Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ixekizumab

Proprietary Product Name: Taltz

Sponsor: Eli Lilly Australia Pty Ltd

November 2018

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
ACR	American College of Rheumatology
ACR Core Set	Consists of 7 disease activity measurements
ACR-N Responder Index	A continuous measure of clinical, laboratory and functional measure in rheumatoid arthritis that characterizes the percentage of improvement from Baseline in rheumatoid arthritis disease activity
ACR Responder	ACR20/50/70 Responder: A patient who had at least 20%/50%/70% improvement in both tender and swollen joint counts and at least 20%/50%/70% improvement in a minimum of 3 of the 5 specified criteria
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	Biologic disease-modifying anti-rheumatic drug
BMI	Body mass index
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
cDMARD	Conventional disease-modifying anti-rheumatic drugs
CEC	Clinical Events Committee
CER	Clinical evaluation report
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CL	Clearance
CPDAI	Composite Psoriatic Disease Activity Index

Abbreviation	Meaning
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Minimum drug-plasma concentration
DAS28-CRP	Disease Activity Score 28 diarthrodial joint count based on C-reactive protein
DLQI	Dermatology Life Quality Index
DMARDs	Disease-modifying anti-rheumatic drugs
DMC	Data Monitoring Committee, a group specifically established for interim safety monitoring
ECG	Electrocardiogram
eCRF	Electronic case report form
EQ-5D 5L	European Quality of Life-5 Dimensions 5 Level
ETV	Early Termination Visit
EU	European Union
Fatigue NRS	Fatigue Severity Numeric Rating Scale
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
Hb	Haemoglobin
HBV	Hepatitis B virus
Hct	Haematocrit
hs-CRP	High sensitivity (assay) C-reactive protein
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgG4	Immunoglobulin G4 subtype

Abbreviation	Meaning
IL	Interleukin (for example, IL-17; a pro-inflammatory cytokine produced by Th17 cells)
Inadequate Responder (Week 16)	A patient who failed to meet defined criteria for improvement in tender and swollen joints at Week 16 and was administered rescue therapy.
ITT	Intent-to-Treat
IV	Intravenous
IXE	Ixekizumab
JIA	Juvenile idiopathic arthritis
LDI-B	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
LLN	Lower limit of normal
LLT	Lowest level term
LOCF	Last observation carried forward
mBOCF	Modified baseline carried forward
MAA	Marketing Authorization Application
MDA	Minimum Disease Activity
MDA_{PASI}	Minimum Disease Activity including Psoriasis Area and Severity Index
MDA_{sPGA}	Minimum Disease Activity including static Physician Global Assessment of psoriasis
MedDRA	Medical Dictionary for Regulatory Activities: a standard terminology recommended by ICH, used to describe, catalogue, analyse, and report all adverse events
MMRM	Mixed-effects model of repeated measures
mSACRAH	Modified Score for Assessment and Quantification of Chronic Rheumatoid Affections of the Hands
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NAb	Neutralising antibody

Abbreviation	Meaning
NAPSI	Nail Psoriasis Severity Index
NRI	Non-responder imputation
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index; PASI75/90/100 – at least 75%/90%/100% improvement in PASI score from baseline
PCS	Physical Component Summary
PDCO	Paediatric Committee
PGA	Physician's Global Assessment of Disease Activity
PI	Product information
PIP	Paediatric Investigation Plan
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetics/Pharmacodynamics
PPD	Purified protein derivative
PPS	Per Protocol Set
PsA	Psoriatic arthritis
Ps	Psoriasis
PsARC	Psoriatic Arthritis Response Criteria
PSUR	Periodic Safety Update Report
RMP	Risk management plan
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's correction factor
QTcLCTPB	QT interval corrected using a large clinical study population based correction factor

Abbreviation	Meaning
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SJC	Swollen joint count
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
sPGA	Static Physician Global Assessment of psoriasis
TB	Tuberculosis
TE-ADA	Treatment-emergent anti-drug antibody
TEAE	Treatment-emergent adverse event
Th	T helper
TJC	Tender joint count
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
ULN	Upper limit of normal
VAS	Visual Analog Scale
V	Volume of distribution
WPAI-SHP	Work Productivity and Activity Impairment Scale – Specific Health Problem

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	22 June 2018
Date of entry onto ARTG:	27 June 2018
ARTG numbers:	253893 and 253892
, *Black Triangle Scheme*	Yes. This product will remain in the scheme for 5 years, starting on the date the new indication was approved.
Active ingredients:	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
Containers:	Prefilled pen; Prefilled syringe
Pack sizes:	1, 2 or 3 single-dose auto-injector or prefilled syringe* *Not all pack sizes or presentations may be marketed.
Approved therapeutic use:	*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).*
Routes of administration:	Subcutaneous injection (SC)
Dosage:	The recommended dose is 160 mg by SC injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks.

Product background

This AusPAR describes the application by the sponsor to register a new indication for Taltz (ixekizumab) for the treatment of active psoriatic arthritis in adult patients who have responded inadequately, or who are intolerant, to previous disease-modifying anti-rheumatic drugs (DMARD) therapy. Taltz may be used as monotherapy or in combination with a conventional DMARD (such as methotrexate).

Taltz is currently approved for the following indications:

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

The following dosage regimen is currently approved in Australia:

> *The approved recommended dose for patients with moderate-to-severe plaque psoriasis is 160 mg by SC injection (two 80 mg injections) at Week 0, followed by an 80 mg injection (one injection) every 2 weeks at Weeks 2, 4, 6, 8, 10 and 12, then 80 mg (one injection) every 4 weeks.*

The proposed recommended dose for patients with psoriatic arthritis is 160 mg by SC injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks. The proposed recommended dose for patients with psoriatic arthritis and coexistent moderate-to-severe plaque psoriasis is the same as the approved recommended dose for patients with moderate-to-severe plaque psoriasis.

No new strengths of the product are being been proposed. The two current strengths are:

- ixekizumab 80 mg/mL solution for injection prefilled pen (AUST R 253893); and
- ixekizumab 80 mg/mL solution for injection prefilled syringe (AUST R 253892).

Current treatment options

Current approved treatment options in Australia for moderately to severely active PsA include non-steroidal anti-inflammatories (NSAIDs); corticosteroids (oral and intra-articular); conventional disease modifying anti-rheumatic drugs (cDMARDS) such as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine and apremilast; tumour necrosis factor inhibitors (TNFi), such as adalimumab, certolizumab pegol, etanercept, golimumab, infliximab; the interleukin 12/23 (IL-12/23) inhibitor ustekinumab; and the interleukin 17A (IL-17A) inhibitor secukinumab.

Ixekizumab

Ixekizumab is an immunoglobulin G4 (IgG4) monoclonal antibody that binds with high affinity (<3 pM) to IL-17A, a pro-inflammatory cytokine. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F. Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases. In psoriasis, the IL-17A ligand plays a major role in driving excess keratinocyte proliferation and activation. Neutralisation of IL-17A by ixekizumab inhibits these actions.

Information on the condition being treated

PsA is a chronic, systemic, immune-mediated arthritis associated with clinically heterogeneous features, including plaque psoriasis, joint damage, dactylitis, enthesitis, and axial involvement.[1,2] It is classified within the group of the spondyloarthritis. PsA can also be associated with progressive joint destruction, impaired function, decreased quality of life and increased mortality.[3,4,5]

[1] Gladman DD. Psoriatic arthritis. *Dermatol Ther*. 2009;22(1): 40-55.
[2] de Vlam K, Gottlieb AB, Mease PJ. Current concepts in psoriatic arthritis: pathogenesis and management. *Acta Derm Venerol*. 2014;94(6): 627-34.
[3] Boehncke WH, Qureshi A, Merola JF, Thaçi D, Krueger GG, Walsh J, Kim N, Gottlieb AB. Diagnosing and treating psoriatic arthritis: an update. *Br J Dermatol*. 2014;170(4): 772-86.
[4] Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005;64(Suppl 2): ii14-7.

The manifestations of dermatological psoriasis precede that of PsA by 10 years on average, although the arthritis related characteristics of PsA precede skin disease in about 1/6 of cases.[6,7] The disease generally develops in the fourth decade of life and affects both men and women equally.[7]

The reported prevalence of inflammatory arthritis in people with psoriasis varies widely from 6% up to 42%. In Europe, the prevalence of PsA has been estimated at 8.1% among patients with psoriasis and increases with time since the diagnosis, reaching 20.5% after 30 years.[8] In about 67% of patients, psoriasis is present before the onset of the arthropathy, whereas in approximately 15% of patients the arthritis precedes the skin disease by more than one year. PsA is associated with an increased risk of cardiovascular disease.

In most patients with PsA, the arthropathy affects peripheral joints alone and may present with dactylitis (inflammation of a single finger or toe) or enthesitis (inflammation at the sites of tendon and ligament attachment to bone). The following patterns of joint involvement are recognised:

- Oligoarticular peripheral arthritis: occurs in 50% of patients; involves up to five joints. Over time many of these patients will develop polyarticular disease.
- Polyarticular peripheral arthritis: occurs in 30% of patients; may resemble rheumatoid arthritis (RA).
- Predominant sacroiliitis and spondylitis and occurs in up to 10% of patients.
- Predominant distal interphalangeal joint involvement in both hands and feet: occurs in 5% of patients.
- Arthritis mutilans: occurs in up to 5% of patients. It presents as osteolysis or dissolution of bone.

The extra-articular features common to the spondyloarthritides may occur with PsA (psoriasis-like skin and nail lesions, conjunctivitis or acute anterior uveitis, chronic gastrointestinal and genitourinary inflammation). Ocular inflammation most commonly presents as conjunctivitis, although up to 7% of patients can develop iritis.

Regulatory status

Taltz (ixekizumab) was approved by the TGA on 6 September 2016 for the initial registration as treatment of adult patients with moderate to severe plaque psoriasis.

Taltz (ixekizumab) has been approved in Europe (January 2018) and US (December 2017) for the treatment of active Psoriatic Arthritis in adult patients. The approved indications in Europe and US are as follows:

Europe

Psoriatic Arthritis

[5] Leung YY, Tam LS, Kun EW, Li EK. Psoriatic arthritis as a distinct disease entity. *J Postgrad Med*. 2007;53(1): 63-71

[6] Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs*. 2014;74(4): 423-41.

[7] Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med 2017*; 376: 957-70.

[8] Christophers E, Barker JN, Griffiths CE, Daudén E, Milligan G, Molta C, Sato R, Boggs R. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. *J Eur Acad Dermatol Venereol*. 2010;24(5): 548-54.

Taltz, alone or in combination with methotrexate, is indicated 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.

Posology:

Plaque psoriasis

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks.

Psoriatic arthritis

The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis.

USA

Psoriatic Arthritis

Taltz is indicated for the treatment of adult patients with active psoriatic arthritis.

Dose and administration:

Plaque Psoriasis

- *Administer by subcutaneous injection.*
- *Recommended dose is 160 mg (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.*

Psoriatic Arthritis

- *Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg every 4 weeks.*
- *For psoriatic arthritis patients with coexistent moderate-to-severe plaque psoriasis, use the dosing regimen for plaque psoriasis.*
- *Taltz may be administered alone or in combination with a conventional DMARD (e.g., methotrexate).*

Product Information

The Product Information (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 time line

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

Description	Date
Submission dossier accepted and first round evaluation commenced	31 August 2017
First round evaluation completed	31 January 2018
Sponsor provides responses on questions raised in first round evaluation	28 February 2018
Second round evaluation completed	17 April 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 May 2018
Sponsor's pre-Advisory Committee response	15 May 2018
Advisory Committee meeting	31 May - 1 June 2018
Registration decision (Outcome)	22 June 2018
Completion of administrative activities and registration on ARTG	27 June 2018
Number of working days from submission dossier acceptance to registration decision*	180 days

*Statutory timeframe for standard applications is 255 working days

III. Quality findings

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

IV. Nonclinical findings

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

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical rationale

The sponsor's clinical rationale notes that, despite the availability of current therapies, many patients still experience an inadequate response or become treatment refractory. Therefore, there is an important clinical need for treatment options that can help patients achieve low disease activity, through clinically meaningful improvements in both articular (that is, arthritis, enthesitis and dactylitis) and extra-articular (skin psoriasis) features of PsA, while reducing physical disability, improving quality of life and inhibiting radiographic evident joint damage, resulting in long-term benefits with an acceptable safety profile.

Guidance

The relevant TGA adopted guideline for this submission is:

- Guideline of clinical investigation of medicinal products for the treatment of psoriatic arthritis (CHMP/EWP/438/04)

The sponsor included a copy of this guideline in their submission.

Evaluator's commentary on the background information

The background information is satisfactory. The stated Clinical rationale for the submission provided is acceptable, although there is an IL-17A inhibitor already approved for psoriatic arthritis (secukinumab) with a similar indication to that being sought by the sponsor for ixekizumab.

Contents of the clinical dossier

The dossier included population-pharmacokinetic data in patients with PsA and psoriasis (Ps), pharmacodynamic data in healthy subjects and pivotal clinical efficacy and safety data in patients with PsA. The dossier is considered to be appropriate for the proposed extension of indication to include patients with PsA.

- 1 population pharmacokinetic (PK) study in patients with PsA and Ps, and exposure-response analyses in patients with PsA.
- 1 clinical pharmacology study in healthy subjects exploring response to vaccination following administration of ixekizumab.
- 2 pivotal Phase III efficacy and safety studies in patients with PsA.
- 1 protocol for a Phase III study assessing the effects of withdrawal of ixekizumab in patients with PsA and the long-term efficacy and safety of the drug.
- 1 integrated safety study (ISS) White Paper on the use of minimal disease activity for the assessment of low disease activity in patients with PsA; a table of significant and notable patients.
- 5 in vitro bioanalytical validation reports.
- Literature references.

Paediatric data

No paediatric data were included in the dossier. The sponsor states that no paediatric data have been submitted for evaluation to the European Medicines Agency (EMA) or the FDA

for the proposed extension of indication. The sponsor states that it has an agreed Paediatric Investigation Plan (PIP) in Europe and that it is required to submit 'Study #6' (last patient last visit September 2012) to the EMA. The sponsor states that FDA correspondence from December 2013 indicates that specific paediatric studies in the juvenile equivalent of psoriatic arthritis and ankylosing spondylitis have been waived historically since studies would be impossible or highly impractical to conduct due to the difficulty in definitively diagnosing patients with these specific conditions in the paediatric population. The sponsor goes on to state that official approval by the FDA of the waiver will be granted on approval of the sBLA, presumably for psoriatic arthritis in adults.

Good clinical practice

The sponsor indicates that the submitted studies have been conducted in accordance with the principles of Good Clinical Practice (GCP).

Evaluator's commentary on the clinical dossier

The clinical dossier is considered appropriate for the application to extend the indications of ixekizumab to include the treatment of patients with PsA. The clinical dossier was well presented and facilitated evaluation of the submission. It is not entirely clear whether the sponsor has a waiver from the EMA specifically relating to psoriatic arthritis studies in the paediatric population. It is noted that a recently published review of PsA comments that the disease can begin in childhood.[7] Two not mutually exclusive clinical subtypes are described in the review: (1) oligoarticular psoriatic arthritis occurring predominantly in girls with a peak onset at 1 to 2 years of age; and (2) a more frequent subtype characterised by any number of affected joints developing between 6 and 12 years of age with a 1: 1 sex ratio. The sponsor is requested to clarify its position as regards submission of paediatric psoriatic arthritis studies in Europe, indicate whether it intends to submit paediatric psoriatic arthritis data to the TGA and provide a justification if it does not intend submitting such data to the TGA.

Pharmacokinetics

Studies providing pharmacokinetic data

The pharmacokinetic (PK) data included one population PK (popPK study) submitted to support the similarity of the PK of ixekizumab in patients with PsA and patients with Ps. The study extends the popPK data previously submitted in the initial application to register ixekizumab for psoriasis (*Primary Population PK and Exposure-Response Analyses Report*) to include data from the two pivotal Phase III PsA studies included in the current submission. The new popPK report is summarised below.

Evaluator's conclusions on pharmacokinetics

Based on the popPK data submitted in the current application it can be reasonably inferred that the PK of ixekizumab in patients with PsA are consistent with the PK of ixekizumab in patients with Ps. Therefore, the PK data in the currently approved PI for the approved indication of Ps can be safely extrapolated to the proposed indication for PsA.

Pharmacokinetic popPK model parameters

To describe ixekizumab PK in patients with PsA, ixekizumab concentration data from the PsA studies (Studies RHAP and RHBE) were integrated with the original ixekizumab concentration data from the Ps studies (Studies RHAG, RHAJ, and RHAZ, all available data). All existing covariate relationships identified in the original Ps analysis were retained in

the new model, and the model parameters including the PsA data were re-estimated. Additional covariate evaluation was conducted for the following factors associated with the PsA patient population in Studies RHAP and RHBE: PsA as an indication; concomitant use of methotrexate (MTX); and prior use of MTX or adalimumab. None of the additional covariates significantly affected the PK of ixekizumab.

The majority of popPK parameters estimated in the combined PsA/Ps PK model were similar to those estimated in the original Ps PK model, indicating the consistency of PK between patients with PsA and Ps. The significant covariates in the updated PsA/Ps popPK model were body weight (increasing body weight increases both clearance (CL) and volume of distribution (V) terms), subcutaneous (SC) injection via the thigh increases bioavailability compared to other SC injection sites (arm, abdomen, or buttock), and increasing anti-drug antibodies (ADA) titre increases CL as does positive neutralising NAb).

Exposure-response data for efficacy (ACR) in PsA patients

Data from the ACR20/50/70[9] Week 24 static popPD model, based on observed ACR response and time-matched ixekizumab serum concentrations at Week 24, showed age and sex to be significant covariates on drug effect. Males tended to have higher response rates than females. For patients aged 55 years or older, ACR20/50/70 response rates were similar irrespective of age. For patients aged 55 years or younger, ACR20/50/70 response rates tended to increase with decreasing age. Many additional covariates were tested in this analysis (for example, body weight, immunogenicity, prior failure on anti-tumour necrosis factor (anti-TNF) treatment, concomitant MTX, and prior MTX treatment) but were not found to significantly affect the ACR score (change in rheumatoid arthritis symptoms). Based on pooled data, the model predicted ACR20/50/70 response rates at Week 24 were similar for the every two weeks administration (Q2W) and the every 4 weeks administration (Q4W) regimens, despite the higher range of exposures in the Q2W regimen compared with the Q4W regimen.

Data from the ACR20/50/70 time-course model over the first 24 weeks of treatment showed that, as for the ACR static model at Week 24, age and sex were identified as significant covariates on drug effect. The only other covariate tested in this model was prior experience with anti-TNF treatment, and this factor was not identified as a significant covariate on the ACR time-course model. Based on the model, both the Q2W and Q4W dosing regimens are predicted to result in similar rates of responses that plateau after approximately 16 weeks of treatment within the age and sex subgroups. There appeared to be no additional benefit on response predicted with higher exposures associated with Q2W dosing relative to Q4W dosing in each of the age and sex subgroups tested, suggesting that increasing dosing frequency from Q4W to Q2W would not be expected to offer additional efficacy based on ACR in patients with active PsA.

Exposure-response data for efficacy (PASI) in PsA patients

Data from the PASI[10] Week 12 static popPD model, based on observed PASI responses in patients from Studies RHAP and RHBE with body surface area (BSA) ≥3 % at baseline and time-matched ixekizumab serum concentrations at Week 12, showed that the Q2W dosing regimen was associated with a higher predicted percentage response rate compared with the Q4W dosing regimen, especially for PASI 90 and PASI 100 responses.

[9] ACR20/50/70 Responder: A patient who had at least 20%/50%/70% improvement in both tender and swollen joint counts and at least 20%/50%/70% improvement in a minimum of 3 of the 5 specified criteria.
[10] Psoriasis Area and Severity Index; PASI75/90/100 = at least 75%/90%/100% improvement in PASI score from baseline

Exposure-response data for safety in PsA patients

Ixekizumab serum concentrations used in the exposure-safety analyses were observed trough concentrations (C_{trough}) at Week 24 from patients who participated in the Double-Blind Treatment Period up to Week 24 in PsA Studies RHAP and RHBE, and the observed C_{trough} at Week 52 for patients who participated in the Extension Period from Weeks 24 to 52 in PsA Study RHAP. Of the treatment emergent adverse events (TEAEs) planned for assessment, sufficient patient numbers for exposure-response assessment of safety were observed only for TEAEs relating to all infections and injection site reactions. An exposure-response relationship was observed for injection site reactions in both the Double-Blind Treatment Period (up to Week 24) and the Extension Period (Weeks 24 through 52). The exposure-response relationship correlates to the serum ixekizumab concentration for the response of interest, with higher concentrations being associated with a greater incidence of injection site reactions. However, this correlation might relate to the higher number of ixekizumab injections associated with the Q2W regimen compared with the Q4W regimen, rather than to the higher serum ixekizumab concentrations observed with the Q2W regimen compared to the Q4W regimen. No exposure-response relationships relating to all infections were observed in PsA patients following the Q2W and Q4W regimens.

