Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ixekizumab

Proprietary Product Name: Taltz

Sponsor: Eli Lilly Australia Pty Ltd

June 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
AS	Ankylosing spondylitis
ASAS	Assessment of Spondylitis International Society
ASAS HI	Assessment of Spondyloarthritis International Society Health Index
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate aminotransferase
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
bDMARD	Biologic disease modifying anti-rheumatic drug(s)
BME	Bone marrow edema
cDMARD	Conventional (non-biologic) disease modifying anti-rheumatic drug(s)
CI	Confidence interval
CL	Clearance
CRP	C-reactive protein
CSR	Clinical study report
CV	Coefficient of variation
DMARD	Disease modifying antirheumatic drug(s)
EMA	European Medicines Agency

Abbreviation	Meaning
ETV	Early termination visit
EU	European Union
FDA	Food and Drug Administration (USA)
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-reactive protein
IBD	Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
ICH	International Conference on Harmonisation
IgG4	Immunoglobulin G subclass 4
IL	Interleukin
ITT	Intent to treat
IV	Intravenous
IXE	Ixekizumab
MACE	Major adverse cerebrovascular event
MedDRA	Medical Dictionary for Regulatory Activities
mNY	Modified New York classification criteria for ankylosing spondylitis
MRI	Magnetic resonance imaging
nr-axSpA	Non-radiographic axial spondyloarthritis
NRI	Non-responders imputation
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug(s)
PBO	Placebo
PCS	Physical component summary
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)

Abbreviation	Meaning
Ps	Plaque psoriasis
PsA	Psoriatic arthritis
PSUR	Periodic Safety Update Report
PTFU	Post-treatment follow-up
Q2W	Every two weeks
Q4W	Every four weeks
RA	Rheumatoid arthritis
r-axSpA	Radiographic axial spondyloarthritis
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SF-36	Medical Outcomes Study 36 item Short Form Health Survey
SIJ	Sacroiliac joint
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
$t_{1/2}$	Half-life
TEAE	Treatment emergent adverse event(s)
TNFi	Tumour necrosis factor inhibitor
USA	United states of America
V2	Central volume of distribution
V3	Peripheral volume of distribution
V_{ss}	Steady state volume of distribution

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	6 March 2020
Date of entry onto ARTG:	11 March 2020
ARTG numbers:	253893, 253892
, *Black Triangle Scheme*	No
Active ingredient:	Ixekizumab
Product name:	Taltz
Sponsor's name and address:	Eli Lilly Australia Pty Ltd 112 Wharf Road, West Ryde NSW 2114
Dose form:	Solution for injection
Strength:	80 mg/mL
Container:	Prefilled pen, prefilled syringe
Pack size:	1, 2 or 3
Approved therapeutic use:	*Ankylosing spondylitis (radiographic axial spondyloarthritis):* *Taltz is indicated for the treatment of active ankylosing spondylitis in adult patients.*
Route of administration:	Subcutaneous
Dosage:	The recommended dose is 80 mg by subcutaneous (SC) injection every 4 weeks. Conventional disease-modifying antirheumatic drugs (cDMARD) (for example, sulfasalazine), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with ixekizumab. For further information regarding dosage, refer to the Product Information (PI).

Product background

This AusPAR describes the application by Eli Lilly Australia Pty Ltd (the sponsor) to register Taltz (ixekizumab) 80 mg/mL solution for injection for the following proposed extensions of indications:

Ankylosing spondylitis (radiographic axial spondyloarthritis)

Taltz is indicated for the treatment of active ankylosing spondylitis in adult patients.

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton including the sacroiliac joints (SIJ) and the spine. Axial spondyloarthritis is increasingly recognised as a single disease entity with two distinct subsets:

- Radiographic axial spondyloarthritis (r-axSpA; also termed ankylosing spondylitis (AS)), characterised by the presence of definitive structural damage of the SIJ on radiographs. These patients fulfil the modified New York (mNY) criteria.[1]
- Non-radiographic axial spondyloarthritis (nr-axSpA), characterised by the lack of definitive structural damage of the SIJ on radiographs. These patients do not fulfil the mNY criteria.

AS affects up to 0.5% of the population and occurs predominantly in men.[2] Disease severity varies considerably between patients. Initially, it usually affects the SIJ (sacroiliitis) before involving other areas of the spine, usually the lumbar spine and then the thoracic and cervical spine. Although primarily thought of as a spinal disease, enthesitis and arthritis of peripheral joints may occur in up to 50% of patients with AS. In addition, other organs such as the eyes, bowel, lungs, heart, and kidneys can be affected.

The Australian Therapeutic Guidelines consider symptom control with nonsteroidal anti-inflammatory drugs (NSAID) as first line therapy for AS, in combination with an appropriate exercise program and other lifestyle changes.[3] Disease modifying therapies, in particular biologic disease-modifying antirheumatic drugs (bDMARD), are added for persistent axial inflammation and enthesitis not responding to NSAIDs. Although patients may be treated with conventional disease-modifying antirheumatic drugs (cDMARD) (including sulfasalazine, methotrexate and leflunomide), these are generally considered to have limited effect on axial inflammation and to be more useful in patients with predominantly peripheral arthritis.

At the time the submission described in this AusPAR was under consideration, current treatment options in Australia for AS include NSAIDs, the interleukin (IL) -17A antibody secukinumab, and five tumour necrosis factor inhibitor (TNFi) drugs: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab.

The approved indications and dosages of bDMARDs for AS include:

- Cosentyx (secukinumab) is indicated for the treatment of adult patients with active ankylosing spondylitis.

  The recommended dose is 150 mg by subcutaneous (SC) injection with initial dosing at Week 0, Week 1, Week 2, Week 3, and Week 4 followed by the same dose every month.

[1] van der Linden S, Valkenburg HA, Cats A (1984). Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum*, 27:361–368

[2] Shaikh S. A (2007). Ankylosing spondylitis: recent breakthroughs in diagnosis and treatment. *The Journal of the Canadian Chiropractic Association,* 51(4), 249–260.

[3] Ankylosing spondylitis (published on March 2017). In: eTG complete (digital). Melbourne: Therapeutic Guidelines Limited; Accessed December 2019.

- Humira (adalimumab) is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

  The recommended dose of Humira for patients with ankylosing spondylitis is 40 mg SC administered every fortnight as a single dose.

  Glucocorticoids, salicylates, nonsteroidal anti−inflammatory drugs, analgesics or disease-modifying anti-rheumatic drugs can be continued during treatment with Humira.

- Cimzia (certolizumab pegol) is indicated for the treatment of adult patients with active, ankylosing spondylitis who have been intolerant to or have had inadequate response to at least one NSAID.

