

**EVIDENCE BRIEFING
AUGUST 2018**

Ixekizumab for axial spondyloarthritis

NIHRI ID	12614	NICE ID	9688
Developer/Company	Eli Lilly and Company Ltd	UKPS ID	644545

Licencing and market availability plans	Currently in phase III clinical trials.
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SUMMARY

Ixekizumab as subcutaneous injection is in clinical development for people with radiographic and non-radiographic axial spondyloarthritis who have not responded favourably to previous non-steroidal anti-inflammatory drug (NSAID) therapy. Axial spondyloarthritis is a chronic form of arthritis that causes significant inflammatory low back and/or buttock pain that persists more than three months. The condition affects the bones and joints at the base of the spine where it connects with the pelvis. When the disease is active, these joints become inflamed. Axial spondyloarthritis is divided into two sub-groups depending on whether the clear structural damage can (radiographic) or cannot (non-radiographic) be seen using radiographic imaging.

Ixekizumab is an engineered antibody designed to bind and obstruct the pro-inflammatory interleukin-17A (IL-17A) signalling molecule. It has been suggested that IL-17 may be a crucial mediator of inflammation in the pathway that leads to the development and progression of axial spondyloarthritis. By blocking this pathway, ixekizumab may help prevent joint inflammation, bone erosion, and bone fusion in a patient population where few alternative therapies exist in instances of previous treatment failure.

PROPOSED INDICATION

Radiographic axial spondyloarthritis (rad-axSpA) and non-radiographic axSpA (nr-axSpA) in adult patients when the response to previous non-steroidal anti-inflammatory drug (NSAID) therapy has been inadequate^a

TECHNOLOGY

DESCRIPTION

Ixekizumab (Taltz) is a humanized monoclonal antibody (IgG) that selectively binds to interleukin 17A (IL-17A). This prevents IL-17A from binding to its receptor, IL-17, thereby attenuating an inflammatory response mediated by IL-17A. It has been suggested that IL-17 may be a crucial mediator of inflammation in axSpA.^{1,2}

Compelling scientific information exists to date suggesting an important role of the IL-23/IL-17 pathway in the pathogenesis of axSpA. The demonstration of increased IL-17 producing Th17 lymphocyte numbers and serum IL-17 levels in radiographic axSpA is consistent with a direct role of Th17 lymphocytes in this disease. IL 17 secreting cells have also been detected in situ in the bone marrow of facet joints obtained from patients with radiographic axSpA. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F.³

In the phase III clinical trial (COAST-V, NCT02696785) in biological disease-modifying anti-rheumatic drugs (bDMARDs)-naïve participants with rad-axSpA, ixekizumab is administered at a starting dose of 80 or 160 mg subcutaneously (SC) at baseline followed by 80 mg ixekizumab SC every two (Q2W) or four weeks (Q4W) to week 14. This is followed by an extended treatment period of 80 mg ixekizumab given SC Q2W or Q4W from week 16 to week 52.³

This course of therapy was also employed in the phase III clinical trial (COAST-W, NCT02696798) in tumour necrosis factor (TNF) inhibitor-experienced participants with rad-axSpA.⁴ The company also noted the same dosing regimen in the phase III clinical trial (COAST-X, NCT02757352) in bDMARD-naïve participants with nr-axSpA, with treatment duration on the trial registry stated as ixekizumab SC every Q2W or Q4W to week 52.^{b,5}

INNOVATION AND/OR ADVANTAGES

For over a decade, the treatment of axSpA has focused on NSAIDs and tumour necrosis factor-alpha (TNF α) inhibitors. Through the innovative targeting of IL-17 pathways, ixekizumab offers an alternative agent in instances of treatment failure where few alternative therapies currently exist.⁶

^a Information provided by Eli Lilly and Company Ltd on UK PharmaScan

^b Company information

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ixekizumab is licensed in the EU/UK for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Ixekizumab is also licensed in the EU/UK alone or in combination with methotrexate for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more, disease-modifying anti-rheumatic drug (DMARD) therapies. Very common adverse events (occurring in >1 in 10 people) of ixekizumab include upper respiratory tract infection and injection site reactions.⁷

A phase III long-term extension study in participants with axSpA (NCT03129100) is ongoing for a period of 104 weeks in participants that have completed the final study visit in the other phase III clinical trials.⁸