ADA-positive incidence in PsA patients

The immunogenicity data summarised in this section focuses on the ixekizumab 80 mg Q4W group, as this is the relevant dosing regimen for the proposed treatment of patients with PsA.

In the primary PsA placebo-controlled integrated analysis based on Studies RHAP and RHBE (Weeks 0 to 24), 6.2% (10/225) of patients in the IXE80Q4W group were classified as treatment-emergent anti-drug antibody (TE-ADA) positive (including 2 (0.9%) neutralising antibody (NAb) positive patients) compared with 0.5% (1/218) of patients in the placebo group (no NAb positive patients). Ten (10) of the 14 TE-ADA positive patients in the IXE80Q4W group were classified as TE-ADA low titre, 4 as TE-ADA moderate titre, and no patients had TE-ADA high titre at any time point during the study period. The median interquartile range (IQR) duration of TE-ADA positive in the IXE80Q4W group was 12.1 weeks. Of the 14 patients in the IXE80Q4W group who were TE-ADA positive over the 24 week period, 2 were NAb positive.

In the PsA Study RHAP (Weeks 0 to 52), 11.3% (12/206) of patients in the IXE80Q4W/IXW80Q4W group were classified as TE-ADA positive. Ten (10) of the 12 TE-ADA positive patients were classified as TE-ADA low titre, 1 patient as TE-ADA moderate titre, and 1 patient as TE-ADA high titre. The time-to-first TE-ADA result occurred at Week 24, Week 36, and Week 44, for 6 patients, 5 patients, and 1 patient, respectively. The median (IQR) duration of TE-ADA positive was 28.0 weeks. Of the 12 patients in the IXE80Q4W/IXW80Q4W group who were TE-ADA positive over the 52 week period, 8 (7.5%) were NAb positive. The time-to-first NAb positive occurred at Weeks 24, 32, 36, and 52, for 2 patients, 2 patients, 3 patients, and 1 patient, respectively.

Effects of immunogenicity on the PK of ixekizumab (PsA/psoriasis)

Population PK analyses, using combined PsA and Ps data as well as updated NAb results based on disease-specific cut points in the NAb assay, suggest that ADA in the moderate titre range (1: ≥160 and 1: <1280) was associated with an approximate 20% to 30% increase in CL, and being NAb positive was associated with an approximate 46% increase in CL. It should be noted, however, that the combined PsA/Ps PK dataset is largely represented by the Ps population, where a higher number of NAb positive samples were in a higher titre range compared with the PsA population. The impact of NAb on CL is smaller in the combined PsA/Ps analysis in the current submission compared to the Ps analysis in the original submission due to the updated NAb results in the PsA and Ps studies being based on new disease-specific cut-points for the NAb assay.

Collectively, from the graphical assessment and the population PK analyses, the majority of PsA patients with low titre positive ADA had ixekizumab concentrations similar to patients who were ADA negative. Of the small number of ADA positive samples with moderate titre (≥1: 160 and <1: 1280), a few were associated with lower drug concentrations when compared with ADA negative samples.

Effect of immunogenicity on efficacy (ACR)

Based on the available data, TE-ADAs appear in to have no significant impact on the efficacy of ixekizumab as assessed by the ACR20 and/or ACR 50 in patients with PsA.

In the primary PsA placebo-controlled integrated analysis set based on Studies RHAP and RHBE (Weeks 0 to 24), of the 14 patients in the IXEQ4W group classified as TE-ADA positive, 12 patients achieved ACR20 response at Week 24. The strength of the TE-ADA titre did not affect achieving ACR20, as 9 of the 10 patients with TE-ADA low titres, and 3 of the 4 with TE-ADA moderate titres achieved ACR20 at Week 24. Both patients classified as NAb positive also achieved ACR20.

In Study RHAP (Weeks 0 to 52), of the 12 patients in the IXE80Q4/IXE80Q4 group who were TE-ADA positive, 10 patients were classified as TE-ADA low titre, 6 of these patients achieved ACR20 response at Week 52 and 5 of these patients achieved ACR50 response at Week 52. One (1) patient with a moderate TE-ADA positive titre did not achieve either ACR20 or ACR50 at Week 52, while 1 patient with high TE-ADA positive titre achieved both ACR20 and ACR50 at Week 52. Of the 7 NAb positive patients in the IXE80Q4/IXE80Q4 group, 5 achieved ACR20 and 4 achieved ACR50.

Effect of immunogenicity on safety (allergic reactions/hypersensitivity)

In the PsA analysis sets, allergic reaction/hypersensitivity TEAEs were observed less frequently in TE-ADA positive patients than in TE-ADA negative patients. In the Ps analysis set, the percentages of patients with allergic reactions/hypersensitivity TEAEs was similar for TE-ADA positive and TE-ADA negative patients.

In all PsA patients treated with ixekizumab (Studies RHAP, RHBE and RHBF), 54 (5.9%) of 1002 TE-ADA negative ixekizumab treated patients had ≥ 1 allergic reaction/ hypersensitivity TEAE compared to 4 (4.7%) of 85 TE-ADA positive PsA patients.

In the all PsA integrated analysis set based on Studies RHAP and RHBE (Weeks 0 to 24), of the 14 patients in the IXEQ4W group classified as TE-ADA positive no patients reported ≥ 1 allergic reaction/ hypersensitivity TEAE. Of the 211 patients in the IXEQ4W group classified as TE-ADA negative, 10 (4.7%) patients reported ≥ 1 allergic reaction/ hypersensitivity TEAE.

In Study RHAP (Weeks 0 to 52), 3 (3.2%) TE-ADA negative PsA patients in the IXE80Q4W/IXE80Q4 group reported ≥ 1 allergic reaction/ hypersensitivity TEAE compared with no TE-ADA positive PsA patients.

Effect of immunogenicity on safety (injection site related reactions)

In the PsA analysis sets, injection site reactions (ISRs) were observed more frequently in TE-ADA positive patients than in TE-ADA negative patients.

In all PsA patients treated with ixekizumab (Studies RHAP, RHBE and RHBF), 173 (5.9%) of 917 TE-ADA negative ixekizumab treated patients had ≥1 ISR-TEAE compared with 24 (28.2%) of 85 TE-ADA positive PsA patients.

In the primary PsA placebo-controlled integrated analysis set based on Studies RHAP and RHBE (Weeks 0 to 24), 35 (16.6%) TE-ADA negative PsA patients in the IXE80Q4W group had ≥ 1 ISR-TEAE compared with 5 (35.7%) in TE-ADA positive PsA patients.

In Study RHAP (Weeks 0 to 52), 21 (22.3%) TE-ADA negative PsA patients in the IXE80Q4W/IXE80Q4W group had ≥ 1 ISR-TEAE compared to 7 (58.3%) of TE-ADA positive PsA patients.

Pharmacodynamics

Studies providing pharmacodynamic data

There was 1 dedicated study providing pharmacodynamic (PD) information in healthy subjects (I1F-MC-RHCA).

Evaluator's conclusions on pharmacodynamics

The PD data from Study RHCA in healthy subjects showed that ixekizumab does not suppress the immune response to inactivated vaccines (that is, tetanus vaccine component of Boostrix and pneumococcal vaccine). The primary immune response analysis showed that ixekizumab plus vaccines was non-inferior to control (vaccines alone), with the difference in the responder rates at 4-weeks after vaccination being 1.4% (90% confidence interval (CI): -16.6%, 19.2%) for the tetanus vaccine and -0.8% (90% CI: -12.9%, 11.0%) for the pneumococcal vaccine. The lower limit for 90% CI for both analyses was greater than the non-inferiority margin of -40%. The results for the pre-specified exploratory and post hoc exploratory immune response analyses supported the findings observed for the primary immune analyses. Injection of ixekizumab plus vaccines was well tolerated and no significant safety issues were reported during the study.

Dosage selection for the pivotal studies

The clinical development of ixekizumab for the treatment of PsA included two pivotal Phase III double blind, randomised, controlled studies, including one study in bDMARD naive patients (Study RHAP (SPIRIT-PI), n=417) and one study in TNFi-experienced patients (Study RHBE (SPIRIT-P2), n=363). The sponsor provided a rationale for the selected doses in Studies RHAP and RHPE in the study reports for each study and in the *Summary of Clinical Pharmacology*. The data summarised below are based on the sponsor's rationale for the dosage selection for the pivotal studies.

The sponsor considered that it was appropriate to evaluate two dosage regimens in the pivotal Phase III studies in patients with PsA in order to enable appropriate evaluation of the benefit/risk ratio associated with continuous ixekizumab therapy. Dose ranging data from Phase II studies of ixekizumab in patients with RA and patients with Ps were used to identify appropriate doses to be evaluated in the Phase III studies of ixekizumab in patients with PsA, as no Phase II studies in PsA were undertaken. The sponsor anticipated that continuous therapy with ixekizumab 80 mg administered SC Q2W and ixekizumab 80 mg administered SC Q4W, each with a 160 mg starting dose, would allow for a robust assessment of safety, efficacy, and benefit/risk profile in the Phase III studies of patients with PsA.

The two dosage regimens being proposed for patients with PsA are: (1) initial dose of 160 mg (2 x 80 mg) followed by 80 mg Q4W for patients with PsA; and (2) initial dose of 160 mg (2 x 80 mg) followed by 80 mg Q2W through to Week 12 and then 80 mg Q4W for patients with *coexistent* PsA and moderate-to-severe plaque Ps. This regimen is the same as that approved for patients with moderate-to-severe plaque Ps.

The sponsor stated that the 80 mg Q2W and 80 mg Q4W dose regimens each with a starting dose of 160 mg, are within the range of doses tested in the Phase II studies in patients with RA and patients with Ps and were found to be well tolerated. There have

been no major dose-related safety concerns detected after multiple dosing in previous studies in patients with RA up to the maximum dose of 2 mg/kg administered IV Q2W for 10 weeks. A 2 mg/kg intravenous (IV) dose is approximately equivalent to a 320 mg SC dose (assuming approximately 50% bioavailability and mean body weight of 80 kg). Additionally, there were no clinically significant dose-related safety concerns detected after multiple dosing in previous studies in patients with Ps up to the maximum dose of 150 mg SC Q4W for 16 weeks. Therefore, the safety profile to date supported dosing in Phase III studies of PsA with 80 mg SC Q4W and 80 mg SC Q2W, which produce lower ixekizumab exposures than 2 mg/kg IV.

Rationale for the ixekizumab 80 mg Q2W dose regimen

The sponsor stated that the 80 mg Q2W dose regimen was selected for evaluation in the Phase III PsA studies, because it demonstrated efficacy in Study RHAK, the Phase II dose-ranging study in patients with RA. In Study RHAK, a dose-response relationship was detected for the ACR20 at the Week 12 primary endpoint across the dose range tested (3, 10, 30, 80, and 180 mg ixekizumab Q2W) in the bDMARD-naive population. In addition, ixekizumab 80 mg and 180 mg Q2W doses demonstrated significantly better ACR20 responses compared with placebo in the TNF-Inadequate Responder Population. Similar to ACR20 responses, a dose-related reduction in the mean change from baseline in DAS28-CRP was observed with increasing doses of ixekizumab at Week 12 in both patient populations.[11]

Numerically higher ACR20 and DAS28-CRP responses were observed at the 180 mg Q2W dose level compared with all other doses across most time points in the 12 week time course in both patient populations. This was evident from the ACR20 and DAS28-CRP responses observed within the first week of Study RHAK, as well as the consistency in clinical efficacy compared to other doses, which was maintained up to the Week 12 time point. The ACR20 response rate and DAS28-CRP response for the 80 mg Q2W dose began to approximate the responses for the 180 mg Q2W dose around Week 12. Results for the mean ACR-N responses in both populations were consistent with those observed for the ACR20 and DAS28-CRP responses.[12] Given that the 80 mg Q2W and 180 mg Q2W dose regimens appeared to demonstrate similar ACR20 response rate and DAS28-CRP response around Week 12 in both bDMARD-naive and TNF-Inadequate Responder patient populations, the sponsor believed that evaluating an 80 mg Q2W dose in the Phase III studies in patients with PsA would provide close to maximal efficacious response while reducing the overall exposure to ixekizumab.

Rationale for the 80 mg Q4W dose regimen

The sponsor stated that the 80 mg Q4W dose regimen was selected for evaluation in the Phase III studies in patients with PsA because it was expected to provide a different exposure compared to the 80 mg Q2W dose regimen (average concentration at steady state ($C_{ave,ss}$) is approximately 50% lower for 80 mg Q4W than for 80 mg Q2W (7.74 µg/mL versus 3.67 µg/mL)).

In addition, an 80 mg Q4W dose regimen was predicted to have similar exposure and clinical responses as the 75 mg Q4W dose regimen, which resulted in significant and consistent improvement of skin symptoms (based on the main efficacy measures of the PASI and static Physician Global Assessment (sPGA) score) in the Phase II Study RHAJ in patients with Ps. Testing an 80 mg Q4W dose regimen in Phase III studies in patients with

[11] Disease Activity Score 28 diarthrodial joint count based on C-reactive protein
[12] A continuous measure of clinical, laboratory, and functional measure in rheumatoid arthritis that characterises the percentage of improvement from baseline in rheumatoid arthritis disease activity.

PsA allowed assessment of whether a dose regimen that demonstrated clinical response on skin symptoms was also effective on arthritic symptoms.

The elimination mechanism for monoclonal antibodies via catabolism is independent of disease condition. Therefore, the PK of ixekizumab in patients with psoriasis was expected to be similar to the PK of ixekizumab in patients with arthritic disease. Although an 80 mg Q4W dosing regimen was not tested in patients with RA, PK/PD modelling up to Week 16 using ACR20 and DAS28-CRP data from Study RHAK in patients with RA predicted that the 80 mg Q4W dosing regimen would be effective on arthritic manifestations. Therefore, the sponsor expected the 80 mg Q4W dose regimen to demonstrate efficacious responses in patients with PsA.

Evaluator's conclusions on dose finding for the pivotal studies

The sponsor's rationale for the two dosage regimens selected for the two Phase III pivotal studies in patients with PSA is considered to be satisfactory. The sponsor has undertaken no Phase II dose-ranging studies in patients with PsA. Therefore, dose ranging data from Phase II studies of ixekizumab in patients with RA and patients with Ps were used to identify appropriate doses to be evaluated in Phase III studies of ixekizumab in patients with PsA. PopPK data provided in the current submission indicates that the PK of ixekizumab in patients with psoriasis and PsA are similar.

Efficacy

Studies providing efficacy data

The submission included two pivotal Phase III studies (Studies RHAP, RHBE) in 780 patients supporting the application to extend the indications of ixekizumab to include the treatment of psoriatic arthritis (PsA). Both studies were stated by the sponsor to have been undertaken in compliance with the principles of Good Clinical Practice (GCP). Both studies are considered to be good quality pivotal clinical trials. Both studies have been fully evaluated.

In addition to the separate study reports for Studies RHAP and RHBE, the submission included a post hoc integrated analysis of efficacy based on pooled data from the placebo-controlled period (Weeks 0 to 24) of both studies. The integrated analysis set included a total of 679 patients, including 224 in the placebo group, 249 in the ixekizumab 80 mg Q4W group and 226 in the ixekizumab 80 mg Q2W group. In the integrated analysis set, efficacy outcomes were assessed in the total pooled population, subgroups of the total population, and in each of the two ixekizumab subgroups. The efficacy data from the integrated analysis has been evaluated.

The results of both Studies RHAP and RHBE have been recently published:

- Study RHAP (SPIRIT-P1) has been published in the Annals of Rheumatic Disease: Mease PJ, van der Heijde, Ritchlin CT et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis, double-blind, placebo-controlled and active (adalimumab)-controlled period of the Phase III trial SPIRIT-P1. Ann Rheum Dis 2017; 76: 79-87.
- Study RHBE (SPIRIT-P2) has been published in the Lancet: Nash P, Kirkham B, Okada M et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumor necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 Phase III trial. Lancet 2017; 389: 2317-27.

Evaluator's conclusions on efficacy

Two pivotal Phase III studies (Studies RHAP and RHBE) convincingly demonstrated the efficacy of ixekizumab (80 mg Q4W and 80 mg Q2W) compared with placebo in the double-blind treatment period (Weeks 0 to 24). The open-label extension period data (Weeks 24-52) from Study RHAP demonstrated that efficacy can be maintained with ixekizumab treatment through to Week 52. There are no efficacy data for ixekizumab for the treatment of PsA beyond 52 weeks.

Overall, the individual efficacy data from Studies RHAP and RHBE and the pooled data from the two studies support the recommended ixekizumab dosage regimen for PsA of 160 initially (2 x 80 mg injections) followed by 80 mg Q4W. The proposed dosing regimen for patients with PsA and co-existent moderate to severe plaque psoriasis is the same as for patients with plaque psoriasis, namely 160 mg (2 x 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. This dosage regimen is supported by the submitted efficacy data.

In Study RHAP (SPIRIT-P1), 417 patients with active PsA of ≥ 6 months duration, who met Classification Criteria for Psoriatic Arthritis (CASPAR) criteria and were Biologic disease-modifying anti-rheumatic drugs (bDMARD) naïve, were randomised to placebo (n=106), adalimumab 40 mg Q2W (n=101), ixekizumab (IXE) Q4W (n=107) or IXEQ2W (n=103). Patients on a stable dose of cDMARD at study entry were eligible for entry into the study as were patients who had a previous history of cDMARD use or who were cDMARD naïve. Patients with active PsA were also required to have active plaque psoriasis or a history of the disease.

In Study RHBE (SPIRIT-P2), 363 patients with active PsA of ≥ 6 months duration, who met CASPAR criteria, were cDMARD experienced and were either inadequate responders to TNFi or intolerant to treatment with this class of drug, were randomised to placebo (n=118), IXEQ4W (n=122) or IXEQ2W (n=123). Patients with active PsA were also required to have active plaque psoriasis or a history of the disease.

In both studies, the primary efficacy endpoint was the ACR20 response at Week 24 for the pairwise comparisons between both ixekizumab regimens and placebo in the intent-to-treat (ITT) population. In both studies, the ACR20 response at Week 24 was statistically significantly greater in both ixekizumab groups compared with the placebo group, and the results were consistent in both studies.

There were 6 major secondary efficacy endpoints (multiplicity-controlled) in Study RHAP and 5 major secondary efficacy endpoints (multiplicity-controlled) in Study RHBE. There were a number of other secondary efficacy endpoints (non-multiplicity controlled) in both studies which explored a variety of clinical outcomes.

In Study RHAP, 4 of the 6 major secondary efficacy endpoints were statistically significant in both ixekizumab groups compared with the placebo group based on the pre-specified procedure controlling for multiplicity (that is, Modified Total Sharp Score (mTSS) at Week 24, Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24, ACR20 at Week 12, and PASI 75 at Week 12 in patients with baseline psoriatic lesions ≥ 3%). The 2 non-statistically significant major secondary efficacy endpoints (multiplicity-controlled) were Leeds Enthesitis Index (LEI) score at Week 12 in patients with LEI score > 0 at baseline and Itch Numeric Rating Scale (NRS) at Week 12 in patients with baseline psoriatic lesions ≥ 3%. The results for other secondary efficacy endpoints (non-multiplicity-controlled) generally favoured the two ixekizumab groups compared with placebo.

In Study RHBE, 4 of the 5 major secondary efficacy endpoints were statistically significant in both ixekizumab groups compared with the placebo group based on the pre-specified procedure controlling for multiplicity (that is, HAQ-DI at Week 24, ACR20 at Week 12,

PASI 75 at Week 12 in patients with baseline psoriatic lesions ≥ 3%, and Minimum Disease Activity (MDA) at Week 24). The 1 non-statistically significant major secondary efficacy endpoints (multiplicity-controlled) was LEI (0) score at Week 12 in patients with LEI score > 0 at baseline. The results for other secondary efficacy endpoints (non-multiplicity-controlled) generally favoured the two ixekizumab groups compared with the placebo group.