  The recommended loading dose of Cimzia for adult patients is 400 mg (given as two SC injections of 200 mg each) initially (Week 0) and at Week 2 and Week 4. After the loading dose, the recommended dose of Cimzia for adult patients with ankylosing spondylitis is 200 mg every 2 weeks or 400 mg every 4 weeks.

- Enbrel (etanercept) is indicated for the treatment of the signs and symptoms of active ankylosing spondylitis in adults.

  The recommended dose of Enbrel is 50 mg per week, given as a SC injection, either once weekly as a single 50 mg injection or twice weekly as two separate 25 mg injections given 3 to 4 days apart.

- Brenzys (etanercept) is indicated for the treatment of the signs and symptoms of active ankylosing spondylitis in adults.

  The recommended dose of Brenzys is 50 mg administered once weekly, given as a SC injection.

- Simponi and Simponi IV (golimumab) is indicated for the treatment of active ankylosing spondylitis in adult patients.

  Simponi 50 mg given as a SC injection once a month, on the same date each month.

  2 mg/kg of Simponi IV given as a 30 minute intravenous infusion at Week 0 and Week 4, then every 8 weeks thereafter.

- Remicade (infliximab) is indicated for the treatment of ankylosing spondylitis for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

  5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 weeks thereafter.

Ixekizumab is an immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds with high affinity (< 3 picomolar) and specificity to IL-17A, a key pro-inflammatory cytokine in the pathophysiology of AS. Increased numbers of IL-17A-producing cells are present in the peripheral blood of patients with AS, as well as elevated levels of IL-17 in the serum. Neutralisation of IL-17A has been shown to inhibit these increases. Ixekizumab is administered as a SC injection of 80 mg every four weeks. The sponsor had proposed that cDMARDs, anti-inflammatories and analgesics may be used concurrently with ixekizumab for the treatment of adults with active AS. At the time the TGA considered this application, ixekizumab was approved for use in Australia in specific adult populations with psoriasis (Ps) and psoriatic arthritis (PsA).

Regulatory status

Taltz received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 6 September 2016 for the following indication:

> *Plaque psoriasis*
>
> *Taltz is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*

The TGA approved an extension of indication for Taltz on 22 June 2018, for the following indication:

> *Psoriatic arthritis*
>
> *Taltz is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately, or who are intolerant, to previous DMARD therapy.*
>
> *Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g. methotrexate).*

At the time the TGA considered this application, Taltz was registered for treatment of Ps and PsA in the European Union (EU), the United States of America (USA), Canada, Switzerland, Singapore, Japan and Taiwan. Additionally, Taltz was registered for treatment of pustular psoriasis and erythrodermic psoriasis in Japan.

Taltz was approved for treatment of active AS in adults in the USA on 23 August 2019 (indications shown below), and was under review for treatment of nr-axSpA. At the time the TGA considered this application, Taltz was under review for treatment of AS in Canada, Japan and Taiwan and under review for treatment of AS and nr-axSpA in the EU and Switzerland.

The indication approved in the USA for the treatment of AS is as follows:

> *Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis.*

Product Information

The PI approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-05753-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	1 April 2019
First round evaluation completed	2 September 2019
Sponsor provides responses on questions raised in first round evaluation	30 October 2019

Description	Date
Second round evaluation completed	19 December 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	18 December 2019
Sponsor's pre-Advisory Committee response	15 January 2020
Advisory Committee meeting	7 February 2020
Registration decision (Outcome)	6 March 2020
Completion of administrative activities and registration on ARTG	11 March 2020
Number of working days from submission dossier acceptance to registration decision*	159

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier contained two Phase III efficacy and safety studies:

- Study I1F-MC-RHBV (COAST-V trial) was a multicentre, randomised, double-blind active and placebo-controlled 16 week study followed by long term evaluation of efficacy and safety of ixekizumab in bDMARD naïve patients with AS.
- Study I1F-MC-RHBW (COAST-W trial) was a multicentre, randomised, double-blind placebo-controlled 16 week study followed by long term evaluation of efficacy and safety of ixekizumab in TNFi-experienced patients with AS.

The supporting data included:

- Pharmacometric modelling that:
  - compared pharmacokinetics (PK) parameters in bDMARD naïve patients and TNFi-experienced patients with AS to previously established PK characteristics in patients with Ps and PsA;

  - used two different exposure-response models to examine the relationship between efficacy as determined by Assessment of Spondyloarthritis International Society 20 (ASAS 20) and ASAS 40 responses;[4] and blood ixekizumab concentrations;
  - considered the impact of 80 mg every two weeks (Q2W) and 80 mg every four weeks (Q4W) on the exposure-response profile; and
  - considered the impact of a 160 mg loading dose versus an 80 mg loading dose on the exposure-response profile.
- A study in patients with rheumatoid arthritis (RA) evaluated for safety only.

Pharmacology

The PK characteristics of ixekizumab in adult patients with Ps and PsA were established in prior submissions. The population pharmacokinetic (PopPK) data included in this submission consisted of measurements taken during the first 16 weeks of treatment (double-blinded, placebo-controlled) in the two Phase III clinical studies. The data analysis was conducted after the two efficacy studies were completed. The results were provided in the dossier to support using the dose regimen established previously in Ps and PsA for patients with AS.

The *post hoc* estimates (geometric mean, (coefficient of variation (CV)%)) of ixekizumab clearance (CL), steady state volume of distribution (V_{ss}) and half-life ($t_{1/2}$) in all patients treated with ixekizumab;[5] were 0.0144 L/hr (38%), 6.13 L (19%) and approximately 12 days (36%), respectively. These estimates were consistent with estimates in the Ps and PsA models (Table 2).

[4] An ASAS 20 response is defined as a ≥ 20% improvement and an absolute improvement from Baseline of ≥ 1 units (range 0 to 10) in ≥ 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of ≥ 20% and ≥ 1 unit (range 0 to 10) in the remaining domain. An ASAS 40 response is defined as a ≥ 40% improvement and an absolute improvement from Baseline of ≥ 2 units (range 0 to 10) in ≥ 3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain.

[5] This included 80 mg Q2W or 80 mg Q4W, after an 80 mg loading dose; and 80 mg Q2W or 80 mg Q4W after a 160 mg loading dose, in bDMARD-naïve patients and TNFi-experienced patients.