PATIENT GROUP

DISEASE BACKGROUND

AxSpA is an umbrella term for a group of chronic inflammatory rheumatic diseases with primary involvement of the axial skeleton (sacroiliac joints and spine). Depending on the presence or absence of definite radiographic sacroiliitis, two major subtypes of axSpA are defined: nr-axSpA (without definite radiographic sacroiliitis) and rad-axSpA, also referred to as ankylosing spondylitis. AxSpA is characterised by the presence of active inflammation in the sacroiliac joints and in the spine, especially at the early stage, which manifests as pain and stiffness, and by new bone formation (leading to bony ankylosis) in the same areas that might result in severe limitation of spinal mobility and functional impairment.²

Axial presentations of spondyloarthritis are often misdiagnosed as mechanical low back pain, leading to delays in access to effective treatments. There is an average delay of 8.5 years between symptom onset and diagnosis, with approximately 15% of cases receiving a diagnosis within three months of initial presentation. Contrary to common misconceptions, axSpA affects similar numbers of women and men, and is not always apparent on plain x-ray.⁹ Rad-axSpA is thought to have a strong hereditary component, with the most commonly associated genetic changes in the human leucocyte antigen B27 (HLA-B27).¹⁰ However, rad-axSpA does still occur in people who are seronegative for human leucocyte antigen B27 (HLA-B27).⁹

Early diagnosis and treatment is important to prevent axSpA progression, where fusion of the spine can occur. Spinal fusion can lead to an increased risk of spinal fracture due to a restricted range of movement. Fusion may also cause a forward curvature of the spine, causing a forward-stooped posture.¹¹

There is no cure for axSpA. The primary goal of treatment is to maximise patients' long term health-related quality of life through control of symptoms, prevention of structural damage, and normalisation of function and social participation.¹²

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of rad-axSpA in England is estimated to be 100,815 people (prevalence rate of 0.238% and incident rate of 0.01%) and the prevalence of nr-axSpA in England is estimated to be 62,650 people (prevalence rate of 0.15%).^{13,14}

Limited data may exist for axSpA as a result of differing classification criteria. A 2015 study estimated the prevalence of rad-axSpA in a UK primary care population to be 1.2 % using European Spondyloarthritis Study Group (ESSG) criteria, 0.3 % using Assessment of Spondyloarthritis International Society (ASAS) criteria, and 0.15 % using Modified New York Criteria (mNY) criteria.¹⁵

According to HES data for England, there were 3,479 admissions in 2016-17 for 'ankylosing spondylitis' (ICD-10 M45.x).¹⁶

In England and Wales up to 700,000 people may suffer from inflammatory back pain (IBP). Although questions remain about the likelihood of axSpA in an individual with IBP, investigating and managing these patients (even to rule out disease) could have considerable cost implications.¹⁷

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Pharmacological therapy of axSpA should always be combined with nonpharmacological treatment including education and regular exercise/physiotherapy. NSAIDs are highly effective against the major symptoms of axSpA (pain and stiffness) and may have disease-modifying properties including delaying progression of structural damage in the spine. NSAIDs, unless contraindicated, are the treatment of choice for the majority of patients with axSpA. Beyond NSAIDs, bDMARDs may offer pain relief.^{18,19}

CURRENT TREATMENT OPTIONS

NICE treatment recommendations include:¹⁹

- Refer people with axSpA to a specialist physiotherapist to start an individualised, structured exercise programme. Consider hydrotherapy as an adjunctive therapy to manage pain and maintain or improve function for people with axSpA.
- NSAIDs at the lowest effective dose to people with pain associated with axSpA, and think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment. If an NSAID taken at the maximum tolerated dose for 2–4 weeks does not provide adequate pain relief, consider switching to another NSAID.
- Choice of biological therapy for pain relief:
 - Golimumab is recommended, within its marketing authorisation, as an option for treating severe nr-axSpA in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.
 - Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active rad-axSpA in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.
 - Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe nr-axSpA in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.
 - Secukinumab is recommended, within its marketing authorisation, as an option for treating active rad-axSpA in adults whose disease has responded inadequately to conventional therapy (NSAIDs or TNF α inhibitors).

- Do not refer people with axSpA to a complex spinal surgery service to be assessed for spinal deformity correction unless the spinal deformity is significantly affecting their quality of life and severe or progressing despite optimal non-surgical management (including physiotherapy).