In Study RHAP, efficacy data for the extension period (Weeks 24-52) were provided for a total of 381 patients who were assigned to 1 of 6 treatment groups (that is, placebo (PBO)/IXEQ4W (n=45), PBO/IXEQ2W (n=46), adalimumab /IXEQ4W (n=49), adalimumab /IXEQ2W (n=48), IXEQ4W/IXEQ4W (n=97) and IXEQ2W/IXEQ2W (n=96)). The data showed that efficacy endpoints of ACR20/50/70, DAS28-CRP, MDA, Psoriatic Arthritis Response Criteria (PsARC), HAQ-DI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Leeds Dactylitis Index (LDI-B), LEI, skin and nail disease assessments, and health outcome/quality-of-life assessments were stable or continued to improve (that is, Nail Psoriasis Severity Index (NAPSI)) during the extension period in the ixekizumab/ixekizumab groups (that is, patients who had received ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W from Week 0 through to Week 52). The majority of Week 24 responders in both the ixekizumab/ixekizumab groups maintained response at Week 52 for most of the key efficacy endpoints.

Overall, in Study RHAP efficacy at Week 52 was observed for patients remaining on IXE80 mg Q4W or IXE80 mg Q2W or switching to IXE80 mg Q4W or IXE80 mg Q2W at Week 24 from placebo or adalimumab 40 mg Q2W for all key endpoints. There was no placebo group in the extension period (Weeks 24-52), but the efficacy data for patients who were initially randomised (Week 0) to IXE80 mg Q4W or IXE80 mg Q2W and continued in the same group through to Week 52 were robust. It is considered that the strength of the extension period efficacy data in these two ixekizumab treatment groups largely mitigates the limitations arising from the absence of a placebo group in this period.

There were no efficacy data in patients treated with ixekizumab for longer than 52 weeks in either Study RHAP or RHBE. However, it appears that both studies are ongoing and that the sponsor intends to submit long-term efficacy data at a future date. The absence of efficacy data for longer than 52 weeks should not preclude approval of ixekizumab for the treatment of PsA, as the available extension period efficacy data from Study RHAP appeared to be reasonably stable through to Week 52 with no significant diminished effects with continued treatment.

The demographic and baseline disease characteristics of the 2 pivotal Phase III studies are considered to be satisfactory. The mean (±SD) CASPAR total score was 4.7 ± 0.5 in Study RHPA and 4.1% ± 0.85 in Study RHBE. The Moll and Wright classification criteria were comparable for the two studies. The median time since PsA diagnosis was longer in Study RHBE compared with Study RHAP (8.2 versus 4.1 years, respectively), while the median time since PsA onset was comparable in the two studies (14.8, versus 15.2, respectively). Enthesitis was present in 58.0% of patients in Study RHAP and 75.2% of patients in Study RHBE, while dactylitis was present in 37.6% and 23.7% of patients in the two studies, respectively. The individual components of the ACR core criteria were similar for the two studies, apart from a higher incidence of patients with CRP > 6 mg/L in Study RHAP compared with Study RHBE (60.0% versus 47.5%).

The mean (±standard deviation (SD)) age in the two studies was comparable (49.5 ± 11.9 years, Study RHAP; 51.9 ± 12.0 years, Study RHBE), and the majority of patients in both studies were aged < 65 years (89.4%, Study RHAP; 82.9%, Study RHBE). In both studies, the majority of patients were female (54.0%, Study RHAP; 53.4%) and White (94.0%, Study RHAP; 91.7%, RHBE). Of note, in both studies the majority of patients had a body mass index (BMI) in the overweight/obese/extreme obese category (74.8% in Study RHAP; 80.4% in Study RHBE). The sponsor is asked to comment on the significance of the

observation and the potential impact it might have on extrapolating the efficacy (and safety data) from the two studies to patients with PsA in the Australian community.

The proportion of patients using MTX at randomisation was higher in Study RHAP compared with Study RHBE (54.2% versus 41.0%), as was current cDMARD use (54.0% versus 51.0%). In accordance with the protocol no patients in Study RHBE were cDMARD naïve, while 14.6% of patients in Study RHAP were cDMARD naïve (no current use or no history of use). In accordance with the protocol all patients in Study RHAP were TNFi naïve, while in Study RHBE inadequate response to 1 or 2 TNFi was reported in 91.5% of patients and intolerance to TNFi in 8.5% of patients.

The submission included an analysis of pooled data from Studies RHAP and RHBE from the placebo-controlled double-blind treatment period (Weeks 0-24). The analysis included a total of 679 patients (placebo (n=224); IXE80Q4W (n=229); IXE80Q2W (n=226)). It is considered that the two patient populations from the two studies are sufficiently similar to allow the efficacy data to be pooled, although all patients in Study RHAP were TNFi naïve while all patients in Study RHBE were TNFi experienced. The pooled efficacy data were consistent with the efficacy data from each of the two individual studies for the comparisons between the two ixekizumab groups and the placebo group, and comparison of efficacy outcomes between the two ixekizumab groups identified no marked differences between the two groups.

Subgroup analyses of ACR20 and ACR50 response rates at Week 24 were undertaken in the pooled data from Studies RHAP and RHBE. Significant subgroup interactions for ACR20 response at Week 24 were observed for gender (efficacy favoured males), weight (efficacy favoured patients in the ≥ 80 to < 100 kg group and patients in the ≥ 50th to < 75th percentile), baseline CRP (efficacy favoured patients with higher baseline CRP of > 6 mg/mL), and duration of disease (efficacy favoured patients with a disease duration of ≥ 5 years). There were no significant subgroup interactions for ACR20 response at Week 24 for baseline cDMARD or MTX use. There no subgroup interactions for ACR20 response at Week 24 based on age (< 65, ≥ 65 to < 75, or ≥ 75 years). Significant subgroup interactions for ACR50 response at Week 24 were observed for duration of disease (efficacy favoured patients with a disease duration of ≥ 5 years), MTX use at baseline (efficacy favoured patients without MTX use), and cDMARD use at baseline (efficacy favoured patients without cDMARD use).

There were no data in the submission in patients with active PsA and co-existent active severe-to-moderate plaque psoriasis exploring the proposed dose of ixekizumab in this patient group (that is, 160 mg initially followed by 80 mg Q2W for 12 weeks and then 80 mg Q4W). The integrated efficacy data for Studies RHAP and RHBE in patients with PsA and co-existent active moderate-to-severe plaque psoriasis showed that both ixekizumab 80 mg Q2W and ixekizumab 80 mg Q2W were more statistically more efficacious compared with placebo at both Weeks 12 and 24. In this patient group, the numerical results for the efficacy outcomes at Weeks 12 and 24 were consistently superior in ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group. Data from the integrated Ps program in patients with moderate-to-severe plaque psoriasis showed that the difference in PASI75/90/100 response rates between ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W at Week 12 were similar in patients with Ps and in patients with coexistent Ps and self-identified PsA. The data indicated that efficacy was greater in patients treated with ixekizumab 80 mg Q2W compared with ixekizumab 80 mg Q4W in both Ps and coexistent Ps and PsA. Overall, the data are considered to support the proposed dosing regimen for patients with PsA and co-existent moderate-to-severe plaque Ps, which is the same dose approved for the treatment patients with moderate-to-severe plaque Ps.

There were no efficacy data in the submission evaluating the effects on PsA of discontinuing treatment with ixekizumab. The submission included the protocol for the

ongoing Phase III Study RHBF which aims to compare ixekizumab 80 mg Q2W with placebo for the maintenance of treatment response, as measured by the time to relapse during the randomised double-blind withdrawal period in cDMARD-inadequate responders and bDMARD-naive patients with active PsA who meet randomisation criteria (Coates criteria for MDA for 3 consecutive months over 4 consecutive visits). The study includes a 36 week, initial, open-label treatment period, examining the effect of IXE80Q2W in patients with active PsA who are cDMARD-inadequate responders and bDMARD-naive, followed by a randomised, double-blind withdrawal period from Week 36 to Week 104 comparing the effects of IXE80Q2W with placebo on time to relapse. The submission included safety data from RHBF as of the cut-off date for the submission.

Safety

Studies providing safety data

In the ixekizumab clinical development program, 1118 patients with active PsA received at least 1 dose of ixekizumab through to September 2016, representing 1050.6 patients-years of exposure. In addition, updated safety data in patients with moderate-to-severe plaque psoriasis included indicate that 5689 patients with this condition received at least 1 dose of ixekizumab through to September 2016, representing 12061.5 patient years of exposure. The safety population was defined as all patients who receive at least 1 dose of study drug.

The key safety data directly related to the application to extend the indications of ixekizumab to include the treatment of patients with PsA are from the two pivotal Phase III studies (Studies RHAP and RHBE). The submission included an integrated safety analysis from the two studies based on the placebo-controlled, double-blind treatment periods (Week 0-24) in a total of 678 patients randomised to placebo (n=224), ixekizumab 80 mg Q4W (n=229) or ixekizumab 80 mg Q2W (n=225). This analysis set excluded patients randomised to adalimumab in Study RHAP. In this evaluation, this integrated data set is termed the 'Primary PsA Analysis Set'. The primary analysis in 'Primary PsA Analysis Set' was conducted using data from the full period (Weeks 0 to 24), but excluding data from Weeks 16 to 24 in inadequate responders at Week 16 in order to avoid falsely attributing risk from rescue medication alone or in combination with the study drug to the randomised therapy. Supplementary analyses were also performed based on the 'Primary PsA Analysis Set' for Weeks 0 to 16 (that is, prior to rescue therapy), and Weeks 0 to 24 including the data from inadequate responders at Week 16. Overall, the findings from the supportive analyses were consistent with the findings from the primary analysis.

In addition to the 'Primary PsA Analysis Set', safety in patients with PsA was also evaluated in the data set referred to as the 'All PsA Analysis Set' in order to provide additional exposure and non-comparative safety data from all of the ixekizumab PsA studies. The primary analysis was conducted on all data after Week 0 for all periods. The sponsor stated, that in line with the Committee for Medicinal Products for Human Use (CHMP) scientific advice, in addition to all patients randomised to ixekizumab in Studies RHAP and RHBE the 'All PsA Analysis Set' also included safety data from patients initially randomised to placebo (Studies RHAP and RHBE) or adalimumab (Study RHAP) who were subsequently re-randomised to ixekizumab at Week 16 (inadequate responders) or Week 24. For Study RHAP, the safety profile for those patients who switched to ixekizumab at Week 16 or 24 was similar to that for patients who were treated with ixekizumab for up to 1 year.

The submission also included updated integrated data safety data on patients with moderate-to-severe plaque psoriasis exposed to at least 1 dose of ixekizumab referred to

as the 'All Ps Analysis Set'. This analysis set included update safety data on 5689 patients from 11 studies.

The evaluation of safety in this report focuses on the data in patients with PsA included in the primary analysis based on the 'PsA Primary Analysis Set' and the 'All PsA Analysis Set', while the safety data from the large integrated safety set in patients with Ps ('All Ps Set') have also been reviewed.

Deaths, TEAEs and serious adverse events (SAEs) were examined for all three analysis safety sets, as were other measures of safety, such as the severity of AEs, investigator assessment of the relationship of AEs to study treatment, AEs resulting in discontinuation of study drug, laboratory parameters, vital signs and electrocardiogram (ECG) data. Adverse events of special interest (AESI) were also examined across the analysis sets.

Patient exposure

Studies RHAP and RHBE

Exposure in the double blind treatment period (Weeks 0-24) in Studies RHAP and RHBE is summarised below in Table 1. A total of 779 patients with active PsA were evaluated in the two studies (229 patients in the IXE80Q4W group; 225 patients in the IXE80Q2W group; 101 patients in the adalimumab 40Q2W group; and 224 patients in the placebo group).

Table 1: Exposure in days in patients (n [%]) in in Studies RHAP and RHBE, double blind treatment period)

	Study RHAP				Study RHBE				
Days	P n= 106	A 40 Q2W n= 101	IXE 80 Q4W n= 107	IXE 80 Q2W n= 102	T IXE n= 209	P= 118	IXE 80 Q4W n= 122	IXE 80 Q2W n= 123	IXE T n= 245
≥ 30	103 (97.2)	98 (97.0)	103 (96.3)	100 (98.0)	203 (97.1)	115 (97.5)	119 (97.5)	120 (97.6)	239 (97.6)
≥ 90	98 (92.5)	98 (97.0)	102 (95.3)	100 (98.0)	202 (96.7)	103 (87.3)	116 (95.1	114 (92.7)	230 (93.9)
≥ 120	66 (62.3)	90 (89.1)	89 (83.2)	88 (86.3)	177 (84.7)	70 (59.3)	102 (83.6)	95 (77.2)	197 (80.4)
≥ 183	1 (0.9)	3 (3.0)	1 (0.9)	0	1 (0.5)	4 (3.4)	3 (2.5)	3 (2.4)	6 (2.4)
PYE	41.3	44.5	45.6	44.5	90.1	44.4	52.4	50.9	103.2

Note: PYE = total patient-years of exposure; P=placebo; T=total; A= adalimumab

Primary PsA analysis set double-blind treatment period (Weeks 0-24)

Exposure in the 'Primary PsA Analysis Set' is summarised below in Table 2. In the 'Primary PsA Analysis Set', the mean ± SD total dose of the study drug was 510.7 ± 99.14 mg in the ixekizumab 80 mg QW4 group and 938.0 ± 204.16 mg in the ixekizumab 80 mg QW2 group, and the mean ± SD number of injections was 6.4 ± 1.24 and 11.7 ± 2.55, respectively.

Table 2: Exposure (days) in patients (n [%]), 'Primary PsA Analysis Set' (Studies RHAP and RHBE).

Primary PsA Analysis Set				
Days	**Placebo (n=224)**	**IXE80Q4W (n=229)**	**IXE80Q2W (n=225)**	**Total IXE (n=454)**
> 0	224 (100.0%)	229 (100.0%)	225 (100.0%)	454 (100.0%)
≥ 7	223 (99.6%)	229 (100.0%)	225 (100.0%)	454 (100.0%)
≥ 14	223 (99.6%)	226 (98.7%)	225 (100.0%)	451 (99.3%)
≥30	218 (97.3%)	223 (97.4%)	220 (97.8%)	443 (97.6%)
≥90	201 (89.7%)	219 (95.6%)	214 (95.1%)	433 (95.4%)
≥120	136 (60.7%)	191 (83.4%)	183 (81.3%)	374 (82.4%)
≥183	NA	NA	NA	NA
PYE	**85.7**	**98.3**	**95.5**	**193.8**

Note: PYE = total patient-years of exposure.

All PsA analysis set

Exposure in the 'All PsA Analysis Set' is summarised below in Table 3. Of note, 610 patients with PsA have been treated with ixekizumab for ≥ 6 months and 365 patients for ≥ 12 months. In the 'All PsA Analysis Set', the mean ± SD total dose of the study drug was 1359.1 ± 900.89 mg in the ixekizumab 80 mg Q4W group and 1259.9 ± 1822.83 mg in the ixekizumab 80 mg Q2W group, and the mean ± SD number of injections was 17.0 ± 11.26 and 20.2 ± 20.07, respectively.

Table 3: Exposure (days) in patients (n [%]), All PsA Analysis Set (RHAP, RHBE, RHBF)

Days	IXE80Q4W (n=365)	IXE80Q2W (n=752)	Pooled IXE (n=1118) [a]
≥ 30	356 (97.5%)	734 (97.6%)	1090 (97.6%)
≥ 60	343 (94.0%)	720 (95.7%)	1063 (95.2%)
≥ 120	320 (87.7%)	471 (62.6%)	791 (70.8%)
≥ 183	296 (81.1%)	314 (41.8%)	610 (54.6%)
≥ 365 (1 year)	183 (50.1%)	182 (24.2%)	365 (32.7%)
≥ 730 (2 years)	103 (28.2%)	105 (14.0%)	208 (18.6%)
≥ 1095 (3 years)	3 (0.8%)	5 (0.7%)	8 (0.7%)
PYE	**465.7**	**584.9**	**1050.6**

Note: PYE = total patient-years of exposure. a = One patient in Study RHAP received ixekizumab due to a drug dispensing error. In the exposure calculations for the 'All PsA Analysis Set', this patient is included in the pooled IXE group but is excluded from the individual dosing regimens.

All Ps analysis set

Exposure in the 'All Ps Analysis Set' is summarised below in Table 4. Of note, 3787 patients with Ps have been treated with ixekizumab for ≥ 365 days. The mean ± SD total dose of ixekizumab was 552 ± 341 mg, and the mean ± SD number of injections was 8.5 ± 7.44.

Table 4: Exposure (days) in patients (n) in patients with psoriasis 'All Ps Analysis Set'

Days	Pooled IXE (n=5689), n (%)
≥ 90	5461 (96.0%)
≥ 120	5374 (94.5%)
≥ 183	5186 (91.2%)
≥ 365	3787 (66.6%)
≥ 730	3162 (55.6%)
≥ 1095	1659 (29.2%)
≥ 1460	281 (4.9%)
PYE	**12061.5**

PYE = total patient-years of exposure

Evaluation of adverse events (other than AESI) with possible regulatory impact

Haematological – other than cytopaenias (AESI)

Primary PsA analysis set

TE-high or TE-low haematology laboratory values (other than cytopaenias (AESI)) reported in patients in the 'Primary PsA Analysis Set' are summarised below in Table 5.There was a small increase in mean corpuscular volume (MCV) in the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups compared with the placebo group, while low erythrocyte, haematocrit (Hct) and haemoglobin (Hb) values were reported more frequently in both the ixekizumab 80 mg Q4W group and the ixekizumab 80 mg Q2W group compared with the placebo group. Overall, ixekizumab had no clinically significant effects as regards abnormally high or low red blood cell parameters compared with placebo

Table 5: Treatment-emergent low or high haematology laboratory values (other than cytopaenias (AESI)) at any time post-baseline, Primary PsA Analysis Set (Studies RHAP and RHBE)

Parameter		Placebo	IXEQ4W	IXEQ2W	Total IXE
MCV (fL)	Low	1/ 218 (0.5%)	2/ 226 (0.9%)	3/ 221 (1.4%)	5/ 447 (1.1%)

Parameter		Placebo	IXEQ4W	IXEQ2W	Total IXE
	High	0/220	0/227	6/221 (2.7%)	6/448 (1.3%)
Erythrocytes (10^{12}/L)	Low	11/214 (5.1%)	3/222 (1.4%)	8/218 (3.7%)	11/440 (2.5%)
	High	2/ 221 (0.9%)	2/ 228 (0.9%)	0/ 224	2/ 452 (0.4%)
Hct (fraction of 1)	Low	15/214 (7.0%)	5/217 (2.3%)	7/215 (3.3%)	12/432 (2.8%)
	High	3/ 221 (1.4%)	1/ 229 (0.4%)	3/ 224 (1.3%)	4/ 453 (0.9%)
Hb (mml/L-Fe)	Low	13/95 (13.7%)	1/102 (1.0%)	2/93 (2.2%)	3/195 (1.5%)
	High	0/ 105	0/ 107	0/ 102	0/ 209
Basophils (10^9/L)	Low	0/ 222	0/ 229	0/ 224	0/ 453
	High	2/ 215 (5.6%)	11/ 221 (5.0%)	10/ 221 (4.5%)	21/ 442 (4.8%)
Eosinophils (10^9/L)	Low	0/ 222	0/ 229	0/ 224	0/ 453
	High	6/ 221 (2.7%)	6/ 225 (2.7%)	2/ 220 (0.9%)	8/ 445 (1.8%)
Monocytes (10^9/L)	Low	0/ 222	0/ 229	0/ 224	0/ 453
	High	11/ 218 (5.0%)	8/ 222 (3.6%)	6/ 220 (2.7%)	14/ 442 (3.2%)

Overall, ixekizumab had no clinically significant effects as regards mean change from baseline in haematological parameters, other than cytopaenias (AESI), compared with placebo.

All PsA Analysis Set

TE-high or TE-low haematology laboratory values (other than cytopaenias (AESI)) reported in patients in pooled ixekizumab group in the 'Primary PsA Analysis Set' are summarised below in Table 6. The results suggest that ixekizumab has no significant haematological toxicity for parameters other than AESI cytopaenias.