Table 2: PopPK for Studies I1F-MC-RHBV and I1F-MC-RHBW; comparison of model-estimated ixekizumab PK parameters between patients with radiographic axial spondyloarthritis, psoriasis and psoriatic arthritis

PK parameter[a]	r-axSpA PK analysis	Ps PK analysis[b]	PsA PK analysis[c]
CL (L/hr)	0.0144 (38%)	0.0161 (37%)	0.0147 (33%)
V_{ss} (L)	6.13 (19%)	7.11 (29%)	6.02 (18%)
$t_{½}$ (days)	12 (36%)	13 (40%)	12 (32%)
%F (range)	72 FIXED[d]	60 to 90	61 to 84[d]

CL = systemic clearance; F = bioavailability; IV = intravenous; PK = pharmacokinetics; r-axSpA = radiographic axial spondyloarthritis; Ps = plaque psoriasis; PsA = psoriatic arthritis; SC = subcutaneous; t½ = half-life calculated as 0.693*(V2+V3)/(CL*24); V_{ss} = volume of distribution at steady state calculated as V2+V3; V2 = volume of distribution for central volume of distribution; V3 = volume of distribution for peripheral volume of distribution.

[a] Data are summarised using the first occurrence of time varying post hoc individual PK parameters in each analysis. Data are reported as geometric mean (geometric CV%); [b] Parameters estimated with data from 3 Ps Studies (Studies I1F-MC-RHAG (RHAG), I1F-MC-RHAJ (RHAJ), and I1FMC-RHAZ (RHAZ)) for analysis (reported in the Ps submission); [c] The data from the 2 PsA Studies (Studies I1F-MC-RHAP and I1F-MC-RHBE) were combined with data from 3 Ps Studies (Studies RHAG, RHAJ, and RHAZ) for analysis, parameters were calculated and summarised using post hoc values from patients in the 2 PsA studies; [d] Only SC administration was evaluated in Studies I1F-MC-RHBV and I1F-MC-RHBW, therefore the typical value of bioavailability was fixed to the mean value across the Ps and PsA Phase III trials from the existing Ps/PsA model (F = 0.72) as the same formulation was utilised in all studies and no IV data are included in the r-axSpA analysis.

Although the PK simulations showed that the 160 mg starting dose resulted in higher blood ixekizumab concentrations in the initial weeks of treatment compared to the 80 mg starting dose, there was no significant difference in the clinical response. Similarly, there was no apparent difference in clinical response in patients treated with 80 mg SC Q2W compared to patients treated with 80 mg SC Q4W.

As has been noted in other patient populations treated with ixekizumab, greater body weight was associated with higher ixekizumab clearance and higher volume of distribution in patients with AS, resulting in lower trough ixekizumab concentrations. However, this apparent difference did not have a meaningful influence on the clinical responses.

Ixekizumab clearance was higher in patients with higher baseline high-sensitivity C-reactive protein (hs-CRP) levels. While the change in clearance was < 10% over the tenth to seventy-fifth percentile range of hs-CRP, the ninetieth percentile was associated with a 26.7% increase in clearance compared to clearance in a patient with median baseline hs-CRP level. The pharmacodynamics model predicted higher clinical responses to ixekizumab in patients with higher baseline hs-CRP, however clinical responses did not reflect the apparent difference.

Considering the outcomes of the two separate studies, higher trough ixekizumab concentrations were observed in bDMARD–naïve patients compared to TNFi-experienced patients, with an approximate 17% higher average clearance in TNFi-experienced patients. This was apparently reflected in clinical responses, where TNFi-experienced patients had numerically lower ASAS 20/40 response rates overall, than bDMARD-naïve patients with comparable ixekizumab concentrations.

Efficacy

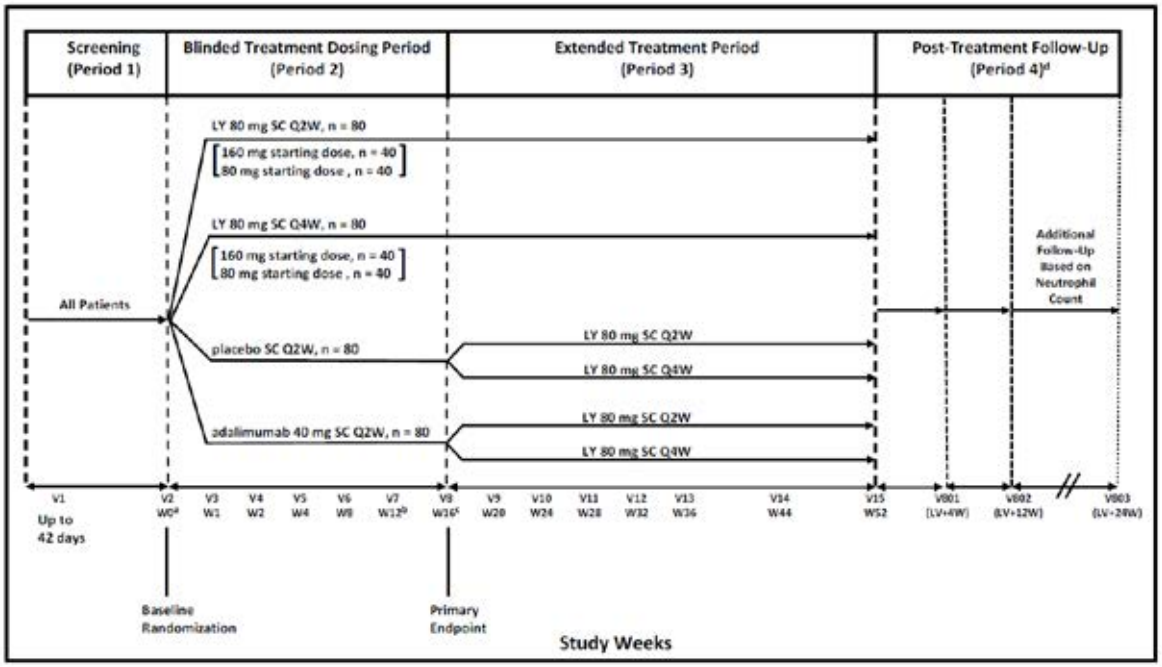
Two Phase III efficacy and safety studies were primarily designed to demonstrate the efficacy of ixekizumab versus placebo, after 16 weeks of treatment, on the signs and symptoms of AS in adults. Additional, descriptive, efficacy data was submitted for up to 52 weeks of treatment.

Study I1F-MC-RHBV (COAST-V trial)

The COAST-V trial was a randomised, double blind placebo controlled parallel group study conducted at 84 sites in 12 countries to examine the efficacy of ixekizumab in bDMARD-naïve patients with AS. This study also included an 'active control' group of patients treated with adalimumab. The study was not designed or powered to either show superiority or non-inferiority of ixekizumab to adalimumab. The primary endpoint of this study was to compare the efficacy of ixekizumab 80 mg Q2W or 80 mg Q4W to placebo at 16 weeks as measured using the ASAS 40 response. The ASAS 40 is derived from patient-reported assessments. An ASAS 40 response is defined as a ≥ 40% improvement and an absolute improvement from Baseline of ≥ 2 units (range 0 to 10) in at least three of four assessment domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domains.

