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

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PrimaryThe primary objective is to compare both ixekizumab regimens (80 mg every 2 weeks [Q2W] or 80 mg every 4 weeks [Q4W]) versus placebo in patients with active radiographic axial spondyloarthritis (rad-axSpA) at Week 16.SecondaryThe major…

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

Summary

ID

NL-OMON43492

Source
ToetsingOnline

Brief title
I1F-MC-RHBV

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: Adalimumab, bDMARD-Naive Patients Radiographic Axial Spondyloarthritis, Ixekizumab (LY2439821)

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 Spondylitis Disease 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 magnetic resonance imaging (MRI) of the spine

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

score)

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

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

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 every 2 weeks [Q2W] or 80 mg every 4 weeks [Q4W]) versus placebo in patients with

active radiographic axial spondyloarthritis (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

Study design

Study I1F-MC-RHBV is a Phase 3, multicenter, randomized, double-blind, active and placebo-controlled, parallel-group, outpatient study examining the efficacy and safety of ixekizumab treatment regimens (80 mg Q2W and 80 mg Q4W SC), as compared to placebo SC in patients with active rad-axSpA who are biologic DMARD naïve, during a double-blind, 16-week treatment period. Starting doses of 80 mg and 160 mg (at Week 0) will be evaluated for each ixekizumab regimen. Adalimumab (at the approved dosing regimen of 40 mg SC Q2W) has been selected as the active control for comparison with placebo.

Study RHBV 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 RHBV may be eligible to enroll into a long-term study (Study I1F-MC-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 RHBV.

Intervention

Study RHBV has 4 treatment groups during the 16-week Blinded Treatment Dosing Period; ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, placebo, and adalimumab 40 mg Q2W at 1:1:1:1 ratio. Randomization will be stratified by country and baseline high sensitivity C-reactive protein (CRP) status (normal or elevated, elevated defined as >5.00 mg/L). 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 patients randomized to adalimumab will receive adalimumab 40 mg Q2W from Week 0 to Week 14. All administrations are SC. 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. At Week 16, adalimumab patients will be re randomized to ixekizumab 80 mg Q4W or Q2W (with a 160mg starting dose). All patients will be on an ixekizumab regimen for the Extended Treatment Period (Weeks 16 to 52) (for safety reasons, adalimumab patients will have a 6-week washout period before receiving ixekizumab). As needed, investigators can modify concomitant medication during the wash-out period to maintain symptom control. 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 RHBV 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 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.

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;Have an established diagnosis of rad-axSpA with sacroiliitis defined radiographically according to the mNY criteria
Patients have a history of back pain *3 months with age at onset <45 years
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.
Patients must have a history of prior therapy for axSpA of at least 12 weeks prior to screening. If taking NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, the dose must be stable for at least 2 weeks prior to baseline randomization.
Are ambulatory male or female patients *18 years of age at time of screening.
Have given written informed consent

Exclusion criteria

Have total ankylosis of the spine
Have received any prior, or are currently receiving, treatment with biologic or other immunomodulatory agents
Had a live vaccination within 12 weeks or have had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months

Have evidence or suspicion of active or latent TB
Have a known immunodeficiency or are immunocompromised.
Have active or history of malignant disease
Have had any major surgery within 8 weeks prior to baseline randomization, or will require major surgery during the study
Are women who are lactating or breastfeeding.
Women who are pregnant

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):	05-07-2016
Enrollment:	19
Type:	Actual

Medical products/devices used

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

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-02-2016
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:	01-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-06-2016
Application type:	Amendment
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:	18-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-01-2017
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:	21-07-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-11-2017
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)

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	EUCTR2015-003932-11-NL
CCMO	NL55638.048.16