Table 6: Treatment-emergent low or high haematology laboratory values (other than cytopaenias (AESI)) at any time post-baseline, All PsA Analysis Set

Parameter	Pooled Ixekizumab group	
	TE-Low	TE-High
Blood basophils (10^9/L)	0/1112	48/1086 (4.4%)

Parameter	Pooled Ixekizumab group	
Blood eosinophils (10^9/L)	0/1112	21/1099 (1.9%)
RBC (10^{12}/L)	25/1087 (2.3%)	8/1110 (0.7%)
Hct (fraction of 1)	25/1072 (2.3%)	12/1112 (1.1%)
Hb (mL/L-Fe)	14/ 365 (3.8%)	5/ 385 (1.3%)
Blood monocytes (10^9/L)	0/1112	30/1084 (2.8%)

All Ps analysis set

In the 'All Ps Analysis Set', the percentage of patients with psoriasis treated with ixekizumab reporting TE-high or TE-low values did not exceed 10% for any of the haematology parameters, other than cytopaenias (AESI).

Renal and urinary disorders

Primary PsA analysis set

Renal and urinary disorders SOC were reported in a similar proportion of patients in the treatment groups in the 'Primary PsA Analysis Set' (that is, 1.8%, n=4, placebo; 1.3%, n=3, IXE80Q4W; 1.8%, n=4, IXE80Q2W; 1.5%, n=7, total IXE). The TEAEs (preferred term) in the total ixekizumab group were renal colic (x2, 0.4%), nephropathy (x 1, 0.2%), urinary incontinence (x 1, 0.2%), nephrolithiasis (x 1, 0.2%), cystitis (x 1, 0.2%), and leucocyturia (x 1, 0.2%). The TEAEs (preferred term) in the placebo group were nephrolithiasis (x2, 0.9%), costovertebral angle tenderness nephrolithiasis (x1, 0.4%), and dysuria nephrolithiasis (x 1, 0.4%). In the 'Primary PsA Analysis Set', blood creatinine TEAEs increased were reported infrequently in all treatment groups (0%, placebo; 0.4% (n=1), IX80Q4W; 0%, IXE80Q2W; and 0.2%, n=1, total IXE).

In the 'Primary PsA Analysis Set', TE-low creatinine clearance laboratory values (µmol/L) at any time post-baseline in the placebo-controlled, double-blind treatment period (Weeks 0 to 24) were reported in 4.7% (9/193) of patients in the placebo group, 5.4% (11/205) of patients in the IXE80Q4W group, 9.3% (18/193) of patients in the IXEQ2W group and 7.3% (29/398) of patients in the total IXE group.

In the 'Primary PsA Analysis Set', there was a statistically significantly larger decrease from minimum baseline to maximum last observation post-baseline in LS mean (± SE) creatinine clearance mL/min values for all ixekizumab groups compared with the placebo group (-0.5 ± 1.09, placebo; -3.7 ± 1.07, IXE80Q4W; -3.9 ± 1.08, IXE80Q2W; -3.8 ± 0.76, total IXE).

All PsA analysis set

In the 'All PsA Analysis Set' (all periods), *Renal and urinary disorders (SOC)* were reported in 2.8% (31/1118) of patients in the pooled ixekizumab group. TEAEs in this SOC reported in ≥ 2 patients were dysuria (n=4, 0.4%), nephrolithiasis (n=3, 0.3%), pollakiuria (n=3, 0.3%), renal colic (n=3, 0.3%), urinary incontinence (n=3, 0.3%), leucocyturia (n=2, 0.2%), proteinuria (n=2, 0.2%), and renal cyst. The TEAE of blood creatinine increased was reported in 1 (0.1%) patient in the pooled ixekizumab group. In the pooled ixekizumab group, TE-low laboratory creatinine clearance (mL/s) values at any time post-baseline were reported in 7.6% (76/997) of patients, and TE-high laboratory serum creatinine levels (µmol/L) were reported in 3.5% (88/1064) of patients.

All Ps analysis set

In the 'All Ps Analysis Set', *Renal and urinary disorders (SOC)* were reported in 4.6% (261/5689) of patients with psoriasis treated with ixekizumab. TEAEs reported in ≥ 10 patients were nephrolithiasis (1.4%, n=78), haematuria (0.7%, n=39), proteinuria (0.4%, n=25), renal colic (0.3%, n=18), dysuria (0.3%, n=16), and renal cyst (0.2%, n=14). SAEs were reported in 26 (0.5%) patients, and events reported in ≥ 2 patients were nephrolithiasis (0.2%, n=10), acute kidney injury (0.1%, n=3), and renal colic (0.1%, n=3). AEs (including death) leading to discontinuation of the study drug were reported in 3 (0.1%) patients, and comprised one event each for glomerulonephritis, nephrotic syndrome, and urinary tract infection.

Skin and subcutaneous

Primary PsA analysis set

Skin subcutaneous tissue disorders (SOC) were reported more frequently in the ixekizumab groups than in the placebo group in patients in the 'Primary PsA Analysis Set' (5.4%, n=12, placebo; 9.6% (n=22),IXE80Q4W; 10.2%, n=23, IXE80Q2W; 9.9%, n=45, total IXE). The incidence of *Skin subcutaneous tissue disorders (SOC)* was statistically significantly higher in the total ixekizumab group compared with the placebo group.

Preferred terms reported in ≥ 3 (0.7%) patients in the total IXE group versus the placebo group, respectively, were alopecia (1.3%, n=6 versus 0.9%, n=2), erythema (0.9%, n=4 versus 0%), skin lesion (0.9%, n=4 versus 0%), eczema (0.7%, n=3 versus 0%), rash (0.7%, n=3 versus 0%), urticaria (0.7%, n=3 versus 0%), pruritus (0.7%, n=3 versus 1.3%, n=3%), and in-growing nail (0.7%, n=3 versus 0%). There were no reported cases of Stevens-Johnson syndrome or toxic epidermal necrolysis in the 'Primary PsA Analysis Set'.

All PsA analysis set

In the 'All PsA Analysis Set' *Skin and subcutaneous tissue disorders (SOC)* were reported in 11.0% (n=123) of patients in the pooled ixekizumab group (n=1118), with TEAEs reported in ≥ 1% of patients being psoriasis (1.2%, n=13), alopecia (1.1%, n=12), pruritus (1.1%, n=12), and rash (1.1%, n=12). SAEs were reported in 1 (0.1%) patient (1 x angioedema). AEs leading to discontinuation of the study drug were reported in 5 (0.4%) patients, and were one each for angioedema, drug eruption, palmar plantar erythrodysaesthesia syndrome, rash, and rash pruritic.

All Ps analysis set

In the 'All Ps Analysis Set', *Skin and subcutaneous tissue disorders (SOC)* were reported in 25.3% (1438/5689) of patients with psoriasis treated with ixekizumab. TEAEs reported in ≥ 1% of patients were pruritus (3.5%), psoriasis (3.4%), dermatitis contact (2.6%), eczema (2.5%), urticaria (1.6%), dermatitis (1.5%), seborrhoeic dermatitis (1.2%), rash (1.1%), intertrigo (1.1%) nail psoriasis (1.0%), and acne (1.0%). SAEs were reported in 26 (0.5%) patients, and events reported in ≥ 2 patients were psoriasis (0.1%, n=6), urticaria (0.1%, n=5), pustular psoriasis (0.1%, n=3), angioedema (< 0.1%, n=2), dermatitis contact (< 0.1%, n=2), and hypersensitivity vasculitis (< 0.1%, n=2). AEs leading to discontinuation of the study drug were reported in 35 (0.9%) patients, and events reported in ≥ 2 patients were psoriasis (0.2%, n=9), pustular psoriasis (0.1%, n=4), urticaria (0.1%, n=3), dermatitis contact (< 0.1%, n=2), eczema (< 0.1%, n=2), pruritus generalised (< 0.1%, n=2), and rash generalised (< 0.1%, n=2).

Clinical chemistry laboratory values, other than hepatic-related, TE-high and TE-low values.

Primary PsA Analysis Set

The sponsor reviewed the TE-high or TE-low clinical chemistry laboratory values other than hepatic-related tests (alanine aminotransferase (ALT), aspartate aminotransferase

(AST), alkaline phosphatase (ALP), and total bilirubin) for the 'Primary PsA Analysis Set' and concluded that there were no clinically relevant changes in these laboratory tests during the study. There were, however, some statistically significant differences and these are summarised below in Table 7.

Table 7: Statistically significant TE-High or TE-Low clinical chemistry laboratory values (other than hepatic-related tests), Primary PsA Analysis Set

Laboratory Value (unit)	TE High or Low*	Placebo N=224 n/Nx (%)	80 mg Q4W N=229 n/Nx (%)	80 mg Q2W N=225 n/Nx (%)	Total IXE N=454 n/Nx (%)
Albumin (g/L)	Low	5/221 (2.3%)	0/224[a]	3/221 (1.4%)	3/445 (0.7%)
C-Reactive Protein (mg/L)	High	38/135 (28.1%)	23/133 (17.3%)[a]	27/147 (18.4%)	50/280 (17.9%)[a]
Calcium (mmol/L)	Low	4/223 (1.8%)	0/229[a]	0/225[a]	0/454[a]
HDL Cholesterol (mmol/L)	High	6/204 (2.9%)	21/205 (10.2%)[a]	12/200 (6.0%)	33/405 (8.1%)[a]
Protein (g/L)	Low	0/222	2/229 (0.9%)	5/223 (2.2%)[a]	7/452 (1.5%)
Triglycerides (mmol/L)	High	0/218	3/224 (1.3%)	4/220 (1.8%)[a]	7/444 (1.6%)
VLDL Cholesterol (mmol/L)	High	25/145 (17.2%)	39/170 (22.9%)	53/152 (34.9%)[a,b]	92/322 (28.6%)[a]

Notes: N = number of patients in the analysis population; n = patients with ≥1 event; Nx = number of evaluable patients; PsA = psoriatic arthritis; TE = treatment-emergent; VLDL = very low-density lipoprotein. * A TE-low result is defined as a change from values greater than or equal to the lower limit of normal (LLN) at baseline, to a value less than the LLN at any time during the treatment period. A TE-high result is defined as a change from values less than or equal to the upper limit of normal (ULN) at baseline, to a value more than the ULN at any time during the treatment period. ULN/LLN: upper/lower limit normal from large clinical trial, population-based reference limits (Lilly reference limits). a. Statistically significant compared with placebo ($p<0.05$). b. Statistically significant comparison of ixekizumab 80 mg Q2W versus Q4W ($p<0.05$).

The sponsor indicated that clinically important cases of clinical laboratory changes comprised 4 patients (2 in each of the ixekizumab groups) with treatment-emergent creatine kinase (CK) levels above 5000 international units (IU)/L. These cases were either transient and/or apparently associated with skeletal muscular contractions, exercise, or exertional-induced rhabdomyolysis.

A statistically significant greater proportion of patients in the ixekizumab 80 mg Q2W group had TE-high serum HDL-cholesterol, TE-high serum triglyceride and TE-high serum VLDL levels compared with the placebo group. A statistically significant greater proportion of patients in the ixekizumab 80 mg Q2W group had TE-high serum very low-density lipoproteins (VLDL) cholesterol levels compared with the ixekizumab Q4W group. In the total ixekizumab group, the proportion of patients with TE-high serum VLDL cholesterol levels was statistically significantly greater compared with the placebo group (28.6% versus 17.2%, respectively, $p<0.05$), as was the proportion of patients with TE-high serum high-density lipoproteins (HDL) cholesterol levels (8.1% versus 2.9%, respectively, $p < 0.05$). The proportion of patients with TE-high serum triglyceride level was numerically greater in the total ixekizumab group compared with the placebo group, but the difference between the two groups was small and not statistically significant (1.6% versus 0%, respectively). The greater incidence of TE-high serum VLDL cholesterol levels in the ixekizumab group compared with the placebo group could potentially increase the risk of cardiovascular disease in the ixekizumab group. However, the mean (±SD) changes from baseline to last observation for serum VLDL cholesterol levels (mmol/L) for the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, and total ixekizumab groups compared with the placebo group were small and not statistically significant (Q4W, 0.04 ± 0.24; Q2W, 0.04 ± 0.32; total ixekizumab, 0.04 ± 0.28; and placebo, 0.03 ± 0.29). The mean changes from baseline at Weeks 4, 12, and 24 in serum VLDL cholesterol levels were relatively consistent, indicating no increase in the parameter over time.

The mean (± SD) change in serum total cholesterol (mmol/L) from baseline to Week 24 was numerically higher in the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W and total

ixekizumab groups compared with the placebo group, with the differences between both the ixekizumab 80 mg Q4W and the total ixekizumab groups compared with the placebo group being statistically significant ($p<0.05$) (Q4W, 0.21 ± 0.69; Q2W, 0.10 ± 0.73; total ixekizumab, 0.16 ± 0.71; and placebo, -0.01 ± 0.65). However, the numerical differences across the treatment groups in change from baseline to Week 24 in serum total cholesterol were small. In addition, the proportion of patients with TE-high serum total cholesterol (mmol/L) was small across the treatment groups, with no notable differences between the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, total ixekizumab and placebo groups (Q4W, 1.3%; Q2W, 0.5%; total ixekizumab, 0.9%; and placebo, 1.4%). The results suggest that there is no clinically meaningful difference across the treatment groups as regards change from baseline to Week 24 in the serum total cholesterol level.

The mean (± SD) change in serum low-density lipoproteins (LDL) cholesterol (mmol/L) from baseline to Week 24 was numerically higher in the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W and total ixekizumab groups compared with placebo, with the differences between both the ixekizumab 80 mg Q4W and the total ixekizumab groups compared with the placebo group being statistically significant ($p<0.05$) (Q4W, 0.12 ± 0.57; Q2W, 0.11 ± 0.63; total ixekizumab, 0.12 ± 0.60; and placebo, -0.03 ± 0.56). However, the numerical differences across the treatment groups in change from baseline to Week 24 in serum LDL cholesterol levels were small. In addition, the proportion of patients with TE-high serum LDL cholesterol (mmol/L) levels was small across the treatment groups, with no notable differences between the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, total ixekizumab and placebo groups (Q4W, 0.5%; Q2W, 0.5%; total ixekizumab, 0.5%; and placebo, 0.9%).The results suggest that there is no clinically meaningful difference across the treatment groups as regards change from baseline to Week 24 in the serum LDL cholesterol levels.

Overall, the results for change from baseline to Week 24 in serum total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides suggest that ixekizumab does not increase the risk of cardiovascular disease based on these biochemical factors compared with placebo.

TEAEs of blood triglycerides increased were reported in 0% of patients in the placebo group, 0.5% (n=1) patient in the ixekizumab 80 mg Q4W group, 0.4% (n=1) patient in the ixekizumab 80 mg Q2W group, and 0.4% (n=2) of patients in the total ixekizumab group. TEAEs of hypercholesterolaemia were reported in 0% of patients in the placebo group, 0.5% (n=1) patient in the ixekizumab 80 mg Q4W group, 0.4% (n=1) patient in the ixekizumab 80 mg Q2W group, and 0.4% (n=2) of patients in the total ixekizumab group.

All PsA Analysis Set

In the 'All Ps Analysis Set', TE-high or TE-low clinical chemistry laboratory values (other than hepatic-related tests) reported in ≥ 10% of in patients in the pooled ixekizumab group were TE-high creatinine clearance mL/s (18.7%, 95/507)), TE-low bicarbonate mmol/L(39.5%, 314/794), TE-high CRP mg/mL(19.8%, 151/761), TE-high Gamma-glutamyltransferase (GGT) U/L (10.7%, 100/934), and TE-high VLDL cholesterol mmol/L (28.5%, 221/776).

Clinical chemistry laboratory values of interest (other than hepatic-related tests) were TE-high serum creatinine kinase U/L (8.2%, 88/1704), TE-high glucose mmol/L (3.4%, 28/812), TE-high serum HDL cholesterol mmol/L (6.6%, 65/989) and TE-high serum triglycerides mmol/L (1.6%, 17/1090).

In the 'All PsA Analysis Set', TE-high serum total cholesterol was reported in 1.5% (n=16) of patients, TE-high serum HDL cholesterol was reported in 6.6% (n=65) of patients, TE-high serum LDL cholesterol was reported in 0.4% (n=4) of patients, and TE-high serum triglycerides was reported in 1.6% (n=17) of patients. TEAE hypercholesterolaemia was reported in 0.6% (n=7) of patients and TEAE blood triglycerides increased was reported

in 0.5% (n=6) of patients. Overall, the lipid profile in patients in the 'All PsA Analysis Set' suggests that changes during the course of exposure to ixekizumab are unlikely to increase the risk of cardiovascular disease.

All Ps analysis set

In the 'All PsA Analysis Set', TE-high or TE-low clinical chemistry laboratory values (other than hepatic-related tests) reported in ≥ 10% of patients with psoriasis treated with ixekizumab were: TE-high creatinine clearance (28.9%); TE-low creatinine clearance (11.2%); TE-low bicarbonate (55.7%); TE-high CRP (13.4%); TE-high creatine kinase (CK) (13.6%); TE-high GGT (15.0%); TE-high immunoglobulin A (IgA) (13.5%); TE-low sodium (10.5%); TE-high VLDL cholesterol (33.4%); Abnormal urine clarity (54.4%); Abnormal urine ketones (12.6%); Abnormal urine leukocyte esterase (14.2%); Abnormal urine occult blood (14.8%); Abnormal urine protein (52.3%). The sponsor commented that the changes were not clinically meaningful.

In the 'All Ps Analysis Set', in patients with psoriasis treated with ixekizumab TE-high serum total cholesterol was reported in 1.6% (n=87) of patients, TE-high serum HDL cholesterol was reported in 8.1% (n=387) of patients, TE-high serum LDL cholesterol was reported in 0.6% (n=29) of patients and TE-high serum triglyceride was reported in 2.8% (n=156) of patients. TEAE hypercholesterolaemia was reported in 0.6% (n=7) of patients and TEAE blood triglyceride increased was reported in 0.5% (n=6) of patients. Overall, the lipid profile in patients in the 'All Ps Analysis Set' suggests that changes during the course of exposure to ixekizumab are unlikely to increase the risk of cardiovascular disease.

The incidence of 'Abnormal URINE protein' (52.3%) appeared to be particular high in the 'All Ps Analysis Set'. However, TEAEs of proteinuria were reported in only 0.4% (n=25) of patients in this analysis set. In addition, *Renal and urinary disorders (SOC)* were reported in only 4.6% (261/5689) of patients in this analysis set. Nevertheless, the sponsor is requested to comment on the high incidence of patients with 'Abnormal urine protein' (52.3%) in the 'All Ps Analysis Set' (see Clinical questions).

ECG analyses

Primary PsA analysis set

Change from baseline to last observation and TE-low or TE-high values at any time post-baseline were assessed for ECG parameters including heart rate, PR interval, QRS interval, and corrected QT interval using Fridericia's correction factor (QTcF) and using a large clinical trial population-based correction factor (QTcLCTPB).[13] The criteria for identifying TE-high or TE-low ECG parameters are summarised below in Table 8.