Patients were randomised to one of four treatment regimens (ixekizumab 80 mg Q2W, n = 83; ixekizumab 80 mg Q4W, n = 81; adalimumab 40 mg Q2W, n = 90; placebo, n = 87). Both of the ixekizumab groups were further divided into approximately equal groups of patients who received 160 mg or 80 mg loading doses. After 16 weeks, the blinding was removed and patients receiving placebo or adalimumab were re-randomised to a dose regimen of ixekizumab 80 mg Q2W or 80 mg Q4W. Patients originally randomised to ixekizumab were retained on their starting regimens. Efficacy measures were re-evaluated at Week 52 (extended treatment period). After 52 weeks, all patients were eligible to enrol in an open-label long term follow up study for a further two years (Figure 1). A total of 331 (97.1%) randomised patients completed the blinded treatment dosing period (from Week 0 (Baseline, Visit 2) to Week 16 (Visit 8) inclusive).

Figure 1: COAST-V trial design



ETV = early termination visit; LV = last visit; LY = ixekizumab; n = number of patients in the specified category; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.

[a] All patients received 3 injections at Baseline. Patients randomised to an ixekizumab treatment group were randomised to a 160 mg or 80 mg starting dose at a 1:1 ratio (within each ixekizumab treatment group); [b] Patients in the adalimumab treatment group were re-randomised at Week 16 to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W. They received their last adalimumab dose at Week 14. Following a 6 week washout period, patients received their first ixekizumab dose at Week 20; [c] All patients received 2 injections at Week 16. Patients randomised to placebo at Week 0 began ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at Week 16 with a 160 mg starting dose; [d] Patients who discontinued from study drug for any reason and who received at least 1 dose of study drug continued to the ETV before entering the post-treatment follow-up (PTFU) period. V801 and V802 were required for all patients; V803 may have been needed depending on neutrophil counts.

Patients were included if they satisfied the following criteria: male or female (non-childbearing potential) aged ≥ 18 years; established diagnosis of r-axSpA with sacroiliitis defined radiographically (based on central reading) according to the mNY criteria and at least one SpA feature according to the ASAS criteria; bDMARD naïve; history of back pain ≥ 3 months with age of onset < 45 years; active disease defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4;[6] and total back pain ≥ 4 on NSAIDs or a history of intolerance to NSAIDs; history of prior therapy for axSpA for at least 12 weeks prior to screening. The extensive exclusion included use of cDMARDs and/or other immunosuppressive therapy within 4 weeks of Baseline (exceptions include I1F-MC-RHBV methotrexate, sulfasalazine, and hydroxychloroquine); oral corticosteroids > 10 mg/day; concurrent or prior use of biologic or other immunomodulatory agents; concurrent or recent use of denosumab, and known exposure to tuberculosis.

Results

Demographic characteristics, disease history, and baseline characteristics were well balanced across the treatment groups and consistent with a population with AS. There

[6] The BASDAI is a patient-reported assessment consisting of 6 questions that relate to 5 major symptoms relevant to AS: 1) Fatigue, 2) Spinal pain, 3) Peripheral arthritis, 4) Enthesitis, 5) Intensity of morning stiffness, and 6) Duration of morning stiffness. Patients need to score each item with a score from 0 to 10 (numerical rating scale (NRS)). BASDAI50 represents an improvement of ≥ 50% of the BASDAI score at baseline with a minimal absolute improvement of 2 units.

were no apparent differences in patient demographics and other baseline characteristics amongst the treatment groups by ixekizumab loading dose. Across all treatment groups, the mean and median baseline hs-CRP levels were 13.5 mg/L and 7.6 mg/L, respectively, and 64.4% of patients had hs-CRP level > 5.0 mg/L at Baseline. At Baseline, 91.8% of patients were receiving NSAIDs, 36.8% of patients were receiving cDMARDs (predominantly sulfasalazine), and 9.4% of patients were receiving oral corticosteroids.

The primary objective was achieved for both ixekizumab treatment groups. A significantly greater percentage of patients achieved an ASAS 40 response at Week 16 in the ixekizumab 80 mg Q2W treatment group, the ixekizumab 80 mg Q4W treatment group and in the adalimumab active reference group compared with the placebo group (see Table 3).

Table 3: COAST-V trial ASAS 40 at Week 16, intent to treat population

	PBO (N = 87)	ADA40Q2W (N = 90)	IXE80Q4W (N = 81)	IXE80Q2W (N = 83)	Total IXE (N = 164)
ASAS 40 at Week 16 (NRI)	16 (18.4%)	32 (35.6%)	39 (48.1%)	43 (51.8%)	82 (50.0%)
95% CI[*b]	(10.3%, 26.5%)	(25.7%, 45.4%)	(37.3%, 59.0%)	(41.1%, 62.6%)	
Odds ratio (95% CI) versus PBO[*a]		2.73 (1.35, 5.52)	4.45 (2.20, 9.03)	5.09 (2.52, 10.28)	
Difference (95% CI) versus PBO[*b]		17.2% (4.4%, 30.0%)	29.8% (16.2%, 43.3%)	33.4% (19.9%, 46.9%)	
p-value versus PBO[*a]		0.005	< 0.001	< 0.001	

PBO = placebo; ADA40Q2W = adalimumab 40 mg Q2W; IXE80Q4W = ixekizumab 80 mg Q4W; IXE80Q2W = ixekizumab 80 mg Q2W; N = number of patients in the analysis population; n = number of patients in the specified category; CI = confidence interval; NRI = non-responder imputation.

Note: Percentage is calculated by n/N*100%.

[*a] Logistic regression analysis with treatment, geographic region, and baseline C-reactive protein (CRP) status in the model; [*b] Confidence intervals are constructed using the simple asymptotic method, without continuity correction (that is, normal approximation to the binomial distribution).

The major secondary objectives at 16 weeks, including ASAS 20 response, Ankylosing Spondylitis Disease Activity Score (ASDAS) change from Baseline,[7] BASDAI 50 response,[8] Bath Ankylosing Spondylitis Function Index (BASFI) change from Baseline,[9] proportion of patients achieving ASDAS inactive disease, Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) spine score change from Baseline,[10] Medical Outcomes Study 36 item Short Form Health Survey (SF-36) physical component summary (PCS) score change from Baseline,[11] and Assessment of Spondyloarthritis International Society Health Index (ASAS HI) change from Baseline,[12] all demonstrated statistically significant improvements in the ixekizumab treatment groups over placebo. The loading dose of ixekizumab did not appear to have an impact on treatment effect at Week 16. The ASAS 40 response rate at 52 weeks was 53.1% in the Q4W population and 50.6% in the Q2W treatment group. ASAS 40 response rates in patients switched from placebo to ixekizumab 20 weeks after the switch (52.3%) and 36 weeks after the switch (46.5%) were similar to those reported for patients who received ixekizumab throughout the trial. ASA40 response rates in patients switched from adalimumab to ixekizumab were also around 50%.