PLACE OF TECHNOLOGY

If licensed ixekizumab may offer a biologic treatment option in both rad-axSpA and nr-axSpA patients who are biologic-naïve or experienced, and have had an inadequate response to previous NSAID therapy.^c

CLINICAL TRIAL INFORMATION

Trial	COAST-V, NCT02696785 , I1F-MC-RHBV, EudraCT2015-003932-11; ixekizumab vs adalimumab vs placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	Press release ²⁰ , Trial registry ³
Location	EU (not incl. UK), USA, Japan, Republic of Korea, and Taiwan
Design	Randomised, active and placebo controlled, parallel assignment
Participants	n=320 (planned); ≥18 years old; ambulatory; diagnosis of rad-axSpA with sacroiliitis; history of back pain ≥3 months with age at onset <45 years; previous inadequate response to at least 2 NSAIDs (for duration 4 weeks) or cannot tolerate NSAIDs; if taking NSAIDs be on a stable dose for at least 2 weeks prior to randomization; history of prior therapy for axSpa for at least 12 weeks prior to screening; bDMARD-Naïve
Schedule	Two treatment regimens of ixekizumab as compared to placebo SC or adalimumab SC: <ul style="list-style-type: none"> 80 or 160 milligrams (mg) ixekizumab SC at baseline followed by 80 mg ixekizumab given SC Q2W to week 14; extended treatment period of 80 mg ixekizumab given SC Q2W from week 16 to week 52. 80 or 160 mg ixekizumab given SC at baseline followed by 80 mg ixekizumab given SC Q4W to week 14; extended treatment period of 80 mg ixekizumab given SC Q4W from week 16 to week 52. Placebo given SC Q2W to week 14; extended treatment period of 80 mg ixekizumab given SC Q2W or Q4W from week 16 to week 52. 40 mg adalimumab SC for Q2W to week 14; extended treatment period of 80 mg ixekizumab given SC Q2W or Q4W from week 20 to week 52.
Follow-up	To be followed by long-term efficacy and safety extension study (NCT03129100) for a duration of 104 weeks.
Primary Outcomes	<ul style="list-style-type: none"> Proportion of participants achieving an assessment of Spondyloarthritis International Society 40 (ASAS40) response
Secondary Outcomes	<ul style="list-style-type: none"> Proportion of participants achieving an ASAS20 response Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)

^c Information provided by Eli Lilly and Company Ltd on UK PharmaScan

	<ul style="list-style-type: none"> • Proportion of participants achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) response • Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) • Proportion of participants 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 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores • Change from baseline in ASAS Health Index (ASAS HI) • Change from baseline in the measure of high sensitivity C-Reactive Protein (CRP) • Change from baseline in mobility on the Bath Ankylosing Spondylitis Metrology Index (BASMI) • Change from baseline in chest expansion • Change from baseline in occiput to wall distance • Change from baseline in MRI sacroiliac joint(s) (SIJ) Spondyloarthritis Research Consortium of Canada (SPARCC) score • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) • Change from Baseline in SPARCC enthesitis score • Change from baseline in severity of Peripheral Arthritis by Tender (TJC) and Swollen Joint Count (SJC) scores of 46/44 joints • Proportion of participants with anterior uveitis or uveitis flares • Change from baseline in the fatigue Numeric Rating Scale (NRS) score • Change from baseline in the Jenkins Sleep Evaluation Questionnaire (JSEQ) • Change from baseline in the Work Productivity Activity Impairment Spondyloarthritis (WPAI-SpA) scores • Change from baseline in ASAS-Nonsteroidal Anti-Inflammatory Drug (NSAID) score • Number of participants with anti-ixekizumab antibodies • Pharmacokinetics: Trough ixekizumab concentration at steady state (C_{trough} ss)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date August 2018