[13] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. The PR interval is the time from the onset of the P wave to the start of the QRS complex. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

Table 8: Criteria for identifying patients with potentially significant low and high TE mean changes

Note: Criteria for Identifying Patients with Potentially Clinically Significant Changes in ECGs		
ECG Measurement	Low	High
Heart Rate (bpm)	Age >=18: <50 and decrease >=15	Age >=18: >100 and increase >=15
PR Interval (msec)	<120	>=220
QRS Interval (msec)	<60	>=120
QTcF (msec)	Male: <330	Age >=16: Male: >450
	Female: <340	Age >=16: Female: >470
QTcLCTPB (msec)	Male: <330	Age <18: Male >444, Female >44
	Female: <340	Age 18-25: Male >449, Female >45
		Age 26-35: Male >431, Female >45
		Age 36-45: Male >446, Female >45
		Age 46-55: Male >452, Female >46
		Age 56-65: Male >441, Female >46
		Age >65: Male >460, Female >46

Overall, in the 'Primary PsA Analysis Set' there were no clinically relevant ECG findings in the ixekizumab groups compared with the placebo group or in the ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group. The results are summarised below:

- No patients in any treatment group had a post-baseline increase from maximum baseline value of 30 ms, 60 ms, or 75 ms in QTcF or QTcLCTPB intervals.
- One patient in the ixekizumab 80 mg Q2W group had QTcF and QTcLCTPB intervals > 500 ms (512.6 ms and 517.7 ms, respectively). This patient was not reported to have any cerebro-cardiovascular TEAEs.
- The proportions of patients with TE-high QTcF intervals, QTcLCTPB intervals, QRS durations, PR intervals, or heart rate values were not significantly different in the ixekizumab groups compared with placebo or in the IXE80Q2W group compared with the IXE80Q4W group. The proportions of patients with TE-high QTcF values (> 450 ms, males; > 470 ms, females) were: 3.2% (3/94), placebo; 1.0% (1/97) IXE80Q4W; 1.1% (1/91), IXE80Q2W; and 1.1% (2/188), total IXE). The proportions of patients with TE-high QTcLCTPB values (> 444 to 460 ms depending on age in males; > 445 465 ms depending on age in females) were: 3.2% (3/93), placebo; 2.1% (1/95) IXE80Q4W; 2.2% (2/91), IXE80Q2W; and 2.2% (4.186), total IXE.
- The mean change from baseline to last observation in heart rate was 0.6 beats per minute (bpm), –1.8 bpm, and –1.1 bpm in the placebo, IXE80Q4W, and IXE80Q2W groups, respectively (IXE80Q4W versus placebo, p=0.008; IXE80Q2W versus placebo, p=0.020). There were no other statistically significant differences between treatment groups in mean change from baseline to last observation for PR interval, QRS duration, QT duration, QTcF interval, or QTcLCTPB interval. The mean (range) changes in QTcF from baseline to last observation values were: -1.8 ms (-46.4, 32.8), placebo; -1.5 ms (-38.2, 31.6), IX80Q4W; 0.68 ms (-43.0, 64.8), IXE80Q2W; and -0.4 ms (-43.0, 64.8) total IXE. The results for mean change in QTcLCTPB from baseline to last observation were consistent with the results for QTcF.

All PsA analysis set

The key ECG findings in the 'All PsA Analysis Set' (total ixekizumab population) were:

- At any time post-baseline, no patient had an increase from maximum baseline value of 30 ms, 60 ms, or 75 ms in the QTcF or QTcLCTPB interval. One patient (same patient as described for the 'Primary PsA Analysis Set') had QTcF and QTcLCTPB intervals > 500 ms.
- TE-high values were reported for QTcF interval in 0.6% (2/346) of patients and for QTcLCTPB interval in 1.5% (5/343) of patients. Among these patients, the longest QTcF interval was 477.3 ms, and the longest QTcLCTPB interval was 483.6 ms. The

proportion of patients with TE-low and TE-high mean heart rates (bpm) was 0.3% (2/646) and 0.5% (3/652), respectively; the proportion of patients with TE-low and TE-high mean PR intervals (ms) was 0.6% (2/353) and 0.9% (3/351), respectively; and the proportion of patients with TE-low and TE-high mean QRS interval was 0% (0/357) and 0.3% (1/352), respectively.

All Ps analysis set

Key ECG findings in the 'All Ps Analysis Set' in patients with psoriasis treated with ixekizumab included:

- At any time post-baseline, 67 (1.7%) and 84 (2.1%) patients had an increase from maximum baseline value of 30 ms in QTcF and/or QTcLCTPB intervals, respectively. One patient had an increase from maximum baseline value of 60 ms and 75 ms in QTcF and QTcLCTPB intervals (maximum post-baseline QTcF was 461.7 ms, and maximum post-baseline QTcLCTPB was 456.5 ms). This patient did not have any cerebro-cardiovascular TEAEs that qualified for independent adjudication but did have a non-serious TEAE of angina pectoris of moderate severity and ≤ 1 day in duration. This event was not temporally associated with the increase in QTc interval.
- At any time post-baseline, 1 patient had a QTcF interval > 500 ms (actual value: 501.1 ms) and 3 (0.1%) patients had QTcLCTPB intervals >500 ms (actual values: 500.5 ms, 503.4 ms, and 507.3 ms). None of these patients had a cerebro-cardiovascular TEAE which qualified for independent adjudication.
- At any time post-baseline, TE-high values were reported for QTcF interval in 86 (2.3%) patients and for QTcLCTPB interval in 202 (5.6%) patients. For heart rate, PR interval, and QRS duration, the proportion of patients with TE-low or TE-high values ranged from 0.4% to 0.9%.

Vital signs

Primary PsA analysis set

Overall, in the 'Primary PsA Analysis set' vital signs remained stable over the placebo-controlled, double-blind treatment period (Weeks 0-24). There were no significant differences between treatment groups in the proportion of patients with TE-high or TE-low diastolic blood pressure, pulse rate, systolic blood pressure, and body weight. TE-high diastolic blood pressure (≥ 90 mmHg and increase ≥ 10 mmHg from baseline) was reported in 19/178 (10.7%) patients in the placebo group, 27/194 (13.9%) patients in the ixekizumab 80 mg Q4W group, and 16/176 (9.1%) patients in the ixekizumab 80 mg Q2W group. TE-high systolic blood pressure (> 100 mg and increased ≥ 15 mmHg from baseline) was reported in 12/142 (8.5%) patients in the placebo group, 12/156 (7.7%) patients in the ixekizumab 80 mg Q4W group, and 11/165 (6.7%) patients in the ixekizumab 80 mg Q2W group.

All PsA analysis set

In the 'All PsA Analysis Set', TE-high diastolic or TE-low blood pressure were reported in 14.2% (128/903) and 10.4% (84/809) of patients in the pooled ixekizumab population, respectively, while TE-low diastolic or TE-low systolic blood pressure were reported in 1.3% (14/1116) and 1.1% (12/1115) of patients, respectively. TE-low or TE-high heart rate (bpm) was reported in 0.2% (2/1107) and 2.5% (28/1106) of patients in the pooled ixekizumab population, respectively. TE-low or TE-high weight (kg) were reported in 4.6% (49/1075) and 7.8% (84/1075) of patients in the pooled ixekizumab population, respectively.

All Ps analysis set

In the 'All Ps Analysis Set', TE-high or TE-low vital signs occurring in >10% of patients with psoriasis treated with ixekizumab at any time post-baseline included TE-high diastolic blood pressure (27.1%), TE-high systolic blood pressure (18.6%), and TE-high weight (15.2%).

Postmarketing data

No post-marketing experience data are available for patients with PsA treated with ixekizumab as this indication had not been approved in any jurisdiction at the time of the submission. The first marketing approval for ixekizumab for the treatment of psoriasis was granted by the FDA on 22 March 2016. The first periodic safety update report (PSUR)/periodic benefit-risk evaluation report (PBRER), completed in accordance with the relevant guideline format;[14] summarised safety and other pertinent data arising from worldwide sources received between the International Birth Date of 22 March 2016 and 22 September 2016. Data in the draft Risk Management Plan indicates that as of 31 December 2016 there have been 3,816,320 mg of ixekizumab sold worldwide, with the majority being sold in the USA (3,575,520 mg).

The sponsor states that a signal for serious immediate hypersensitivity reactions consistent with anaphylaxis was identified from post-marketing spontaneous AE reports of ixekizumab (3 reports of serious immediate hypersensitivity consistent with anaphylaxis). This event stated to have been reported in the first PSUR (PSUR 01) for ixekizumab. Based on the findings from post-marketing spontaneous reports and mechanistic plausibility, the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of Anaphylaxis was added as a rare event (frequency ≥ 0.01% to < 0.1%) in the 'Undesirable Effects' of reference safety information. In addition, the language in 'Special Warnings and Special Precautions for Use' of reference safety information was adjusted to include anaphylaxis.

The Australian PI includes a reference to anaphylaxis as rare event under *Postmarketing Date* in the *Adverse Effects* section of the document. No other safety information is included under *Postmarketing Data*.

Evaluator's conclusions on safety

The submission included safety data on 1118 patients with active PsA exposed to least 1 dose of ixekizumab, representing 1050.6 patients-years of exposure, through to September 2016 (Studies RHAP, RHBE and RHBF). Based on the 'rule of threes', the total number of patients with PsA exposed is sufficient to identify adverse reactions with a frequency of at least 0.3%. In addition, the submission included updated safety data on 5689 patients with moderate-to-severe plaque Ps exposed to at least 1 dose of ixekizumab, representing 12061.5 years of exposure, from 11 studies through to September 2016. Based on the 'rule of threes', the total number of patients with Ps exposed is sufficient to identify adverse reactions with a frequency of at least 0.05%.

The safety data were provided in three separate integrated analysis sets comprising the 'Primary PsA Analysis Set' (pooled data from Studies RHAP and RHBE from Weeks 0 to 24), the 'All PsA Analysis Set' (pooled data from Studies RHAP, RHBE, and RHBF for all treatment periods from Week 0 through to last visit before the database lock), and the 'All Ps Analysis Set' (pooled updated data from 11 studies in patients with Ps). The safety data from the three analysis sets were consistent, and the safety profiles in patients with PsA and Ps were similar. In this overview, only the safety data from the two analysis sets in

[14] ICH E2C (R2): Periodic Safety Update Reports for Marketed Drugs

patients with PsA treated with ixekizumab or placebo will be reviewed. The safety data (Weeks 0 to 24) for adalimumab 40 mg Q2W from Study RHAP has been previously discussed and are considered to be consistent with those observed with ixekizumab.

The totality of the submitted safety data from the three integrated analyses sets allowed the safety of ixekizumab for the proposed extension of indication to patients with PsA to be adequately characterised. The submitted safety data are considered to have satisfactorily established the safety of ixekizumab at the proposed doses for the treatment of patients with PsA.

Exposure

In the 'Primary PsA Analysis Set', the proportion of patients with PsA who had been treated for ≥ 120 days was greater in both the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups (83.2% versus 86.3%, respectively) compared with the placebo group (62.3%). In this analysis set, the number of patients in the three treatment groups who had been treated for ≥ 183 days was negligible (≤ 1 patient in each of the three groups).

In the 'All PsA Analysis Set', a total of 1118 patients with PsA received at least 1 dose of ixekizumab, comprising 365 patients in the ixekizumab 80 mg Q4W group and 752 patients in the ixekizumab 80 mg Q2W group. In the 'All PsA Analysis Set', 610 (54.6%) patients with PsA had been treated with ixekizumab for ≥ 6 months (296 (81.1%), 80Q4W group; 314 (41.8%), 80Q2W group), 365 (32.7%) patients had been treated for ≥ 12 months (183 (50.1%), 80Q4W group; 182 (24.2%), 80Q2W group), and 208 (18.6%) patients had been treated for ≥ 24 months (103 (28.2%) 80Q4W group; 105 (14.0%), 80Q2W group).

TEAEs (all causality)

In the 'Primary PsA Analysis Set', the proportion of patients with at least 1 TEAE (all causality) was statistically significantly greater ($p<0.05$) in both ixekizumab groups compared with the placebo group (66.8%, 80Q4W versus 69.3%, 80Q2W versus 56.7%, placebo). The proportion of patients in this analysis set was similar in both ixekizumab groups, and the majority of TEAEs in both groups were mild or moderate in severity. TEAEs (irrespective of causality) reported in ≥ 5% of patients in the ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W groups compared with the placebo group were, respectively, injection site reaction (9.6% versus 14.2% versus 0.4%), upper respiratory tract infection (7.0% versus 6.7% versus 7.1%), injection site erythema (3.9% versus 7.6% versus 0%), and nasopharyngitis (6.6% versus 3.1% versus 4.0%).

In the 'All PsA Analysis Set', the proportion of patients with at least 1 TEAE (all causality) in the pooled ixekizumab group was 65.7% (incidence rate = 69.9 per 100 person-years). In this analysis set, TEAEs reported in ≥ 5% of patients were injection site reaction (11.8%), upper respiratory tract infection (8.0%), nasopharyngitis (6.8%) and injection site erythema (4.5%).

TEAEs (treatment-related)

In the 'Primary PsA Analysis Set', the proportion of patients with at least 1 TEAE (treatment related) was notably greater in both ixekizumab groups compared with the placebo group (29.3%, 80Q4W versus 39.6%, 80Q2W versus 18.3%, placebo). The proportion of patients in this analysis set with TEAEs (treatment-related) was notably higher in the ixekizumab 80 mg Q2W group than in the ixekizumab 80mg Q4W group (39.6% versus 29.3%, respectively). TEAEs (treatment-related) reported in ≥ 2% of patients in the ixekizumab 80 mg Q4W group or the 80 mg Q2W ixekizumab group compared with placebo were, respectively, injection site reaction (9.2% versus 13.8% versus 0.4%), injection site erythema (7.6% versus 3.9% versus 0%), upper respiratory tract infection (3.1% versus 3.1% versus 1.3%), and injection site hypersensitivity (0.4% versus 2.7% versus 0%). The main difference between the two ixekizumab groups and the

placebo group, as regards TEAEs (treatment-related), related to the higher incidence of injection site reactions in the two ixekizumab groups compared with placebo. In addition, injection site reactions were more commonly reported in the more frequently administered ixekizumab group (80Q2W) than in the less frequently administered ixekizumab group (80Q4W).

In the 'All PsA Analysis Set', TEAEs (treatment-related) reported in ≥ 1% of patients in the pooled ixekizumab group were injection site reaction (11.6%), injection site erythema (4.4%), upper respiratory tract infection (2.4%), nasopharyngitis (1.0%), and diarrhoea (1.0%).

Deaths

There were no deaths in the 'Primary PsA Analysis Set', and 2 (0.2%) deaths in the 'All PsA Analysis Set'. The 2 deaths in the 'All PsA Analysis Set' were due to a cerebrovascular accident in a male with cardiovascular risk factor at study entry (initially randomised to adalimumab and subsequently re-randomised to ixekizumab 80 mg Q4W), and pneumonia in a male randomised to ixekizumab 80 mg Q2W.

SAEs

In the 'Primary PsA Analysis Set', SAEs were reported more frequently in patients in both ixekizumab groups compared with the placebo group (3.9%, 80Q4W versus 4.9%, 80Q2W versus 2.7%, placebo). SAEs were reported in a comparable proportion of patients in the two ixekizumab groups. No individual SAEs were reported in more than 1 patient in either of the two ixekizumab groups. The greatest incidence of SAEs grouped by SOC was reported for *Infections and infestations.* This was the only SOC in which there was a notable numerical difference between an ixekizumab group and the placebo group (5 (2.2%) patients in the 80Q2W group versus 0 (0%) patients in the placebo group; p=0.026). For *Infections and infestations (SOC)* there was no clinically important difference in the incidence of SAEs between the ixekizumab 80 mg Q4W group (1 (0.4%) patient) compared with the placebo group (0 (0%) patients. No type of infection or type of pathogen predominated.

In the 'All PsA Analysis Set', 6.5% (n=73) of patients in the pooled ixekizumab group experienced at least 1 SAE. SAEs reported in ≥ 2 patients were pneumonia (n=3, 0.3%), lower respiratory tract infection (n=2, 0.2%), carotid artery stenosis (n=2, 0.2%), cerebrovascular accident (n=2, 0.2%), fall (n=2, 0.2%), acute myocardial infarction (n=2, 0.2%), cholecystitis acute (n=2, 0.2%), cholelithiasis (n=2, 0.2%), coronary artery disease (n=2; 0.2%) and osteoarthritis (n=2, 0.2%).

Discontinuations of the study drug due to AEs

In the 'Primary PsA Analysis Set', discontinuation of the study drug due to AEs was reported in a numerically higher proportion of patients in the ixekizumab 80 mg Q2W group than in either the ixekizumab 80 mg Q4W group or the placebo group (5.3% versus 3.1% versus 3.6%, respectively). In each of the three treatment groups, the proportion of patients discontinuing the study drug due to TEAEs was notably lower than the proportion of patients reporting adverse events, indicating that most events were manageable by treatment modalities other than treatment discontinuation. The only TEAE resulting in discontinuation of the study drug reported in ≥ 1 patient in either the ixekizumab 80 mg Q4W group or the ixekizumab 80 mg Q2W group was injection site reaction (0.4% versus 0.9%), with no patients in the placebo group discontinuing due to this TEAE.

In the 'All PsA Analysis Set' (n=1118), 5.7% of patients in the pooled ixekizumab group had an AE resulting in discontinuation of the study drug. AEs reported in ≥ 0.2% of patients (adjusted for gender number where relevant) were interferon gamma release assay positive (0.9%), latent tuberculosis (0.5%), injection site reaction (0.4%), tuberculin test positive (0.3%), prostate cancer (0.2%), cerebrovascular accident (0.2%), myalgia

(0.2%), abortion spontaneous (0.2%), pregnancy (0.2%) and unintended pregnancy (0.2%).

Adverse event of special interest

Infections

In the 'Primary PsA Analysis Set', the proportion of patients with ≥ 1 infection-related TEAE was numerically higher in both ixekizumab groups compared with the placebo group (33.6%, 80Q4W versus 32.0%, 80Q2W, versus 27.7%, placebo), while the proportion of patients with ≥ 1 infection-related SAE was small in each of the three treatment groups (0.4%, 80Q4W versus 2.2%, 80Q2W versus 0%, placebo) as was the proportion of patients discontinuing the study drug due to infection-related AEs (0.9%, 80Q4W versus 0.4%, 80Q2W versus 0.4%, placebo). Overall, there was no clinically meaningful difference in infection-related AEs between the two ixekizumab groups.

Infection-related TEAEs reported in ≥ 2% of patients in either the ixekizumab 80 mg Q4W group or the ixekizumab 80 mg Q2W group (versus placebo) were, respectively: upper respiratory tract infection (7.0% versus 6.7% versus 7.1%); nasopharyngitis (6.6% versus 3.1% versus 4.0%); sinusitis (3.9% versus 2.7% versus 2.2%); urinary tract infection (3.5% versus 1.8% versus 2.2%); bronchitis (1.7% versus 3.1% versus 3.1%); pharyngitis (0.9% versus 2.2% versus 0.9%); and tonsillitis (2.2% versus 0% versus 0%).

No patients in the placebo group reported infection-related SAEs, while 1 (0.4%) patient in the ixekizumab 80 mg Q4W reported an infection-related SAE (1x gastroenteritis) and 5 (2.2%) patients in the ixekizumab 80 mg Q2W group reported 5 infection-related SAEs (1 x abscess jaw, 1 x anal abscess, 1 x herpes zoster, 1 x oesophageal candidiasis, 1 x perirectal abscess). AEs leading to discontinuation of the study drug were reported in 1 (0.4%) patient in the placebo group (1 x lower respiratory tract infection), 2 (0.9%) patients in the ixekizumab 80 mg Q4W group (1 x subcutaneous abscess, 1 x urinary tract infection) and 1 (0.4%) patient in the ixekizumab 80 mg Q2W group (1 x folliculitis).

In the 'All PsA Analysis Set' (n=1118), 37.2% of patients in the pooled ixekizumab group experienced at least 1 infection-related TEAE, 1.3% of patients experienced ≥ 1 infection related SAE, and 1.3% of patients discontinued the study drug due to an infection-related AE. Infection-related TEAEs reported in ≥ 2% of patients in the pooled ixekizumab group were upper respiratory tract infection (8.0%), nasopharyngitis (6.8%), urinary tract infection (3.4%), sinusitis (3.2%), bronchitis (3.0%), pharyngitis (2.4%), and tonsillitis (2.1%). Infection-related SAEs reported in ≥ 2 (≥ 0.2%) of patients in the pooled ixekizumab group were pneumonia (0.3%, n=3) and lower respiratory tract infection (0.2%, n=2). The only Infection-related AE resulting in discontinuation of the treatment drug reported in ≥ 2 (≥ 0.2%) patients in the pooled ixekizumab group was latent tuberculosis (0.5%, n=6). No patients were reported to have active tuberculosis.

Cytopaenias

In the 'Primary PsA Analysis Set', there were statistically significant or clinically meaningful reductions in each of the two ixekizumab groups compared with the placebo group with respect to lymphocyte surface marker (LSM) changes in laboratory values for leukocytes, neutrophils, and platelets from the last observation during baseline to the last observation post-baseline. There were no meaningful differences between the two ixekizumab groups and the placebo group in LSM changes in lymphocyte laboratory values. The LSM changes from last observation during baseline to last observation post-baseline for the laboratory values for leukocytes, neutrophils, lymphocytes and platelets were numerically greater in the ixekizumab 80 mg Q4W group compared with the ixekizumab 80 mg Q2W group, but the differences are not clinically meaningful.