Study I1F-MC-RHBW (COAST-W trial)

The COAST-W trial was a randomised, double blind placebo controlled parallel group study conducted at 106 sites in 15 countries to examine the efficacy of ixekizumab in patients with AS who were TNFi-experienced (defined as having had prior treatment with one or two TNFi and discontinued at least one TNFi due to intolerance, or as a result of inadequate response to at least 12 weeks of treatment in the opinion of the investigator). The primary endpoint of this study was to compare the efficacy of two ixekizumab regimens (80 mg Q2W or 80 mg Q4W) to placebo at 16 weeks as measured using the ASAS 40 response, defined earlier. The study was not designed and powered to compare the efficacy of the two dose regimens against each other.

[7] The ASDAS is a composite index to assess disease activity in AS. The parameters used for the ASDAS (with C-reactive protein (CRP) as acute phase reactant) are total back pain (BASDAI question 2), patient global, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6), and CRP in mg/L. Four disease activity states have been defined by ASAS consensus: ASDAS < 1.3 defines inactive disease; 1.3 ≤ ASDAS < 2.1 defines moderate disease activity; 2.1 ≤ ASDAS ≤ 3.5 defines high disease activity; ASDAS > 3.5 defines very high disease activity. Clinically important improvement is defined as change ≥ 1.1 units, and major improvement is defined as change ≥ 2.0 units.

[8] BASDAI 50 represents an improvement of ≥ 50% of the BASDAI score at baseline with a minimal absolute improvement of 2 units.

[9] The BASFI is a patient-reported assessment that establishes a patient's functional baseline and subsequent response to treatment. To complete the BASFI, a patient is asked to rate the difficulty associated with 10 individual basic functional activities. Patients respond to each question using a numerical rating scale (NRS) scale (range 0 to 10) with a higher score indicating worse function. The patient's final BASFI score is the mean of the 10 item scores completed on an NRS.

[10] The SPARCC MRI index is a scoring method for spine and SIJ inflammation in patients with AS. The SPARCC MRI index assess the presence, 3-dimensional extent, and signal intensity of active inflammatory lesions represented by bone marrow edema (BME), in the spine and SI joints of affected patients.

[11] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

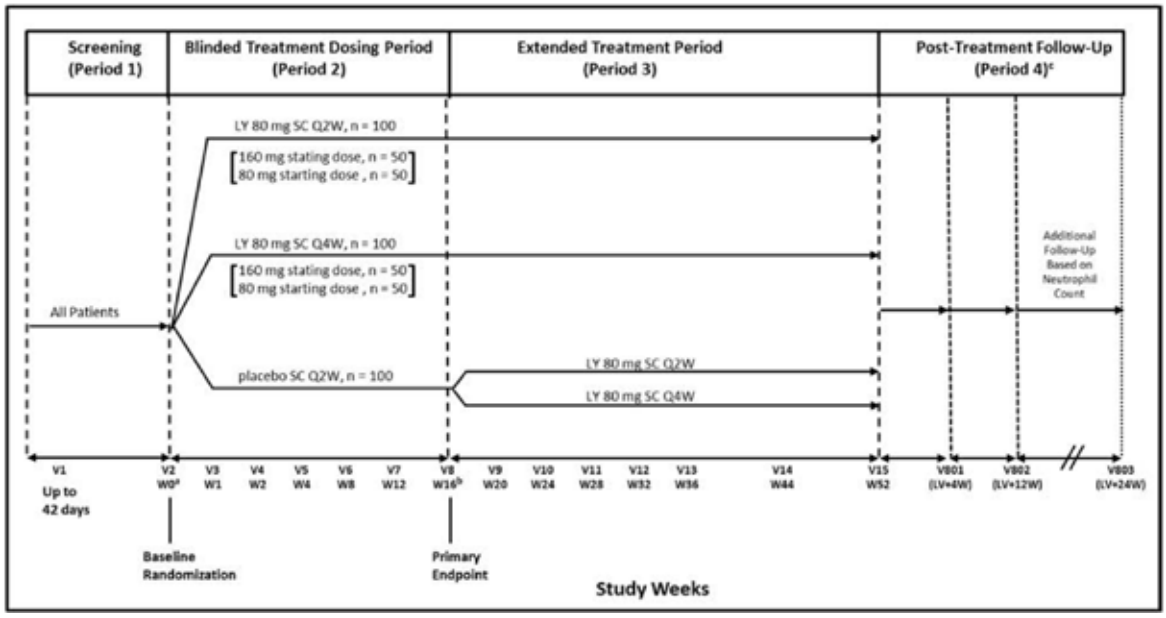
[12] The ASAS HI is a disease-specific health-index instrument designed to assess the impact of interventions for SpA, including axSpA. The 17 item instrument has scores ranging from 0 (good health) to 17 (poor health). Each item consists of one question that the patient needs to respond to with either 'I agree' (score of 1) or 'I do not agree' (score of 0). A score of '1' is given where the item is affirmed, indicating adverse health. All item scores are summed to give a total score or index.

Patients were randomised to one of three treatment regimens (ixekizumab 80 mg Q2W, n = 98; ixekizumab 80 mg Q4W, n = 114; placebo, n = 104). Both of the ixekizumab groups were further divided into equal groups of patients who received 160 mg or 80 mg starting doses. After 16 weeks, the blinding was removed and patients receiving placebo were re-randomised to a dose regime of ixekizumab 80 mg Q2W or 80 mg Q4W. Patients on ixekizumab regimens were retained on their starting regimen. Efficacy outcomes were reassessed at 52 weeks (extended treatment period, Week 17 to Week 52). After 52 weeks, all patients were eligible to enrol in an open-label long term follow up study for a further two years (see Figure 2).

A total of 282 (89.2%) randomised patients completed the blinded treatment dosing period.

The same inclusion and exclusion criteria were applied as in the COAST-V trial, other than patients in the COAST-W trial had to be TNFi-experienced.

Figure 2: COAST-W trial design



ETV = early termination visit; LV = last visit; LY = ixekizumab; n = number of patients in the specified category; PTFU = Post-Treatment Follow-Up; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.

[a] All patients received 2 injections at Baseline. Patients randomised to an ixekizumab treatment group were randomised to a 160 mg or 80 mg starting dose at a 1:1 ratio (within each ixekizumab treatment group); [b] All patients received 2 injections at Week 16. Patients randomised to placebo at Week 0 began ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at Week 16 with a 160 mg starting dose; [c] Patients who discontinued from study drug for any reason and who received at least 1 dose of study drug continued to the ETV before entering the PTFU Period. V801 and V802 were required for all patients; V803 may have been needed depending on neutrophil counts.

