-self report (16 items) (QIDSSR16)
at screening or baseline randomization; or are clinically judged by the investigator to be at risk for suicide.;[21] Have presence or personal history or family history (1st degree relative) of demyelinating disorder. Note: 1st degree means child, parent, or sibling, provided a blood

relationship exists.;[22] Patients who have:
* in the past 12 weeks prior to baseline randomization:
o had a serious infection (for example, pneumonia, cellulitis),
o have been hospitalized for an infection,
o or have received intravenous (IV) antibiotics for an infection,
or in the past 24 weeks prior to baseline randomization had a serious bone or joint infection
* or have ever had,
o an infection of an artificial joint,
o an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, Pneumocystis jirovecii pneumonia, symptomatic histoplasmosis, or coccidioidomycosis);[23] Have a known immunodeficiency or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient.;[24] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline randomization.;[25] Have any other active or recent infection within 4 weeks of baseline randomization that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study. Note: These patients may be rescreened one time >=4 weeks after resolution of symptoms.;[26] Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study.;[27] Have had surgical treatment of a joint that is to be assessed in the study within 8 weeks prior to baseline randomization or will require surgical treatment of a joint that is to be assessed in the study during the first 16 weeks of the trial.;[28] Have had any major surgery within 8 weeks prior to baseline randomization or will require major surgery during the study that, in the opinion of the investigator and in consultation with Lilly or its designee, would pose an unacceptable risk to the patient. Prior/Concurrent Therapy or Clinical Trial Experience;[29] Have received cDMARDs, and/or other therapies such as, but not limited to: gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents within 4 weeks prior to baseline randomization. Exception: MTX (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed IF at stable dose for at least 4 weeks prior to baseline randomization;AND;if used, must not be in any combination with other cDMARDs. Note: If MTX is used, local standard of care is to be followed for concomitant administration of folic acid with MTX.;[30] Use of oral corticosteroids >10 mg/day prednisone or its equivalent. Note: If patients are taking prednisone or its equivalent and the dose is <=10 mg/day, the dose must be stable for at least 4 weeks prior to baseline randomization.;[31] Have received any prior, or are currently receiving, treatment with biologic or other immunomodulatory agents, including investigational therapies (such as but not limited to Janus kinase (JAK) inhibitors, IL-1, IL-6 , IL-23, IL-17 [including ixekizumab], IL-17R, T cell, or B cell targeted therapies). Note: Previous TNF inhibitor therapy is permitted.;[32] Are currently enrolled in, have participated, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 30 days prior to screening or a period of at least 5 halflives of the last administration of the drug, whichever is longer.
Note: Investigational products that are biologic or other immunomodulatory agents are not permitted, regardless of washout period (described in criterion above).;[33] 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.;[34] Have received prior, or are currently receiving, treatment with denosumab.;[35] Have received any parenteral glucocorticoid administered by intra-articular, intramuscular, or IV injection within 6 weeks prior to baseline randomization, or for whom a parenteral injection of glucocorticosteroids is anticipated during the Blinded Treatment Dosing Period (Period 2) of the study.;[36] Use of any opiate analgesic at average daily doses >30 mg/day of morphine or its equivalent, or use of variable doses of any opiate analgesic within 6 weeks prior to baseline randomization.;[37] Had a live vaccination within 12 weeks prior to baseline randomization, or intend to have a live vaccination during the course of the study or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline randomization. Investigators are to review the vaccination status of their patients and follow the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy. Note: Killed/inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatment is unknown.;[38] Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline randomization, or intend to have this vaccination with BCG during the course of the study or within 12 months of completing treatment in this study.;Diagnostics Assessments;[39] Have a body temperature >=38°C (100.5°F) at baseline randomization. Note: These patients may be rescreened one time >=4 weeks after documented resolution of elevated temperature.;[40] Have evidence or suspicion of active or latent TB (refer to Section 5.3 of the protocol for rescreening and Section 8.4.6 of the protocol for details on determining full TB exclusion criterion).;[41] Are positive for human immunodeficiency virus serology (HIV); that is, positive for human immunodeficiency virus antibody (HIVAb).;[42] Have evidence of or test positive for hepatitis B virus (HBV) by testing positive for: 1) HBV surface antigen (HBsAg+), OR 2) anti-hepatitis B core antibody positive (HBcAb+) and are HBV DNA positive. Note: Patients who are HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 8.4.10.2. of the protocol.;[43] Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab) and 2) positive via a confirmatory test for HCV (for example, HCV-polymerase chain reaction).;[44] Have electrocardiogram (ECG) abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study.;Laboratory tests may not be repeated unless there is a technical error or clinical reason to
believe a result may need to be retested within the screening period. Laboratory tests can be repeated a maximum of 1 time, and results must be received and reviewed prior to randomization. For eligibility, the most recent lab panel must not meet any of the following criteria:;[45] At screening, have a neutrophil count <1500 cells/µL (<1.50x103/µL or <1.50 GI/L).;[46] At screening, have a lymphocyte count <800 cells/µL (<0.80x103/µL or <0.80 GI/L).;[47] At screening, have a platelet count <100,000 cells/µL (<100x103/µL or <100 GI/L).;[48] At screening, have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (>2.5xULN).;[49] At screening, have a total white blood cell (WBC) count <3000 cells/µL (<3.00x103/µL or <3.00 GI/L).;[50] At screening, have hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients. [51] Have other clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, per investigator assessment.;Other Exclusions;[52] Have donated blood >450 mL within the last 4 weeks prior

to screening, or intend to donate blood during the course of the study. Note: Patients who have donated blood may be rescreened one time >=4 weeks have passed since initial screening.;[53] Are women who are lactating or breastfeeding.;[54] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.;[55] Are Lilly employees or its designee or are employees of third-party organizations involved in the study.;[56] Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient.;[57] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.;pregnant women

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):	28-07-2016
Enrollment:	16
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:	26-01-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-04-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-10-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-03-2017

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-07-2017
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:	20-12-2017
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:	13-02-2019
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	EUCTR2015-003937-84-NL
CCMO	NL55640.048.16

Study results

Results posted: 30-10-2020

First publication
30-10-2020