The proportion of patients with treatment-emergent laboratory values < lower limit of normal (LLN) at any time post-baseline for both leukocytes and neutrophils was

statistically significantly greater in each of the two ixekizumab groups compared with the placebo group, while the values for lymphocytes and platelets did not differ significantly across the three treatment groups.

The overall percentage of patients with a worsening leukocyte count (worsening grade from baseline to post-baseline) was greater in both the ixekizumab groups compared with the placebo group (13.5%, 80Q4W versus 13.8%, 90Q2W versus 3.2%, placebo). There were no patients in the three treatment groups with a shift in leukocyte count from baseline normal, Grade 1, or Grade 2 values to post-baseline Grade ≥ 3 values. In the majority of patients in the three treatment groups (> 85%) the baseline leukocyte count (Grade) remained the same throughout the course of the study.

The overall percentage of patients with a worsening neutrophil count (worsening grade from baseline to post-baseline) was greater in both the ixekizumab groups compared with the placebo group (10.5%, 80Q4W versus 8.9%, 80Q2W versus 2.7% placebo). There were no patients in the three treatment groups with a shift in leukocyte count from baseline normal or Grade 1 values to post-baseline Grade ≥ 2 values. In the majority of patients in the three treatment groups (> 89%) the baseline neutrophil count (grade) remained the same throughout the course of the study.

The overall percentage of patients with a worsening platelet count (worsening grade from baseline to post-baseline) was similar in the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W and placebo groups (5.3% versus 2.7% versus 3.2%, respectively). There were no patients in the three treatment groups with a shift in platelet count from baseline normal or Grade 1 values to post-baseline Grade ≥ 2 values. In the majority of patients in the three treatment groups (> 94%) the baseline leukocyte count (Grade) remained the same throughout the course of the study. The overall percentage of patients with a worsening neutrophil count (worsening grade from baseline to post-baseline) was similar in the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W and placebo groups (12.2% versus 15.6% versus 12.2%, respectively). There was 1 (0.4%) patient in the ixekizumab 80 mg Q2W group with a shift in neutrophil count from baseline normal, Grade 1 or Grade 2 values to post-baseline Grade 3. There were no patients in the three treatment groups with a shift in neutrophil count from baseline normal, Grade 1, Grade 2 or Grade 3 values to post-baseline Grade 4. In the majority of patients in the three treatment groups (> 81%) the baseline neutrophil count (Grade) remained the same throughout the course of the study.

In the 'Primary PsA Analysis Set', the proportion of patients who reported TEAEs identified by preferred terms related to the haematopoietic leukopaenia sub- Standardised MedDRA Querie (SMQ) was small in the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W and placebo groups (1.7% versus 1.8% versus 0.9%, respectively). There were no SAEs, and no discontinuations of the study drug due to AEs. There were no TEAEs identified by the haematopoietic thrombocytopaenia sub-SMQ in the three treatment groups. No patients had treatment-emergent bleeding events accompanied by TE-thrombocytopaenia.

In the 'All PsA Analysis Set', the proportion of patients in the pooled ixekizumab group with ≥ 1 TE-low laboratory value was 14.2% for leukocytes (153/1075), 12.5% for neutrophils (136/1092), 13.4% for lymphocytes (131/979), and 5.0% for platelets (54/1082). Shift (worsening) from baseline to TE-leukopaenia Grade 3 was observed in 1 (0.1%) patient, and no patients shifted (worsened) from baseline to TE-leukopaenia Grade 4. Shift (worsening) from baseline to TE-neutropaenia Grade 3 was observed in 3 (0.3%) patients, and no patients shifted (worsened) from baseline to TE-neutropaenia Grade 4. Shift (worsening) from baseline to TE-lymphopaenia Grade 3 was observed in 4 (0.4%) patients, and no patients shifted (worsened) from baseline to TE-lymphopaenia Grade 4. Shift (worsening) from baseline to TE-thrombocytopaenia Grade 3 was observed in 1 (0.1%) patient, and no patients shifted (worsened) from baseline to TE-thrombocytopaenia Grade 4. Haemopoietic leukopaenia sub-SMQ TEAEs were

observed in 2.2% of patients and haematopoietic thrombocytopaenia sub-SMQ TEAEs were observed in 0.4% of patients.

Allergic reactions/hypersensitivities

In the 'Primary PsA Analysis Set', the proportion of patients with ≥ 1 allergic reaction/hypersensitivity TEAE was higher in the both ixekizumab groups than in the placebo group (6.2%, 80Q2W versus 4.4%, 80Q4W versus 1.8%, placebo). There were no SAEs reported in ixekizumab or placebo groups, while discontinuation of the study drug due to these events was reported in 2 (0.9%) patients in the ixekizumab 80 mg Q4W group (1 x hypersensitivity and 1x rash pruritic). TEAEs reported in ≥ 2 (≥ 0.9%) patients in the either of the two ixekizumab groups were (ixekizumab 80 mg Q4W versus ixekizumab 80 mg Q2W versus placebo, respectively): eczema (0% versus 1.3% versus 0%); rash (0% versus 1.3% versus 0%); urticaria (0.4% versus 0.9% versus 0%); rhinitis allergic (0% versus 0.9% versus 0%); and angioedema (0.9% versus 0% versus 0%). There were no cases of anaphylaxis reported in the ixekizumab or placebo groups.

In the 'All PsA Analysis Set', in the pooled ixekizumab group the proportion of patients with ≥ 1 allergic reaction/hypersensitivity TEAE was 5.4% and the proportion of patients with ≥ 1 SAE was 0.1% (1x angioedema). Discontinuation from the study drug due to these events was reported in 0.4% of patients (1 x angioedema, 1 x drug eruption, 1 x hypersensitivity, 1x rash, 1x rash pruritic). The only TEAE reported in ≥ 1% of patients was rash (1.1%).

Injection site reactions

In the 'Primary PsA Analysis Set', injection site reactions occurred notably more frequently in both the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups (17.5% versus 25.3%) compared with the placebo group (4.5%). TEAEs reported in ≥ 1.0% of patients in the either of the two ixekizumab groups were (ixekizumab 80 mg Q4W versus ixekizumab 80 mg Q2W versus placebo, respectively): injection site reaction (9.6% versus 14.2% versus 0.4%); injection site erythema (3.9% versus 7.6% versus 0%); injection site hypersensitivity (0.4% versus 2.7% versus 0%); injection site pruritus (0.9% versus 1.8% versus 0%); injection site swelling (0.4% versus 1.3% versus 0%); and injection site bruising (1.3% versus 0% versus 1.3%). There were no patients in the ixekizumab or placebo groups with a SAE injection site reaction. Discontinuations of the study drug due to injection site reactions were reported in 0.4% (n=1) of patients in the ixekizumab 80 mg Q4W group (1 x injection site reaction), 1.8% (n=4) of patients in the ixekizumab 80 mg Q2W group (2 x injection site reaction, 1 x injection site hypersensitivity, 1 x injection site rash), and 0.4% (n=1) of patients in the placebo group (1 x injection site pain).

In the 'All PsA Analysis Set', injection site reactions were reported 18.9% (n=211) of patients in the pooled ixekizumab group. Injection site reaction preferred terms reported for ≥ 1% of patients were injection site reaction (11.8%), injection site erythema (4.5%), injection site pain (1.2%, n=13), and injection site hypersensitivity (1.0%). There were no patients in the ixekizumab or placebo groups with a SAE injection site reaction. Discontinuations of the study drug due to injection site reactions were reported in 0.5% (n=6) of patients (4 x injection site reactions, 1 x injection site hypersensitivity, 1 x injection site rash).

Cerebro-cardiovascular events

In the 'Primary PsA Analysis Set', cerebro-cardiovascular TEAEs, including Major Adverse Cardiac Event (MACE), were reported infrequently in the ixekizumab and placebo groups. In the 'All PsA Analysis Set', there were 12 (1.1%) patients with ≥ 1 Clinical Events Committee (CEC)-confirmed cerebro-cardiovascular event, including MACE; all were SAEs and 4 (0.4%) patients discontinued due to an event. There were no patients with CEC-confirmed MACE in the 'Primary PsA Analysis Set' and 5 (0.4%) patients with ≥ 1 CEC-confirmed

MACE in the 'All PsA Analysis Set' (vascular death (preferred term cerebrovascular accident (CVA)) in 1 patient, non-fatal myocardial infarction in 1 patient and non-fatal stroke in 3 patients). There was no evidence that exposure to ixekizumab increased the risk of cerebro-cardiovascular events.

Malignancies

In the 'Primary PsA Analysis Set', TEAE malignancies were reported infrequently in the ixekizumab and placebo groups. TEAE malignancies were also reported infrequently in the 'All PsA Analysis Set'.

Hepatic events

In the 'Primary PsA Analysis Set', no clinically significant differences in hepatic function laboratory abnormalities or hepatic TEAEs were observed in the ixekizumab and placebo groups. The results for ixekizumab treated patients in the 'Primary PsA Analysis Set' were consistent with the findings in the 'All PsA Analysis'. No patients in either of the analysis sets met Hy's law criteria for drug induced liver injury.

Depression and suicide/self-injury

In the 'Primary Analysis Set', the incidences of depression, as assessed by Quick Inventory of Depressive Symptomatology (QIDS SR-16; this scale is a self-report measure of depression) and reported events, was low and did not differ between the ixekizumab and placebo groups. There was no suicide/self-injury behaviour reported in the 'Primary PsA Analysis Set'. In the 'All PsA Analysis Set', 50% of patients in the pooled ixekizumab group reported improvement in QIDS SR-16 total score, 32.5% reported worsening, and 17.5% stayed the same. In the 'All PsA Analysis Set', the majority of patients stayed the same (93.3%) as regards thoughts of suicide or death based on QIDS-SR_{16} Item 12, while 5.0% improved and 1.6% worsened.

Inflammatory bowel disease (IBD)

In the 'Primary PsA Analysis Set', no patient had TEAEs of IBD identified by MedDRA narrow preferred terms (Crohn's disease, acute haemorrhagic ulcerative colitis, colitis ulcerative, proctitis ulcerative, and inflammatory bowel disease). In the 'All PsA Analysis Set', 1 (0.1%) patient in the pooled ixekizumab group had an IBD TEAE (ulcerative colitis) identified by MedDRA narrow preferred terms. The event was considered serious but did not result in discontinuation of study drug.

Interstitial lung disease (ILD)

In the 'Primary PsA Analysis Set', no patient had ILD TEAEs. In the 'All PsA Analysis Set', 1 (0.1%) patient in the pooled ixekizumab group had an ILD TEAE (pulmonary granuloma).

Renal and urinary tract disorders (SOC)

The data in patients with PsA indicated a small increase in the number and percentage of patients with reductions in serum creatinine levels associated with ixekizumab treatment. However, the changes from baseline are not considered to be clinically significant. There is no evidence that ixekizumab is associated with clinically meaningful renal toxicity.

Skin and subcutaneous tissue disorders (SOC)

In the 'Primary PsA Analysis Set', Skin and subcutaneous tissue disorders (SOC) were reported more frequently in the ixekizumab groups compared with the placebo group (10.2% 80Q2W versus 9.9% 80Q4W versus 5.4%, placebo). In the 'All PsA Analysis Set', *Skin and subcutaneous tissue disorders (SOC)* were reported in 11.0% of patients, with SAEs being reported in 1 (0.1%) patient (1 x angioedema) and discontinuation due to AEs being reported in 5 (0.4%) patients (1x angioedema, 1x drug eruption, 1 x palmar plantar erythrodysaesthesia syndrome, 1 x rash, and 1 x rash pruritic). There were no reported

cases of Stevens-Johnson syndrome or toxic epidermal necrolysis in patients with PsA treated with ixekizumab.

Haematological laboratory abnormalities (other than cytopaenias (AESI))

The data in patients with PsA raised no clinically significant safety issues relating to haematological laboratory abnormalities, other than cytopaenias (AESI).

Clinical chemistry laboratory values (other than hepatic-related) TE-high and TE-low

In the 'Primary PsA Analysis Set', the only TE clinical chemistry laboratory values of note (other than hepatic-related) were greater incidences of TE-high serum HDL cholesterol and TE-high serum VLDL cholesterol in patients in both ixekizumab groups (80Q4W, 80Q2W) compared with the placebo group. Review of TE-high serum clinical chemistry values for total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides observed with exposure to ixekizumab in the 'Primary PsA Analysis Set' and the 'All PsA Analysis Set' do not give rise to concerns.

Vital signs and ECG findings

The data on patients with PsA raise no significant clinical concerns relating to changes in vital signs or ECG findings associated with ixekizumab treatment.

Special groups

No significant clinical concerns were identified in the 'Primary PsA Analysis Set' as regards the safety of ixekizumab for the treatment of PsA based on age (patients aged ≥ 18 years), gender or weight. No conclusions regarding the safety of ixekizumab for the treatment of PsA in different racial groups can be made as the majority of patients in the 'Primary PsA Analysis Set' were categorised as 'White' (92.6%). There were no safety data in patients with PsA and hepatic or renal impairment. There was no safety data in pregnant or lactating women with PsA treated with ixekizumab. There was no safety data on drug-drug interactions in patients with PsA treated with ixekizumab. There has been no post-marketing experience in patients with PsA treated with ixekizumab.

First round benefit-risk assessment

First round assessment of benefits

The data from the Studies RHAP and RHBE convincingly support the benefits of treatment with ixekizumab (80Q4W and 80Q2W) for the treatment of patients with PsA compared with placebo from Weeks 0 to 24. The extension data (Weeks 24 to 52) from Study RHAP showed that response for the key efficacy endpoints in both the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups were relatively similar at Weeks 12, 24 and 52, with no diminishment in efficacy through to Week 52. The extension data (Weeks 24 to 52) from Study RHAP also showed that response at Week 24 for key efficacy endpoints observed in patients randomised to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at baseline (Week 0) could be maintained through to Week 52. The pooled data from the placebo-controlled period (Weeks 0 to 24) of Studies RHAP and RHBE showed no meaningful clinical differences in efficacy outcomes between ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W.

No efficacy data in patients treated with ixekizumab for longer than 24 weeks was provided for Study RHBE but extension data are expected in a subsequent report. No efficacy data for patients treated with ixekizumab for longer than 52 weeks were included in the submission, but long-term data are expected in subsequent reports for Studies RHAP and RHBE.

No formal dose comparisons between the ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W groups were performed for the efficacy outcomes for Studies RHAP and RHBE, as the studies were not powered to undertake such analyses. However, formal dose comparisons were performed with the integrated data. In Study RHAP adalimumab at the TGA approved dose of 40 mg Q2W was selected as the active control for comparison with placebo to provide internal evidence of assay sensitivity. The adalimumab group was not used to show equivalence or non-inferiority with the ixekizumab groups.

Double-blind, placebo-controlled period (Weeks 0 to 24) Studies RHAP and RHBE

Study RHAP

Study RHAP included patients (n=417) with active PsA of ≥ 6 months duration, who met CASPAR criteria, and who were bDMARD naïve. Patients were initially randomised (1: 1: 1: 1) to one of 4 treatment groups (placebo (n=106), adalimumab 40Q2W (n=101), IXE80Q4W (n=107), or IXE80Q2W (n=103)) and treated double-blind from Weeks 0 to 24. Patients on a stable dose of cDMARD at study entry were eligible for entry into the study as were patients who had a previous history of cDMARD use or who were cDMARD naïve. Patients with active PsA were also required to have active plaque psoriasis or a history of this condition.

The results for the comparisons between each ixekizumab dose group and the placebo group (double-blind treatment placebo-controlled period) for the 1 primary and 6 major secondary efficacy endpoints (multiplicity-controlled) are shown below in Table 9. The efficacy endpoints are listed in the sequence in which they were tested using the multiplicity-controlled analysis. This analysis used a gated testing procedure requiring statistical demonstration of an endpoint at the 2.5% significance level before proceeding to testing of the next endpoint in the pre-specified sequence at the 2.5% significance level. The pre-specified statistical analysis demonstrated that the primary efficacy endpoint of ACR20 response at Week 24 was statistically significantly greater in both the ixekizumab groups compared with the placebo group, as were the major secondary efficacy endpoints of HAQ-DI at Week 24, mTSS at Week 24, ACR20 at Week 12, and PASI at Week 12 in patients with baseline psoriatic lesions involving ≥ 3% BSA. Based on the multiplicity-controlled statistical testing procedure, the differences between both ixekizumab groups compared with the placebo group were not statistically significant for the major secondary efficacy endpoints of mean change in LEI score from baseline to Week 12 in patients with baseline enthesitis, or mean change in Itch NRS score from baseline to Week 12 in patients with baseline psoriatic lesions involving ≥ 3% BSA.

Table 9: Study RHAP primary and major secondary efficacy endpoints for placebo-controlled period (Weeks 0 to 24); ITT population

PBO	IXEQ4W	IXEQ2W	Δ IXE80Q4W-PBO (95%CI), p-value		Δ IXE80Q2W-PBO (95%CI), p-value	
ACR20 response rate at Week 24 (NRI), difference in response rate						
30.2% (32/106)	57.9% (62/107)	62.1% (64/103)	27.8% (15.0, 40.6)	p<0.001	31.9% (19.1, 44.8)	p<0.001
HAQ-DI LSM (SE) change from baseline to Week 24 (MMRM), difference in LSM						
- 0.18 (0.05), n=63	- 0.44 (0.05), n=83	- 0.50 (0.05), n=84	-0.26 (-0.40,-0.12)	p<0.001	-0.32 (-0.46, -0.18)	p<0.001

PBO	IXEQ4W	IXEQ2W	Δ IXE80Q4W-PBO (95%CI), p-value		Δ IXE80Q2W-PBO (95%CI), p-value	
mTSS LSM (SE) change from baseline to Week 24 (MMRM), difference in LSM						
0.49 (0.09), n=61	0.17 (0.08), n=82	0.08 (0.08), n=85	0.33 (-0.55,-0.10)	p=0.004	-0.41 (-0.63,-0.19)	p<0.001
ACR20 response rate at Week 12 (NRI), difference in response rate						
31.1% (33/106)	57.0% (61/107)	60.2% (62/103)	25.9% (13.0, 38.7)	p<0.001	29.1% (16.1, 42.0)	p<0.001
PASI 75 response rate at Week 12 (NRI), difference in response rate, in patients with psoriatic lesions involving BSA ≥ 3%						
7.5% (5/67)	75.3% (55/73)	69.5% (41/59)	67.9% (56.2, 79.6)	p<0.001	62.0% (48.7, 75.4)	p<0.001
LEI LSM (SE) change from baseline score at Week 12 (MMRM), difference in LSM, in patients with enthesitis at baseline						
-0.8 (0.24), n=53	-0.9 (0.21), n=70	-1.5 (0.24), n=54	0.0 (-0.65, -0.56)	p=0.884	-0.7 (-1.32, -0.04)	p=0.038
ITCH NRS LSM (SE) change from baseline score at Week 12 (MMRM), difference in LSM, in patients with psoriatic lesions ≥ 3% BSA						
-0.2 (0.27), n=66	-2.6 (0.27), n=69	-2.8 (0.30), n=57	-2.8 (-3.55, -2.12)	NA	-3.1 (-3.82, -2.30)	NA

Study RHBE

Study RHBE included patients (n=363) with active PsA of ≥ 6 months duration, who met CASPAR criteria, who were both cDMARD and bDMARD experienced and who were inadequate responders to TNF inhibitors or unable to tolerate this class of drugs. Patients with active PsA were also required to have active plaque psoriasis or a history of this condition. In this study, patients were randomised (1: 1: 1) to one of 3 treatment groups (placebo (n=118), IXE80Q4W (n=122), IXE80Q2W (n=123)) and treated double-blind from Weeks 0 to 24.

The primary efficacy endpoint in Study RHBE, ACR20 response at Week 24, was identical to the primary efficacy endpoint in Study RHAP. The study included 5 major secondary efficacy endpoints (multiplicity-controlled). The primary and major secondary efficacy endpoints were analysed using the same method to control for multiple pairwise comparisons as used in Study RHAP. The results for the 1 primary and 5 major secondary efficacy endpoints (multiplicity-controlled) are summarised below in Table 10. The efficacy endpoints are listed in the sequence in which they were tested using the pre-specified multiplicity-controlled analytical method.