Results

Demographic characteristics, disease history, and baseline characteristics were generally balanced across treatment groups and consistent with a population with AS. There were no apparent differences in patient demographics and other baseline characteristics amongst the treatment groups by ixekizumab starting dose. In the study, 65.5% of enrolled patients had elevated CRP (> 5.0 mg/L) at Baseline, and 62.9% of enrolled patients had been treated with only one prior TNFi. Across all treatment groups, the mean and median baseline hs-CRP levels were 17.8 mg/L and 8.7 mg/L, respectively. Within each treatment group, around 20% had previously been treated with infliximab, between 40 and 46% had been treated with etanercept, around 40% with adalimumab, 16% with

golimumab and 10% to 15% with certolizumab pegol. At Baseline, 76.3% of patients were receiving NSAIDs, 27.2% of patients were receiving cDMARDs (sulfasalazine or methotrexate), and 11.4% of patients were receiving oral corticosteroids.

The primary objective was achieved for both ixekizumab treatment groups. A significantly greater percentage of patients achieved an ASAS 40 response at Week 16 in each of the ixekizumab treatment groups compared with the placebo group (Table 4).

Table 4: COAST-W ASAS 40 at Week 16, intent to treat population

	PBO (N = 104)	IXE80Q4W (N = 114)	IXE80Q2W (N = 98)	Total IXE (N = 212)
ASAS 40 at Week 16 (NRI), n (%)	13 (12.5%)	29 (25.4%)	30 (30.6%)	59 (27.8%)
95% CI*[b]	(6.1%, 18.9%)	(17.4%, 33.4%)	(21.5%, 39.7%)	
Odds ratio (95% CI) versus PBO*[a]		2.41 (1.17, 4.95)	3.06 (1.48, 6.33)	
Difference (95% CI) versus PBO*[b]		12.9% (2.7%, 23.2%)	18.1% (7.0%, 29.2%)	
p-value versus PBO*[a]		0.017	0.003	

PBO = Placebo; IXE80Q4W = ixekizumab 80 mg Q4W; IXE80Q2W = ixekizumab 80 mg Q2W; N = number of patients in the analysis population; n = number of patients in the specified category; CI = confidence interval; NRI = non-responder imputation.

Note: Percentage is calculated by n/N*100%.

*[a] Logistic regression analysis with treatment, geographic region, baseline CRP status and number of prior TNFi in the model; *[b] Confidence intervals are constructed using the simple asymptotic method, without continuity correction (that is, normal approximation to the binomial distribution).

Major secondary objectives at 16 weeks, including ASAS 20 response, ASDAS change from Baseline, BASDAI change from Baseline, BASFI change from Baseline, SPARCC MRI spine score change from Baseline, and SF-36 PCS score change from Baseline demonstrated statistically significant improvements in the ixekizumab treatment groups over placebo. The ASAS HI change from Baseline was significantly greater than in the placebo group for the ixekizumab 80 mg Q4W, but not for the more frequent dosing regimen. The loading dose of ixekizumab did not appear to have an impact on treatment effect at Week 16. At 52 weeks, the ASAS 40 response rate in the Q4W group was 34.2%, and in the Q2W was 30.6%. ASAS 40 response rates in patients switched from placebo to ixekizumab 20 weeks after the switch (36.6%) and 36 weeks after the switch (38.7%) were similar to those reported for patients who received ixekizumab throughout the trial.

Summary efficacy information for the integrated data for the COAST-V and COAST-W trials supported statistically significant improvements in clinical outcomes in ixekizumab treatment groups compared to placebo. The studies were not designed to compare efficacy outcomes between the two dosing regimens.

Safety

Safety data is derived from the blinded treatment periods (Week 0 to Week 16, 'primary radiographic AxSpA set', see Table 5) and the extended treatment periods (Week 17 to

Week 52) of the two pivotal studies in AS, and from one study in patients with RA (Study I1F-MC-RHAF).

Table 5: Treatment-emergent adverse events in the primary radiographic axial spondyloarthritis safety set

Treatment Group	PBO N = 190	IXE Q4W N = 195	IXE Q2W N = 181	Total IXE N = 376
Category, n (%)				
Patients with ≥ 1 TEAE	85 (44.7)	110 (56.4)[a]	96 (53.0)	206 (54.8)[a]
Upper respiratory tract infection[b]	7 (3.7)	16 (8.2)	8 (4.4)	24 (6.4)
Nasopharyngitis[b]	8 (4.2)	11 (5.6)	9 (5.0)	20 (5.3)
Injection site reaction[b]	3 (1.6)	3 (1.5)	15 (8.3)[a, c]	18 (4.8)
Diarrhoea	2 (1.1)	6 (3.1)	6 (3.3)	12 (3.2)
Arthralgia	3 (1.6)	9 (4.6)	3 (1.7)	12 (3.2)
Injection site pain[b]	4 (2.1)	4 (2.1)	5 (2.8)	9 (2.4)
Pharyngitis	2 (1.1)	3 (1.5)	5 (2.8)	8 (2.1)
Headache	1 (0.5)	3 (1.5)	4 (2.2)	7 (1.9)
Injection site erythema[b]	1 (0.5)	3 (1.5)	4 (2.2)	7 (1.9)
Pruritus	0	2 (1.0)	4 (2.2)a	6 (1.6)
Iridocyclitis	0	3 (1.5)	3 (1.7)	6 (1.6)
Back pain	3 (1.6)	1 (0.5)	4 (2.2)	5 (1.3)
Hypertension	5 (2.6)	2 (1.0)	3 (1.7)	5 (1.3)
Bronchitis	1 (0.5)	3 (1.5)	2 (1.1)	5 (1.3)
Musculoskeletal pain	2 (1.1)	4 (2.1)	1 (0.6)	5 (1.3)
Alanine aminotransferase increased	1 (0.5)	5 (2.6)	0	5 (1.3)
Oropharyngeal pain[b]	0	5 (2.6)a	0	5 (1.3)
Vulvovaginal mycotic infection[d]	0	0	1 (2.4)	1 (1.3)
Dry eye	1 (0.5)	1 (0.5)	3 (1.7)	4 (1.1)

Treatment Group	PBO N = 190	IXE Q4W N = 195	IXE Q2W N = 181	Total IXE N = 376
Rhinorrhoea	1 (0.5)	1 (0.5)	3 (1.7)	4 (1.1)
Dyspepsia	0	1 (0.5)	3 (1.7)	4 (1.1)
Malaise	0	1 (0.5)	3 (1.7)	4 (1.1)
Urinary tract infection	0	1 (0.5)	3 (1.7)	4 (1.1)
Eczema	0	2 (1.0)	2 (1.1)	4 (1.1)

ADR = adverse drug reaction; ISS = Integrated Summary of Safety; IXE = ixekizumab; IXE Q2W = ixekizumab 80 mg every 2 weeks; IXE Q4W = ixekizumab 80 mg every 4 weeks; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; Primary R-axSpA Analysis Set = Primary Radiographic axSpA Placebo-Controlled Integrated Analysis Set; TEAE = treatment-emergent adverse event.