Trial	COAST-W, NCT02696798 , I1F-MC-RHBW, EudraCT2015-003937-84; ixekizumab vs placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	Trial registry ⁴
Location	EU (incl. UK), USA, Canada and other countries
Design	Randomised, placebo controlled, parallel assignment
Participants	n=300; ≥18 years old; ambulatory; diagnosis of rad-axSpA with sacroiliitis; history of back pain ≥3 months with age at onset <45 years; prior treatment

	with at least 1 and not more than 2 TNF inhibitors; previous inadequate response to at least 2 NSAIDs (for duration 4 weeks) or cannot tolerate NSAIDs; history of prior therapy for axSpa for at least 12 weeks prior to screening
Schedule	Two treatment regimens of ixekizumab as compared to placebo SC: <ul style="list-style-type: none"> • 80 or 160 mg ixekizumab SC at baseline followed by 80 mg ixekizumab given SC Q2W to week 14; extended treatment period of 80 mg ixekizumab given SC Q2W from week 16 to week 52. • 80 or 160 mg ixekizumab given SC at baseline followed by 80 mg ixekizumab given SC Q4W to week 14; extended treatment period of 80 mg ixekizumab given SC Q4W from week 16 to week 52. • Placebo given SC Q2W to week 14; extended treatment period starting dose of 160 mg ixekizumab given SC at week 16 followed by 80 mg ixekizumab given SC Q2W or Q4W from week 16 to week 52.
Follow-up	To be followed by long-term efficacy and safety extension study (NCT03129100) for a duration of 104 weeks.
Primary Outcomes	<ul style="list-style-type: none"> • Proportion of participants achieving an assessment of ASAS40 response
Secondary Outcomes	<ul style="list-style-type: none"> • Proportion of participants achieving an ASAS20 response • Change from baseline in ASDAS • Proportion of participants achieving BASDAI50 response • Change from baseline in BASFI • Proportion of participants achieving ASDAS inactive disease • Change from baseline in SF-36 PCS and MCS scores • Change from baseline in ASAS HI • Change from baseline in MRI of the spine (ASSpiMRI - Berlin Score) • Change from baseline in the measure of high sensitivity CRP • Change from baseline in mobility on the BASMI • Change from baseline in chest expansion • Change from baseline in occiput to wall distance • Change from baseline in MASES • Change from baseline in SPARCC enthesitis score • Change from baseline in severity of peripheral arthritis by TJC and SJC scores of 46/44 joints • Proportion of participants with anterior uveitis or uveitis flares • Change from baseline in the fatigue NRS score • Change from baseline in the JSEQ • Change from baseline in the WPAI-SpA scores • Change from baseline in ASAS-NSAID score • Number of participants with anti-ixekizumab antibodies • Pharmacokinetics: Ctrough ss
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date January 2019

Trial	COAST-X, NCT02757352 , I1F-MC-RHBX, EudraCT2015-003938-27; ixekizumab vs placebo; phase III
Sponsor	Eli Lilly and Company

Status	Ongoing
Source of Information	Trial registry ^b
Location	EU (not incl. UK), USA, Canada and other countries
Design	Randomised, placebo controlled, parallel assignment
Participants	n=305 (planned); ≥18 years old; ambulatory; diagnosis of nr-axSpA; history of back pain ≥3 months with age at onset <45 years; active nr-axSpA defined as BASDAI ≥4 and total back pain ≥4 on a NRS at screening and baseline; objective signs of inflammation by presence of sacroiliitis on MRI and/or presence of elevated CRP; previous inadequate response to at least 2 NSAIDs (for duration 4 weeks) or cannot tolerate NSAIDs; history of prior therapy for axSpA for at least 12 weeks prior to screening
Schedule	Two treatment regimens of SC ixekizumab, Q2W or Q4W to week 52, as compared to placebo SC. Dosing information is not stated on the trial registry.
Follow-up	To be followed by long-term efficacy and safety extension study (NCT03129100) for a duration of 104 weeks.
Primary Outcomes	<ul style="list-style-type: none"> • Proportion of participants achieving an assessment of Spondyloarthritis International Society 40 (ASAS40) response
Secondary Outcomes	<ul style="list-style-type: none"> • Proportion of participants achieving an ASAS40 response • Change from baseline in ASDAS • Change from baseline in BASFI • Change from baseline in MRI sacroiliac joint(s) SIJ SPARCC score • Percent of participants without clinically meaningful changes in background therapy • Proportion of participants achieving BASDAI • Proportion of participants achieving ASDAS inactive disease • Change from baseline in the measure of high sensitivity CRP • Change from baseline in mobility on the BASMI • Change from baseline in chest expansion • Change from baseline in occiput to wall distance • Change from baseline in MASES • Change from baseline in SPARCC enthesitis score • Change from baseline in severity of peripheral arthritis by TJC and SJC scores of 46/44 joints • Proportion of participants with anterior uveitis or uveitis flares • Change from baseline in the fatigue NRS score • Change from baseline in ASAS HI • Change from baseline in the JSEQ • Change from baseline in the WPAI-SpA scores • Change from baseline in SF-36 PCS and MCS scores • Change from baseline in ASAS-NSAID score • Number of participants with anti-ixekizumab antibodies • Pharmacokinetics: C_{trough} ss
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date March 2019