The pre-specified statistical analysis demonstrated that the primary efficacy endpoint of ACR20 response at Week 24 was statistically significantly greater in both the ixekizumab groups compared with placebo, as were the major secondary efficacy endpoints of HAQ-DI at Week 24, ACR20 at Week 12, PASI at Week 12 in patients with baseline psoriatic lesions

involving ≥ 3% BSA, and MDA (6E) at Week 24. However, the LEI (0) response rates in patients with baseline LEI > 0 were not statistically significantly different for both ixekizumab groups compared with placebo. Radiological damage was not assessed in this study.

Table 10: Study RHBE primary and major secondary efficacy endpoints for the placebo-controlled period (Weeks 0-24) ITT population

PBO	IXEQ4W	IXEQ2W	Δ IXE80Q4W-PBO (95%CI), p-value		Δ IXE80Q2W-PBO (95%CI), p-value	
ACR20 response rate at Week 24 (NRI), difference in response rate						
19.5% (23/118)	53.3% (65/122)	48.0% (59/123)	33.8% (22.4, 45.2)	p<0.001	28.5% (17.1, 39.8)	p<0.001
HAQ-DI LSM (SE) change from baseline to Week 24 (MMRM), difference in LSM						
- 0.2 (0.08), n=64	- 0.6 (0.07), n=95	- 0.4 (0.07), n=91	-0.4 (-0.5, -0.3)	p<0.001	-0.3 (-0.4, -0.1)	p<0.001
ACR20 response rate at Week 12 (NRI), difference in response rate						
22.0% (26/118)	50.0% (61/122)	48.0% (59/123)	28.0% (16.4, 39.6)	p<0.001	25.9% (14.4, 37.5)	p<0.001
PASI 75 response rate at Week 12 (NRI), difference in response rate, in patients with psoriatic lesions involving BSA ≥ 3%						
10.4% (7/67)	57.4% (39/68)	61.8% (42/86)	46.9% (33.1, 60.8)	p<0.001	51.3% (37.6, 65.0)	p<0.001
MDA (E6] response rate at Week 24 (NRI), difference in response rate						
3.4% (4/188)	27.9% (34/122)	23.6% (29/123)	24.5% (15.9, 33.1)	<0.001	20.2% (12.0, 28.4)	<0.001
LEI (0) response rated at Week 24 (NRI), difference in response rate, in patients with LEI > 0 at baseline						
21.7% (15/69)	35.3% (24/68)	31.0% (26/84)	13.6% (-1.4, 28.5)	0.091	9.2% (-4.7, 23.1)	0.271

Extension period (Weeks 24-52)

Study RHAP

In Study RHAP, patients who completed the double-blind treatment period (Weeks 0 to 24) were eligible to enter the extension period (Weeks 24-52) and be treated with either open-label ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W. The extension period included a total of 381 patients assigned to 1 of 6 treatment groups comprising 2 groups of placebo-treated patients (Weeks 0 to 24) re-randomised at Week 24 to either ixekizumab 80 mg Q4W (n=45) or ixekizumab 80 mg Q2W (n=46), 2 groups of adalimumab-treated patients (Weeks 0 to 24) re-randomised at Week 24 to either ixekizumab 80 mg Q4W

(n=49) or ixekizumab 80 mg Q2W (n=48), 1 group of patients randomised at baseline (Week 0) to ixekizumab 80 mg Q4W continuing the same dose in the extension period (n=97), and 1 group of patients randomised at baseline (Week 0) to ixekizumab 80 mg Q2W continuing the same dose of ixekizumab in the extension period (n=96). The extension period is ongoing. The response rates at Week 52 for key efficacy endpoints in the 6 treatment groups are summarised below in Table 11.

Table 11: Study RHAP response rates (NRI) at Week 52 for each of the treatment groups in the extension period (Weeks 24 to 52)

PBO/IXE Q4W	PB0/IX EQ2W	A/IXEQ 4W	A/IXEQ 2W	IXE80Q4W/IX E80Q4W	IXE80Q 2W/IXE 80Q2W
ACR20 response rates					
57.8% (26/45)	71.7% (33/46)	69.4% (34/49)	58.3% (28/48)	69.1% (67/97)	68.8% (66/96)
ACR50 response rates					
42.2% (19/45)	45.7% (21/26)	59.2% (29/49)	43.8% (21/48)	54.6% (53/97)	53.1% (51/96)
ACR70 response rates					
20.0% (9/45)	30.4% (14/26)	34.7% (17/49)	29.2% (14/48)	39.2% (38/97)	39.6% (38/96)
HAQ-DI response rated in patients achieving improvement in score ≥ 0.35 (MICD) in patients with baseline score ≥ 0.35					
43.2% (16/37)	40.0% (16/40)	60.5% (26/43)	47.6% (20/42)	57.1% (52/91)	57.1% (48/84)
PASI 75 response rates in patients with baseline psoriatic lesions involving ≥ 3% of BSA					
61.3% (19/31)	65.5% (19/29)	64.7% (22/34)	66.7% (22/33)	78.8% (52/66)	81.8% (45/55)
MDA_{PASI} response rates					
33.3% (15/45)	41.3% (19/46)	40.8% (20/49)	31.3% (15/48)	43.3% (42/97)	39.6% (38/96)
LEI (0) response rate in patients with baseline LEI > 0					
40.9% (9/22)	42.3% (11/26)	50.0% (14/28)	26.1% (6/23)	55.4% (36/65)	50.0% (26/52)
LDI-B (0) response rates in patients with baseline LDI-B > 0.					
70.0% (7/10)	57.1% (8/14)	75.0% (6/8)	70.0% (7/10)	85.7% (30/35)	87.5% (21/24)

A= adalimumab

In the ITT population, the benefits of treatment with both ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W were consistent at Weeks 12, 24 and 52. There was no evidence of loss of response with continued exposure to ixekizumab through to Week 52. The results for the extension period in Study RHAP are considered to meet the relevant EU guideline relating to psoriatic arthritis that has been adopted by the TGA. The guideline states that '*although efficacy may be demonstrated in 12-24 weeks trial, maintenance of the effect in longer trials (e.g., 1 year) should be demonstrated*'. The guideline also states that data after stopping therapy should be provided. There were no data assessing the effects of stopping treatment included in the submission. However, there is currently a study underway exploring the effects of stopping treatment (Study RHBF). This study should be submitted to the TGA for evaluation when it has been completed. It is considered that the absence of withdrawal data should not preclude approval of ixekizumab, given the robustness of the submitted efficacy data. The response rates for key efficacy endpoints (NRI) at Weeks 12, 24 and 52 for patients randomised to the ixekizumab groups at Week 0 (80Q4W, 80Q2W), ITT population, are summarised below in Table 12.

Table 12: Study RHAP consistency of response rates (NRI) for selected efficacy endpoints through to Week 52 in the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups; ITT population

IXE80Q4W (ITT population)			IXE80Q2W (ITT population)		
Week 12	**Week 24**	**Week 52**	**Week 12**	**Week 24**	**Week 52**
ACR20 response rates					
57.0% (61/107)	57.9% (62/107)	62.6% (67/107)	60.2% (62/103)	62.1% (64/103)	64.1% (66/103)
ACR50 response rates					
33.6% (36/107)	40.2% (43/107)	49.5% (53/107)	39.8% (41/103)	46.6% (48/103)	49.5% (51/103)
ACR70 response rates					
15.0% (16/107)	23.4% (25/107)	35.5% (53/107)	16.5% (17/103)	28.6% (48/103)	36.8% (38/103)
HAQ-DI response rated in patients achieving improvement in score ≥ 0.35 (MICD) in patients with baseline score ≥ 0.35					
49.0% (49/100)	49.0% (49/100)	52.0% (52/100)	64.4% (58/90)	57.8% (52/90)	53.3% (48/90)
PASI 75 response rates in patients with baseline psoriatic lesions involving ≥ 3% of BSA					
75.3% (55/73)	71.2% (52/73)	71.2% (52/73)	69.5% (41/59)	79.7% (47/59)	76.3% (45/79)
MDA_{PASI} response rates					
21.5% (23/107)	29.9% (32/107)	39.3% (42/107)	33.0% (34/103)	40.8% (42/103)	36.9% (38/103)
LEI (0) response rate in patients with baseline LEI > 0					

IXE80Q4W (ITT population)			IXE80Q2W (ITT population)		
27.9% (19/68)	42.6% (29/68)	52.9% (36/68)	47.4% (27/57)	38.6% (22/57)	45.6% (26/57)
LDI-B (0) response rates in patients with baseline LDI-B > 0.					
74.4% (29/39)	79.5% (31/39)	76.9% (30/39)	69.2% (18/26)	76.9% (20/26)	80.8% (21/26)

The benefits of treatment of treatment achieved in responders at Week 24 were maintained through to Week 52. The results for key efficacy endpoints are summarised below in Table 13.

Table 13: Study RHAP response rates at Week 52 for patients in the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups who achieved a response at Week 24 for key efficacy endpoints, maintenance primary population

Week 52 response rates	IXE80Q4W	IXE80Q2W	Δ IXE80Q2W – IXE80Q2W (95% CI)
ACR20	80.6% (50/62)	81.5% (53/65)	0.9% (-12.7, 14.5)
ACR50	81.4% (35/43)	77.1% (37/48)	-4.3% (-20.9, 12.3)
ACR70	80.0% (20/25)	80.0% (28/35)	0% (-20.5, 20.5)
HAQ-DI (MICD)	83.7% (41/89)	82.4% (42/51)	-1.3% (-16.0, 13.4)
LEI (0)	69.0% (20/29)	86.4% (19/22)	17.4 (-4.7, 39.5)
LDI-B (0)	83.9% (26/31)	95.0% (19/20)	11.1 (-5.0, 27.2)
MDA_{PASI}	84.4% (27/32)	69.0% (29/42)	-15.3 (-34.1, 3.5)

HAQ-DI (MICD) = Improvement from baseline in HAQ-DI score of ≥ 0.35 (minimal clinically important difference) in patients with baseline scores ≥ 0.35; LEI (0) response rates in patients with baseline LEI > 0; LDI-B (0) response rates in patients with baseline LDI-B > 0

Radiographic assessment of structural damage was also undertaken at Week 52. The mean (± SD) mTSS increase from baseline at Week 52 (linear extrapolation) was numerically greater in patients who had been randomised (Week 0) to ixekizumab 80 mg Q4W than in patients who had been randomised to ixekizumab 80 mg Q2W (0.54 ± 2.12), n=80 versus 0.09 ± 0.95), n=80, respectively), suggesting that the radiological progression with continued exposure was not as great in the ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group. The proportion of patients with no radiological progression at Week 52, defined as a change from baseline in mTSS of ≤ 0, was similar in patients who had been randomised to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W (70.1% (68/97) versus 72.9% (70/96), respectively).

The sponsor is not seeking an indication claiming that ixekizumab slows or prevents structural joint damage, which would generally require an observation period of 2 years (psoriatic arthritis guideline). However, the sponsor proposes including radiographic response data from Study RHAP in the PI. This is considered to be acceptable.

Benefits in subgroups

The pooled data from patients in Studies RHAP and RHBE for the placebo-controlled period (Weeks 0 to 24) included subgroup efficacy analyses based on the ACR20 and ACR50 response rates at Week 24. The subgroups were categorised as: demographics (gender, age, weight, BMI, race, ethnicity, geographic region); disease characteristics (CRP, time since PsA onset, time since PsA diagnosis, baseline enthesitis, baseline dactylitis); previous therapy (cDMARD use at baseline, methotrexate use at baseline); and other characteristics (smoking, baseline psoriasis, baseline moderate-to-severe psoriasis). In each of the subgroups, the response rates for ACR20 and ACR50 consistently favoured patients in both ixekizumab groups (80Q4W, 80Q2W) compared with placebo.

Significant subgroup interactions for ACR20 response at Week 24 were observed for sex (efficacy favoured males), weight (efficacy favoured patients in the ≥ 80 to < 100 kg group and patients in the ≥ 50th to < 75th percentile), baseline CRP (efficacy favoured patients with higher baseline CRP of > 6 mg/mL), and duration of disease (efficacy favoured patients with a disease duration of ≥ 5 years). There were no significant subgroup interactions for ACR20 response at Week 24 for baseline cDMARD or MTX use. There no subgroup interactions for ACR20 response at Week 24 based on age (< 65, ≥ 65 to < 75, or ≥ 75 years). The mean age (SD) of the patients in the integrated data set (n=679) was 51.0 (11.9) years, with the majority of patients being aged < 65 years (86.1%, n=584), 12.8% (n=87) aged ≥ 65 to < 75 years and 1.0% (n=7) aged ≥ 75 years.

Significant subgroup interactions for ACR50 response at Week 24 were observed for duration of disease (efficacy favoured patients with a disease duration of ≥ 5 years), MTX use at baseline (efficacy favoured patients without MTX use), and cDMARD use at baseline (efficacy favoured patients without cDMARD use).

Benefits of treatment in patients with coexistent PsA and moderate-to-severe plaque Ps

There were no data in the submission in patients with coexistent PsA and moderate-to-severe plaque psoriasis treated with exactly the same ixekizumab dosage regimen as that proposed for the treatment of the patients with coexistent conditions. Nevertheless, the totality of submitted data support the use of the ixekizumab 80 mg regimen approved for patients with Ps for the treatment of patients with coexistent PsA and Ps (160 mg starting dose (2 x 80 mg), followed by 80 mg Q2W through to Week 12 and then 80 mg Q4W). In the pooled data for Studies RHAP and RHBE (Weeks 0-24), 83 of the patients randomised to ixekizumab or placebo had PsA and coexistent moderate-to-severe plaque psoriasis at baseline (PASI total score ≥ 12, sPGA ≥ 3, and BSA ≥ 10%). Of the 83 patients, 27 had been randomised to placebo, 32 to IXE80Q4W and 24 IXE80Q2W.

The results for the placebo, IXE80Q4W and IXE80Q2W groups for the efficacy endpoints of PASI 75/90/100, sPGA (0) response rate and percent improvement in PASI total score at Weeks 12 and 24 for patients with moderate-to-severe baseline psoriasis are summarised below in Table 14. For each of the selected efficacy endpoints at both Weeks 12 and 24 the outcomes were statistically significantly greater in both ixekizumab groups compared with placebo. The pairwise comparisons between the ixekizumab groups numerically favoured the ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group for most of the selected efficacy outcomes, but the observed differences between the two groups were not statistically significant (p>0.05).

Table 14: Integrated data set placebo-controlled period Weeks 0 to 24 (Studies RHAP and RHBE) in patients with moderate-to-severe plaque psoriasis, selected efficacy outcomes at Weeks 12 and 24

PBO	IXEQ4W	IXEQ2W	IXE80Q4W-PBO (95%CI); p-value		IXE80Q2W-PBO (95%CI); p-value	
PASI 75 response rate at Week 12 (NRI) in patients with moderate to severe plaque psoriasis						
3.7% (1/27)	71.9% (23/32)	75.0% (18/24)	68.2% (51.0, 85.3)	p<0.001	71.3% (52.6, 90.0)	p<0.001
PASI 75 response rate at Week 24 (NRI) in patients with moderate to severe plaque psoriasis						
11.1% (3/27)	65.6% (21/32)	70.8% (17/24)	54.5% (34.2, 74.8)	p<0.001	59.7% (38.0, 81.4)	p<0.001
PASI 90 response rate at Week 12 (NRI) in patients with moderate to severe plaque psoriasis						
0% (0/26)	46.9% (15/32)	62.5% (15/24)	46.9% (29.6, 64.2)	p<0.001	62.5% (43.1, 81.9)	p<0.001
PASI 90 response rate at Week 24 (NRI) in patients with moderate to severe plaque psoriasis						
11.1% (3/27)	46.9% (15/32)	66.7% (16/240	35.8% (14.8, 56.7)	p=0.006	55.6% (33.3, 77.8)	p<0.001
PASI 100 Week 12 (NRI) in patients with moderate to severe plaque psoriasis						
0% (0/26)	25.0% (8/32)	25.0% (6/24)	25.0% (10.0, 40.0)	p=0.006	25.0% (7.7, 42.3)	p<0.001
PASI 100 response rate at Week 24 (NRI) in patients with moderate to severe plaque psoriasis						
0 (0%)	28.1% (9/32)	50.0% (12/24)	28.1% (12.5, 43.7)	p=0.004	50.0% (30.0, 70.0)	p<0.001
sPGA (0) response rate at Week 12 (NRI) in patients with baseline moderate to severe plaque psoriasis						
0% (0/27)	25.0% (8/32)	25.0% (6/24)	25.0% (10.0, 40.0)	p=0.006	25.0 % (7.7, 42.3)	p=0.007
sPGA (0) response rate at Week 24 (NRI) in patients with moderate to severe plaque psoriasis						
0% (0/27)	28.1% (9/32)	50.0% (n=24)	28.1% (12.5, 43.7)	p=0.004	50.0% (30.0, 70.0)	p<0.001

PBO	IXEQ4W	IXEQ2W	IXE80Q4W-PBO (95%CI); p-value		IXE80Q2W-PBO (95%CI); p-value	
PASI total score percent improvement (LSM) from baseline at Week 12 (MMRM) in patients with moderate to severe plaque psoriasis						
15.5%, n=26	81.0%, n=32	89.3%, n=22	65.5% (49.7, 81.2)	p<0.001	73.9% (56.5, 91.2)	p<0.001
PASI total score percent improvement (LSM) from baseline at Week 24 (MMRM) in patients with moderate to severe plaque psoriasis						
24.6%, n=15	86.0%, n=23	92.0%, n=19	61.4% (44.8, 78.0)	p<0.001	67.4 % (49.1 , 85.6)	p<0.001

Benefits of the two ixekizumab regimens

The benefits of treatment with ixekizumab were satisfactorily demonstrated for both the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W regimens. In general, the placebo-controlled double-blind data (Weeks 0-24) favoured in the ixekizumab 80 mg Q2W group in Study RHAP in the ixekizumab 80 mg Q4W group in Study RHBE, but statistical comparisons (nominal) were not significant (p>0.05) for most of the endpoints. The extension data from Study RHAP showed that the results for the key efficacy endpoints were numerically similar for patients who had been randomised to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at baseline (Week 0) and continued treatment from Week 24 to Week 52.

First round assessment of risks

The risks of ixekizumab for the treatment of PsA at the proposed dose have been adequately characterised in the submitted data and are consistent with the known risks of ixekizumab for the treatment of Ps. No new safety signals related to ixekizumab emerged from the PsA studies or from the updated safety data from the Ps studies.