[a] $p < 0.05$ versus PBO; [b] Upper respiratory tract infection, Nasopharyngitis, Injection site reaction, Injection site pain, Injection site erythema, and Oropharyngeal pain have been previously identified as ADRs for ixekizumab; [c] $p < 0.05$ versus IXE Q4W; [d] Denominator adjusted because gender-specific event for females: N = 42 (placebo), N = 36 (ixekizumab 80 mg Q4W), N = 32 (ixekizumab 80 mg Q2W).

A total of 657 patients with AS have been exposed to ixekizumab in the pivotal studies ('all axSpA set'). The mean duration of exposure and total exposure to ixekizumab in the primary r-AxSpA set were 111.7 days and 55.4 patient years respectively in the ixekizumab 80 mg Q2W treatment groups and 109.5 days and 58.4 patient years respectively in the ixekizumab 80 mg Q4W treatment groups. The mean (standard deviation) total dose of ixekizumab in the 80 mg Q2W treatment groups was 653.3 (105.83) mg and in the 80 mg Q4W treatment groups was 341.7 (66.64) mg. In the all axSpA set, total exposure to ixekizumab was 306.3 patient-years in 80 mg Q2W groups and 321.7 patient years in the 80 mg Q4W groups. In the RA study, 75 patients were exposed to ixekizumab at doses between 0.06 mg/kg and 2.0 mg/kg, either as a single infusion, or every two weeks for a total of up to five doses.

In the all axSpA set and in the primary r-axSpA set the most frequently reported adverse events (AE) were infections (43% in the all axSpA exposure set), almost half of these were reported as nasopharyngitis (11.3%) or upper respiratory tract infection (10.2%). Injection site reactions were the second most frequently reported AEs (13.3% in the all axSpA exposure set). This is consistent with safety reports in Ps and PsA patients. Serious adverse events (SAE) were reported by 6.7% of the all axSpA exposure set: these included Crohn's disease (n = 3), blood creatine phosphokinase increased (n = 2), bradycardia (n = 2), cellulitis (n = 2), osteoarthritis (n = 2) and urinary tract infection (n = 2). One death was reported. This was a suicide on Day 54 after the first dose of ixekizumab, by a patient with a prior history of depression. The death was not considered related to the study drug. In the all axSpA exposure set, 5.5% of patients in ixekizumab treatment groups discontinued due to AE. These included eight patients with infections/infestations and seven patients with gastrointestinal disorders. In the RA study, three patients discontinued study drug, two patients with moderate leukopaenia and one with worsening polyarthritis.

In the all axSpA set, 12 patients reported at least one inflammatory bowel disease (IBD) related AE. These included five patients with new cases of Crohn's disease, three patients reporting ulcerative colitis, and four patients whose reported AE's were adjudicated as ulcerative colitis (2), probable Crohn's disease (1) and non-specific colitis (1).

Other AE of special interest included cytopaenias, allergic reactions/hypersensitivity, cerebro-cardiovascular events (major adverse cardiovascular events (MACE)), malignancies, hepatic events, depression, suicide, and interstitial lung disease.

Allergic reactions/hypersensitivity were recorded for 7% of the all axSpA set, none were anaphylactic. Eczema (n = 11), rash (n = 11) and urticaria (n = 5) accounted for more than half of the reports. One patient developed severe erythema multiforme, acute gastroenteritis, lower dyspeptic syndrome and Crohn's disease, with elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (both between 5 times and 10 times the upper limit of normal), considered related to the study drug. Hepatic AEs were recorded by 33 patients (5.2%) in the all axSpA set, none were classified as SAEs.

Six patients in the all axSpA set reported cerebro-cardiovascular events, one each acute myocardial infarction, aphasia (transient ischemic attack), cerebral haemorrhage (not considered a MACE), atrial fibrillation, Bradycardia and atrioventricular block. Five patients reported a depression-related or suicide-related AE. Three patients reported malignancy (bladder cancer, promyelocytic leukaemia, ovarian cancer), and all discontinued study drug. There were no reports of clinically important cytopaenia or of interstitial lung disease.

No consistent temporal relationship was observed between the presence of anti-drug antibodies (ADA) and the occurrence of TEAEs. Additionally, there was no impact of treatment emergent ADA titre on the type or severity of AEs.

According to the report, cumulatively approximately 8,755 subjects have received ixekizumab in clinical trials for a range of conditions, and to date it is estimated that a total of approximately 33,100 patients have received ixekizumab worldwide. The safety data in a Periodic Safety Update Report (PSUR) included with the submission remain consistent with the data from the clinical trials. No new safety signals have been identified. Serious infections, serious hypersensitivity and IBD remain important potential risks for ixekizumab.

Risk management plan

An updated risk management plan (RMP) was not required for this submission.[13] The RMP evaluator has stated that 'the proposed extension of indication to approve use for the treatment of ankylosing spondylitis is not considered significant from an RMP perspective.' This is accepted.

Risk-benefit analysis

Delegate's considerations

Proposed indication

The sponsor has requested approval for ixekizumab in the treatment of active ankylosing spondylitis in adult patients. The two pivotal studies were performed in bDMARD-naïve and TNFi-experienced adult populations respectively, and the inclusion criteria applied for enrolment into the studies were consistent with the diagnosis of AS. All of the enrolled patients had received prior symptomatic treatment with NSAIDs, and all but two enrolled patients had received prior treatment with cDMARDS. A large proportion of participants in the trials were concurrently treated with sulfasalazine, methotrexate or hydroxychloroquine (37% bDMARD-naïve, 27% TNFi-experienced) and NSAIDs (93.3%

[13] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

bDMARD-naïve, 76.2% TNFi-experienced). The study did not consider treatment with ixekizumab prior to cDMARDs. This could provide a reason for restricting ixekizumab to second line therapy for AS after cDMARDS, however in view of current understanding that cDMARDS are generally of limited value in axial inflammation, this could constitute an inappropriate delay to accessing an effective treatment. The proposed indication is supported by the data. None of the bDMARD treatment options currently registered in Australia have been restricted to second line use after cDMARDs or alternative bDMARDs, and only certolizumab pegol has been restricted to second line use after NSAIDS.

Dosage

The sponsor requested that the following statement regarding dosage was included in the PI:

> 'For patients who have had an inadequate response or are intolerant to at least 1 TNF inhibitor, a dose of 160 mg (two 80 mg injections) by subcutaneous injection at week 0, followed by 80 mg every 4 weeks may be considered.'