Trial	COAST-Y, NCT03129100 , I1F-MC-RHBY, EudraCT2016-002634-69; ixekizumab vs placebo; phase III extension study
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	Trial registry ⁸
Location	EU (incl. UK), USA, Canada and other countries
Design	Randomised, placebo controlled, parallel assignment
Participants	n=750 (planned); ≥18 years old; completed the final study visit in Study RHBV (NCT02696785), RHBW (NCT02696798), or RHBX (NCT02757352)
Schedule	Two treatment regimens of SC ixekizumab, scheduled dose 1 and scheduled dose 2, as compared to placebo SC. Dosing information is not stated on the trial registry.
Follow-up	This is a long-term efficacy and safety extension study of 104 wks, including a double-blind, placebo-controlled 40-wk randomized withdrawal-retreatment period.
Primary Outcomes	<ul style="list-style-type: none"> • Proportion of participants who do not experience a flare
Secondary Outcomes	<ul style="list-style-type: none"> • Change from baseline in Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) • Proportion of participants achieving ASAS20 response • Proportion of participants achieving an ASAS40 response • Proportion of participants with change of ASDAS ≥1.1 Units • Proportion of participants with inactive disease on the ASDAS (<1.3 Units) • Change from baseline in the individual components of the ASAS criteria • Proportion of participants achieving BASDAI50 response • Change from baseline in the measure of high sensitivity CRP • Change from baseline in BASFI • Change from baseline in BASMI • Change from baseline in chest expansion in centimeters • Change from baseline in occiput to wall distance • Change from baseline in MASES • Change from baseline in SPARCC enthesitis score • Change from baseline in severity of peripheral arthritis by TJC score of 46/44 joints • Change from baseline in severity of peripheral arthritis by SJC score of 46/44 joints • Proportion of participants with anterior uveitis or uveitis flares • Change from baseline in the Fatigue NRS score • Change from baseline on the QIDS-SR16 • Change from baseline in SF-36 PCS score • Change from baseline in SF-36 MCS score • Change from baseline in ASAS-HI • Change from baseline on the EQ-5D-5L • Change from baseline in the WPAI-SpA scores • Change from baseline in the JSEQ • Proportion of participants with no new syndesmophyte formation • Number of participants with anti-ixekizumab antibodies
Key Results	-
Adverse effects (AEs)	-

Expected reporting date

Estimated study completion date March 2021

ESTIMATED COST

The NHS indicative price of ixekizumab 80mg/1ml solution for injection pre-filled pen or pre-filled syringe is £1125.²¹

ADDITIONAL INFORMATION

Eli Lilly and Company Ltd

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Golimumab for treating non-radiographic axial spondyloarthritis (TA497). January 2018.
- NICE technology appraisal. Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (TA407). September 2016.
- NICE technology appraisal. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (TA383). February 2016.
- NICE guideline. Spondyloarthritis in over 16s: diagnosis and management (NG65). June 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No guidance identified.

OTHER GUIDANCE

- Assessment of Spondyloarthritis International Society (ASAS). ASAS Handbook: A Guide to Assess Spondyloarthritis. 2009²²
- The European Spondylarthropathy Study Group (ESSG). Preliminary Criteria for the Classification of Spondylarthropathy. 1991²³

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- ¹³ National Institute for Health and Care Excellence (NICE). *Resource impact report: TNF alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233) (TA383)*. Available from: <https://www.nice.org.uk/guidance/ta383/resources/resource-impact-report-pdf-2304666397> [Accessed 3 August 2018]
- ¹⁴ National Institute for Health and Care Excellence. *Resource impact report: Ankylosing spondylitis - secukinumab (after NSAIDs or TNF-alpha inhibitors) (TA407)*. Available from: <https://www.nice.org.uk/guidance/ta407/resources/resource-impact-report-pdf-2663964253> [Accessed 3 August 2018]
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