The Food and Drug Administration (FDA; USA) Prescribing Information recommends a loading dose of 160 mg (two 80 mg SC injections) ixekizumab at Week 0 for all patients, followed by 80 mg every four weeks.[14] In the opinion of the TGA evaluator, there is insufficient evidence to indicate that there is a clinically meaningful difference in efficacy based on loading dose.

Both of the pivotal studies were relatively small, with several subgroups exploring different dosage regimes. ASAS 40 at 16 weeks in patients on the two weekly regimen of ixekizumab (bDMARD-naïve 51.8%, TNFi-experienced 30.6%) did not appear to be higher than in patients on the four weekly regimen (bDMARD-naïve 48.1%, TNFi-experienced 25.4%). A larger, better powered study may have detected a statistical and clinically meaningful difference, but in the absence of this data, it would be appropriate to dose all patients with the lowest effective dose.

Deficiencies of the data

The pivotal study in bDMARD naïve patients was small, and although it included an active comparator arm with adalimumab, was insufficiently powered to detect a statistically or clinically meaningful difference in the primary efficacy outcome between the experimental treatment in its multiple dose regimens and adalimumab. The study did not include an alternative IL-17A antibody, which may have been more informative of relative value. The pivotal study in TNFi patients was also small. Multiple secondary and exploratory measures of efficacy were included in the design of both studies, which may have been better served by a larger study population. Nevertheless, ASAS 40 at 16 weeks was significantly higher in the ixekizumab groups (48.1% in the bDMARD-naïve population and 25.4% in the TNFi-experienced population receiving 80 mg SC every four weeks) than in their respective placebo treated groups (bDMARD-naïve 18.4%, TNFi-experienced 12.5%). The responses are sustained to 52 weeks and together these findings support the requested indication. Lower response rates in TNFi-experienced patients at similar ixekizumab concentrations may reflect a population that was older, had a longer disease duration, and more severe disease activity at Baseline.

The submission presented safety data for up to 52 weeks following the first dose of ixekizumab. The AEs associated with ixekizumab in patients with AS were broadly similar in nature and frequency to those reported by studies with patients with psoriasis, and to those reported in studies of another IL-17 antibody, secukinumab. The risks of serious infection, serious hypersensitivity reactions and new or recurrent inflammatory bowel

[14] FDA Prescribing Information for Taltz (ixekizumab), 80 mg/mL solution for injection August 2019. Available from the FDA website.

disease have been identified in this population as in other patient groups treated with ixekizumab. No new safety signals were identified by these studies. A longer follow-up period should be applied to ensure adequate opportunity to detect infrequent, but serious potential AEs including malignancies, and MACE, which do seem to be a risk with this class of medicines. This deficiency may be addressed by post-market surveillance activities.

Ixekizumab has not been studied in patients < 18 years of age, in subjects with significant organ dysfunction, and in those with concurrent hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV) infection. However, populations with inadequate clinical data in regard to this treatment are identified in the current RMP.

Conditions of registration

The sponsor must submit the final clinical study reports of the fully completed pivotal studies (Study I1F-MC-RHBV, Study I1F-MC-RHBW) and the ongoing long term extension study (Study I1F-MC-RHBY), including, but not restricted to, results addressing the maintenance of response after treatment withdrawal, on completion of the respective studies.

Proposed action

Pending advice from Advisory Committee on Medicines (ACM) and the sponsor's pre-ACM response, the Delegate considers the benefit/risk profile of ixekizumab to be positive and recommends approval for the indication:

> *Taltz is indicated for the treatment of active ankylosing spondylitis in adult patients.*

However, the Delegate also recommends that the dosing information does not include the following statement:

> 'For patients who have had an inadequate response or are intolerant to at least 1 TNF inhibitor, a dose of 160 mg (two 80 mg injections) by subcutaneous injection at Week 0, followed by 80 mg every 4 weeks may be considered.'

There is insufficient evidence in the dossier to support this statement.

Request for Advisory Committee on Medicines advice

The committee is requested to provide advice on the following specific issues:

1. What are the views of the Committee on restricting the indication for AS to second line treatment after cDMARDs?
2. What are the views of the Committee on whether a loading dose of 160 mg at Week 0 is justified to achieve efficacy in either bDMARD naïve or TNFi-experienced populations?
3. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee considerations[15]

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Taltz, a solution for injection, containing 80 mg/ml of ixekizumab.

The ACM considered this product to have an overall positive benefit-risk profile for the proposed indication:

Taltz is indicated for the treatment of active ankylosing spondylitis in adult patients.

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***What are the views of the Committee on restricting the indication for AS to second line treatment after cDMARDs?***

The ACM was of the view that cDMARDs generally offer limited benefit in the treatment of axial inflammation. Restricting the indication for AS to second line could potentially delay other treatments which may be more beneficial to the patient. Therefore, the ACM was of the view that the restriction was not appropriate, and that ixekizumab could be used as a first line therapy.

2. ***What are the views of the Committee on whether a loading dose of 160 mg at Week 0 is justified to achieve efficacy in either bDMARD naïve or TNFi-experienced populations?***

The ACM advised that there is limited efficacy data to support the adminstration of a loading dose at Baseline. The ACM was of the view that ixekizumab should be administered without a loading dose.

3. ***The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.***

The ACM expressed concern regarding the auto-injector device and the possibility of needle-stick injury to patients when self-administering their injections. This is because the administration button depresses even when the twist off base cap is in place. When the cap is removed the needle will extend beyond the clear base cap and release the medicine. To prevent medicine from spilling from the device, patients may instinctively use their fingers to stop the spill and incur a needle-stick injury in the process.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Taltz (ixekizumab) 80 mg/mL solution for injection for the following extension of indications:

Ankylosing spondylitis (radiographic axial spondyloarthritis)

Taltz is indicated for the treatment of active ankylosing spondylitis in adult patients.

[15] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

As such, the full indications at this time were:

Plaque psoriasis

Taltz is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Psoriatic arthritis

Taltz is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately, or who are intolerant, to previous DMARD therapy.

Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g. methotrexate).

Ankylosing spondylitis (radiographic axial spondyloarthritis)

Taltz is indicated for the treatment of active ankylosing spondylitis in adult patients.

Specific conditions of registration applying to these goods

- The approval does not impose any requirement for the submission of periodic safety update reports (PSUR). The sponsor should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.
- The sponsor must submit, as Category 1 submissions to the TGA, the final clinical study reports of the fully completed pivotal studies (Study I1F-MC-RHBV, Study I1F-MC-RHBW) and the ongoing long term extension study (Study I1F-MC-RHBY), including, but not restricted to, results addressing the maintenance of response after treatment withdrawal, on completion of the respective studies.
- For all injectable products the PI must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Taltz approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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