TEAEs (all causality)

TEAEs (all causality) in the relevant safety data sets are summarised below in Table 15. TEAEs selected for inclusion in the table include events reported in ≥ 2% of patients in either the ixekizumab 80 mg Q4W group or the ixekizumab 80 mg Q2W group in the 'Primary PsA Analysis Set'. The TEAEs are listed in descending order of frequency in the ixekizumab 80 mg Q4W group. In the 'Primary PsA Analysis Set', total patient-years of exposure were 85.7 for the placebo group, 98.3 for the ixekizumab 80 mg Q4W group and 95.5 years for the ixekizumab 80 mg Q2W group, while in the 'All PsA Analysis Set' the total patient-years of exposure for the total ixekizumab pooled group (80 mg Q4W plus 80 mg Q2W) was 1050.6 patient-years. In Study RHAP, total patient years of exposure for adalimumab 40 mg Q4W was 44.5 years

Table 15: TEAE occurring in ≥ 2% of patients in either the ixekizumab 80 mg Q4W or 80 mg Q2W groups in descending order of frequency in the 80 mg Q4W group ('Primary PsA Analysis Set), with data summarised for the 'Primary Analysis Set', 'All PsA Analysis Set' and Study RHAP

	Primary PsA Analysis Set (Weeks 0 to 24)			Study RHAP	All PsA Analysis Set
	PBO (n=224)	IXE 80 mg Q4W	IXE 80 mg Q2W	A 40 mg Q2W	Pooled IXE group
	(n=224)	(n=229)	(n=225)	(n=101) (Weeks 0-24)	(n=1118)
Patients with ≥ 1 TEAE	127 (56.7%)	153 (66.8%) a	156 (69.3%) a	65 (64.4%)	734 (65.7%)
Injection site reaction	1 (0.4%)	22 (9.6%) a	32 (14.2%) a	2 (2.0%)	132 (11.8%)
URTI	16 (7.1%)	16 (7.0%)	15 (6.7%)	5 (5.0%)	89 (8.0%)
Nasopharyngitis	9 (4.0%)	15 (6.6%)	7 (3.1%)	7 (6.9%)	76 (6.8%)
Headache	4 (1.8%)	10 (4.4%)	6 (2.7%)	3 (3.0%)	29 (2.6%)
Injection site erythema	0	9 (3.9%) a	17 (7.6%) a	2 (2.0%)	50 (4.5%)
Sinusitis	5 (2.2%)	9 (3.9%)	6 (2.7%)	2 (2.0%)	36 (3.2%)
Urinary tract infection	5 (2.2%)	8 (3.5%)	4 (1.8%)	4 (4.0%)	38 (3.4%)
Diarrhoea	6 (2.7%)	7 (3.1%)	10 (4.4%)	3 (3.0%)	34 (3.0%)
Back pain	2 (0.9%)	7 (3.1%)	3 (1.3%)	3 (3.0%)	29 (2.6%)
Oropharyngeal pain	1 (0.4%)	7 (3.1%) a	2 (0.9%)	0	21 (1.9%)
Psoriatic arthropathy	9 (4.0%)	5 (2.2%)	5 (2.2%)	3 (3.0%)	23 (2.1%)

	Primary PsA Analysis Set (Weeks 0 to 24)			Study RHAP	All PsA Analysis Set
Cough	4 (1.8%)	5 (2.2%)	5 (2.2%)	2 (2.0%)	17 (1.5%)
Arthralgia	2 (0.9%)	5 (2.2%)	0	1 (1.0%)	8 (0.7%)
Tonsillitis	0	5 (2.2%) [a]	0	0	24 (2.1%)
Bronchitis	7 (3.1%)	4 (1.7%)	7 (3.1%)	4 (4.0%)	34 (3.0%)
Muscle spasms	3 (1.3%)	3 (1.3%)	5 (2.2%)	1 (1.0%)	11 (1.0%)
ALT increased	1 (0.4%)	3 (1.3%)	5 (2.2%)	3 (3.0%)	14 (1.3%)
Hypertension	5 (2.2%)	2 (0.9%)	7 (3.1%)	3 (3.0%)	33 (3.0%)
Pharyngitis	2 (0.9%)	2 (0.9%)	5 (2.2%)	0	27 (2.4%)
Injection site hypersensitivity	0	1 (0.4%)	6 (2.7%) a	1 (1.0%)	11 (1.0%)
Nausea	3 (1.3%)	1 (0.4%)	5 (2.2%)	4 (4.0%)	14 (1.3%)

PBO = placebo; IXE = ixekizumab; A = adalimumab. [a] = $p < 0.05$ ixekizumab versus placebo

In the 'Primary PsA Analysis Set', TEAEs occurred more frequently in patients in both ixekizumab groups compared with patients in the placebo group. The most notable differences between the ixekizumab groups and the placebo group related to the higher risks of injection site reaction and injection site erythema in the ixekizumab groups. In addition, injection site hypersensitivity occurred more frequently in the ixekizumab 80 mg Q2W group than in the placebo group. The cluster of injection site reaction, injection site erythema and injection site hypersensitivity occurred more frequently in the ixekizumab 80 mg Q2W group than in the ixekizumab 80 mg Q4W group. No other risks were notably more frequent in patients in the ixekizumab groups compared with the placebo group.

Based on TEAEs (all causality), the risk profile of the pooled ixekizumab group in the 'All PsA Analysis Set' was similar to the risk profiles of the two ixekizumab groups in the 'Primary PsA Analysis Set'. The comparable risk profiles of ixekizumab in the two analysis sets provide reassurance relating to the long-term safety of the drug for the treatment of PsA, given that the patient-years of exposure to ixekizumab was approximately 11-fold longer in the 'All Ps Analysis Set' compared with the 'Primary PsA Analysis Set'. In the 'All PsA Analysis Set', 365 patients in the ixekizumab group had been treated for ≥ 1 year, 208 patients for ≥ 2 years, 8 patients for ≥ 3 years, and no patients for ≥ 4 years.

Based on TEAEs (all causality), the risk profiles of the two ixekizumab groups in the 'Primary PsA Analysis Set' were comparable to the risk profile of adalimumab 40 mg Q2W from Study RHAP, apart from the higher incidence of injection-related TEAEs in one or both of the ixekizumab groups compared with the adalimumab group. Comparison of TEAEs between the two ixekizumab groups in the 'Primary PsA Analysis Set' and the adalimumab group in Study RHAP should be interpreted having regard to the approximately 2 fold longer duration of exposure in the ixekizumab groups compared with the adalimumab group.

Deaths

There were no deaths in the 'Primary PsA Analysis Set' and 2 (0.2%) deaths in the 'All PsA Analysis Set'. The 2 deaths in the 'All PsA Analysis Set' included a male with a history of cardiovascular risk factors who died due to a CVA (preferred term) following 537 days of exposure to ixekizumab (dose at time of death 80 mg Q4W), and another male who died due to pneumonia following 19 days of exposure to ixekizumab (dose at time of death 80 mg Q2W). Treatment with ixekizumab for PsA does not appear to be associated with an increased risk of death.

Serious adverse events (SAEs)

In the 'Primary PsA Analysis Set', SAEs were reported more frequently in both ixekizumab groups compared with the placebo group (3.9% (n=9), 80Q4W versus 4.9% (n=11), 80Q2W versus 2.7% (n=6), placebo). No individual SAEs (preferred terms) in the two ixekizumab groups were reported in ≥ 2 patients. No particular pattern in the reported SAEs in the two ixekizumab groups emerged. Overall, SAEs are not considered to be a significant risk for patients with PsA treated with ixekizumab.

SAEs, grouped by SOC, in the ixekizumab 80 mg Q4W group were reported in a total of 9 (3.9%) patients and comprised: *Infections and infestations* 0.4%, n=1 (gastroenteritis); *Reproductive and breast disorders* 0.4%, n=1 (uterine polyp); *Gastrointestinal disorders* 0.4%, n=1 (pancreatitis); *Nervous system disorders* 0.9%, n=2 (one each cervico-brachial syndrome, post-traumatic headache); *Injury, poisoning, procedural complications* 0.4%, n=1 (fibula fracture); *Musculoskeletal and connective tissue disorders* 0.9%, n=2 (one each lumbar spinal stenosis, myofascial pain syndrome); *Ear and labyrinthine disorders* 0.4%, n=1 (vertigo); *Hepatobiliary disorders* 0.4%, n=1 (cholelithiasis); and *Neoplasms benign, malignant, and unspecified (incl cysts and polyps)* 0.4%, n=1 (prostate cancer).

SAEs, grouped by SOC, in ixekizumab 80 mg Q2W group were reported in a total of 11 (4.9%) patients and comprised: *Infections and infestations* 2.2%, n=5 (one each for abscess jaw, anal abscess, herpes zoster, oesophageal candidiasis, perirectal abscess); *Reproductive and breast disorders* 0.9%, n=2 (one each for uterine prolapse, acquired phimosis); *Gastrointestinal disorders* 0.9%, n=2 (one each for anal fistula, impaired gastric emptying); *Nervous system disorders* 0.4%, n=1 (cervical myelopathy); *Injury, poisoning, procedural complications* 0.4%, n=1 (one each for fall, foot fracture); *Blood and lymphatic system* 0.4%, n=1 (iron deficiency anaemia); *Metabolism and nutrition disorder* 0.4%, n=1 (diabetes mellitus); and *Pregnancy, puerperium,* and *Perinatal conditions* 0.4%, n=1 (spontaneous abortion).

In the 'All PsA Analysis Set', SAEs were reported in 73 (6.5%) patients in the pooled ixekizumab group, and preferred terms reported in ≥ 2 patients were pneumonia (0.3%, n=3), lower respiratory tract infection (0.2%, n=2), carotid artery stenosis (0.2%, n=2), cerebrovascular accident (0.2%, n=2), fall (0.2%, n=2), acute myocardial infarction (0.2%, n=2), coronary artery disease (0.2%, n=2), cholecystitis acute (0.2%, n=2), cholelithiasis (0.2%, n=2); and osteoarthritis (0.2%, n=2).

Adverse events leading to discontinuation of the study drug

In the 'Primary PsA Analysis Set', AEs leading to discontinuation of the study drug were reported in a similar proportion of patients in the placebo and ixekizumab 80 mg Q4W groups, and more frequently in the ixekizumab 80 mg Q2W group than in both the placebo and ixekizumab 80 mg Q4W groups (3.1% (n=7), 80Q4W versus 5.3% (n=12), 80Q2W versus 3.6% (n=8), placebo). The only AE leading to treatment discontinuation of the study drug reported in ≥ 2 patients in either of the two ixekizumab groups was injection site reaction (0.9%, n=2) in the ixekizumab 80 mg Q2W group. No particular pattern in the AEs leading to discontinuation of the study drug was observed in two ixekizumab groups, apart from a small number of discontinuations due to clustered injection site related events. In the two ixekizumab groups, the proportion of patients discontinuing the study drug due to AEs was notably lower than the proportion of patients experiencing TEAEs (all causality), which suggests that the majority of adverse events in the two treatment groups were manageable by treatment modalities other than discontinuation. Overall, AEs leading to discontinuation of the study drug are not considered to be a significant risk for patients with PsA treated with ixekizumab.

AEs, grouped by SOC, leading to treatment discontinuation in the ixekizumab 80 mg Q4W arm were reported in a total of 7 (3.1%) patients and comprised: *General disorders and administration site conditions* 0.4%, n=1 (injection site reaction); *Infections and infestations* 0.9%, n=2 (one each subcutaneous abscess, urinary tract infection); *Investigations* 0.4%, n=1 (interferon gamma release assay positive); *Skin and subcutaneous tissue disorders* 0.4%, n=1 (rash pruritic); *Immune system disorders* 0.4%, n=1 (hypersensitivity); and *Neoplasms benign, malignant, and unspecified (including cysts and polyps)* 0.4%, n=1 (prostate cancer).

AEs, grouped by SOC, leading to treatment discontinuation in patients in the ixekizumab 80 mg Q2W group were reported in a total of 12 (5.3%) patients and comprised: *General disorders and administration site conditions* 1.8%, n=4 (two injection site reactions, one each injection site hypersensitivity, injection site rash); *Infections and infestations* 0.4%, n=1 (folliculitis); *investigations* 0.4%, n=1 (interferon gamma release assay positive); *Hepatobiliary disorders* 0.4%, n=1 (hypertransaminasaemia); *gastrointestinal disorders* 0.4%, n=1 (abdominal pain); *Metabolism and nutrition disorder* 0.4%, n=1 (diabetes mellitus); *Pregnancy, puerperium, and perinatal conditions* 0.4%, n=1 (spontaneous abortion); *Psychiatric disorders* 0.4%, n=1 (depression); and *Respiratory, thoracic and mediastinal disorders* 0.4%, n=1 (nasal necrosis).

In the 'All PsA Analysis Set', AEs leading to discontinuation of the study drug were reported in 64 (5.7%) patients in the pooled ixekizumab group and the preferred terms reported in ≥ 2 patients were: interferon gamma release assay positive (0.9%, n=10); latent tuberculosis (0.5%, n=6); injection site reaction (0.4%, n=4); tuberculin test positive (n=3, 0.3%); CVA (n=2, 0.2%); and myalgia (0.2%, n=2). In this analysis set, prostate cancer leading to discontinuation of the study drug was reported in 0.2% (n=1) of male patients and abortion spontaneous, pregnancy, and unintended pregnancy were each reported in 0.2% (one event each) of female patients.

Adverse events of special interest (AESI)

The key risks, based on AESI, in the 'Primary PsA Analysis Set' and the 'All PsA Analysis Set' are summarised below in Table 16.

Table 16: Adverse events of special interest in the 'Primary PsA Analysis Set' and the 'All PsA Analysis Set'

	Primary PsA Analysis Set (Weeks 0-24)			All PsA Analysis Set
	PBO (n=224)	IXE 80 mg Q4W (	IXE 80 mg Q2W	Pooled IXE group
	(n=224)	(n=229)	(n=225)	(n=1118)
TEAEs of special interest	77 (34.4%)	113 (49.3%)	126 (56.0%)	582 (52.1%)
Infection-related TEAE	62 (27.7%)	77 (33.6%)	72 (32.0%)	416 (37.2%)
Candida Infection (HLT)	1 (0.4%)	4 (1.7%)	8 (3.6%) a	28 (2.5%)
Oral candidiasis (PT)	0	1 (0.4%)	4 (1.8%) a	12 (1.1%)
Cytopaenias TEAEs (based on MedDRA SMQ)	2 (0.9%)	2 (0.9%)	4 (1.8%)	28 (2.5%)
TE-neutropaenia (laboratory)	6/219 (2.7%)	24/226 (10.6%) a	19/218 (8.7%) a	136 (12.5%)
TE-neutropaenia Grade 3 or 4	0	0	0	3 (0.3%)
TE-leukopaenia (laboratory)	7/213 (3.3%)	31/222 (14.0%) a	30/218 (13.8%) a	154 (14.2%)
TE-leukopaenia Grade 3 or 4	0	0	0	1 (0.1%)
TE-lymphopaenia (laboratory)	20/189 (10.6%)	22/197 (11.2%)	31/200 (15.5%)	131 (13.4%)
TE-lymphopaenia Grade 3 or 4	0	0	1 (0.4%)	4 (0.4%)
TE-thrombocytopaenia (laboratory)	7/219 (3.2%)	12/219 (5.5%)	6/221 (2.7%)	54 (5.0%)
TE-thrombocytopaenia Grade 3 or 4	0	0	0	0
Allergic Reactions/Hypersensitivities	4 (1.8)	10 (4.4)	14 (6.2) a	60 (5.4%)
Potential anaphylaxis	0	0	0	0
Injection-site reactions	10 (4.5%)	40 (17.5%)[a]	57 (25.3%)[a,b]	211 (18.9%)
Discontinuations	1 (0.4%)	1 (0.4%)	4 (1.8%)	6 (0.5%)
Cerebro-cardiovascular (confirmed)	2 (0.9)	0	0	12 (1.1%)

	Primary PsA Analysis Set (Weeks 0-24)			All PsA Analysis Set
MACE (confirmed)	0	0	0	5 (0.4%)
Malignancies	0	2 (0.9)	0	6 (0.5%)
Hepatic-related TEAEs (broad & narrow terms)	10 (4.5%)	7 (3.1%)	11 (4.9%)	45 (4.0%)
Depression TEAE (PT)	3 (1.3)	4 (1.7)	4 (1.8)	15 (1.3%)
Suicide/self-injury	0	0	0	0
IBD TEAE (narrow terms)	0	0	0	1 (0.1%)
ILD TEAE (narrow terms)	0	0	0	0
Renal and urinary disorders (SOC)	4 (1.8%)	3 (1.3%)	4 (1.8%)	31 (2.8%)
Skin and subcutaneous tissue disorders (SOC)	12 (5.4%)	22 (9.6%)	23 (10.2%)	23 (11.0%)

Notes: [a] = $p < 0.05$ for ixekizumab group versus placebo; [b] = $p < 0.05$ for ixekizumab 80 mg Q4W versus Q2W.

In the' Primary Ps Analysis Set', the main differences in the incidence of AESI across the treatment groups related to the significantly higher proportion of patients in one or both of the ixekizumab groups compared with the placebo group with injection site reactions, TE-leukopaenia (laboratory assessment), TE-neutropaenia (laboratory assessment), allergic reactions/hyper sensitivities, and *Candida* infections. However, apart from injection-related reactions it is considered that the observed differences are not clinically significant. Injection-related reactions occurred more frequently in the ixekizumab 80 mg Q2W group than in the ixekizumab Q4W group but the number of patients discontinuing the study drugs due to injection-related reactions was small in both treatment groups. Cytopaenias (TEAEs SMQ) (neutropaenia, leukopaenia, lymphopaenia, and thrombocytopaenia) occurred infrequently in both ixekizumab groups and in the placebo group. Infection-related TEAEs occurred very commonly in both ixekizumab groups and the placebo group, but the numerically higher proportion of patients with these events in both ixekizumab groups compared with the placebo group is considered to be not clinically significant.

In the 'All PsA Analysis Set', the risks of treatment with long-term exposure to ixekizumab based on adverse events of special interest were consistent with the risks of treatment based on shorter durations of exposure to ixekizumab observed in the 'Primary PsA Analysis Set'.

Immunogenicity

In the 'Primary PsA Analysis Set', 5.1% (23/447) of patients in the total ixekizumab group were TE-ADA positive, and 4 (0.9%) of these patients were NAb positive. None of the TE-ADA positive patients had events that were considered to be potential anaphylaxis TEAEs. In this analysis set, 14 (6.2%) patients in the ixekizumab 80 mg Q2W group were TE-ADA positive (2, 0.9%, NAb-positive) and 9 (1.4%) patients in the ixekizumab 80 mg Q4W group were TE-ADA positive (2, 0.9%, NAb-positive). There was no confirmed cases

allergic reactions/hypersensitivity TEAEs in this analysis set. Of note, in this analysis set, 1 (0.5%) patient in the placebo group was TE-ADA positive.

In the 'All PsA Analysis Set', 85 (8.5%) patients in the pooled ixekizumab group were TE-ADA positive, including 4 (4.7%) patients reporting non-anaphylaxis allergic reactions/ hypersensitivity TEAEs. No patients in this analysis set had events that were considered to be potential anaphylaxis TEAEs.

In the updated 'All Ps Analysis Set', 21.7% (n=896) patients with psoriasis exposed to ixekizumab were TE-ADA positive, including 2 patients with confirmed anaphylaxis and no patients with non-anaphylaxis allergic reactions/hypersensitivity TEAEs.

Overall, the available data do not support an association between TE-ADA status and allergic reaction/hypersensitivity TEAEs.

Special groups

The available data suggest that the risks of ixekizumab treatment in patients with PsA are similar irrespective of age (≥ 18 years) or gender. In the 'All PsA analysis Set', there were 996 (89.1%) patients aged < 65 years and 122 (10.9%) aged ≥ 65 years, and 517 (46.2%) male patients and 601 (53.8%) female patients. There were only 6 (0.5%) patients with PsA aged ≥ 75 years treated with ixekizumab. However, based on the available safety data it is considered that adult patients (≥ 18 years) with PsA should not be excluded from ixekizumab treatment on the basis of age alone. There were no data in patients with PsA aged < 18 years, and ixekizumab should not be administered to patients aged < 18 years.

There are no satisfactory data on the risks of ixekizumab treatment in patients other than those whose racial origin was categorised as 'White', due to most patients in the pooled ixekizumab group ('All PsA Analysis Set') being included in this racial group (94.5%, n=1056). There are no data on the risks of ixekizumab treatment in patients with PsA and coexistent hepatic or renal impairment. However, there was no suggestion that treatment with ixekizumab is associated with clinically significant hepatic or renal toxicity in patients with PsA and normal hepatic or renal function. There are no data on the risks of treatment in patients with higher grade congestive cardiac failure (New York Heart Association (NYHA) Class III/IV).[15] Most of the patients with PsA in the studies had no cardiac impairment and there was no suggestion of clinically significant cerebro-cardiovascular toxicity in patients treated with ixekizumab. Patients with active or latent TB were excluded from the PsA studies as were patients with active HIV, hepatitis B, or hepatitis C. Patients who had recently received live vaccination or BCG vaccination were also excluded from the PsA studies. Pregnant women were excluded from the studies and experience in lactating women is lacking.

First round assessment of benefit-risk balance

The benefit-risk balance is favourable for ixekizumab for the treatment of active psoriatic arthritis in adult patients who have responded inadequately, or who are intolerant, to previous DMARD therapy.

The data from the Studies RHAP and RHBE convincingly support the benefits of treatment with ixekizumab (80Q4W and 80Q2W) for the treatment of patients with PsA compared

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

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with placebo from Weeks 0 to 24. The extension data (Weeks 24 to 52) from Study RHAP showed that response for the key efficacy endpoints in both the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups were relatively similar at Weeks 12, 24 and 52, with no diminishment in efficacy through to Week 52. The extension data (Weeks 24 to 52) from Study RHAP also showed that response at Week 24 for key efficacy endpoints observed in patients randomised to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at baseline (Week 0) could be maintained through to Week 52.

The risks of ixekizumab for the treatment of PsA at the proposed dose have been adequately characterised in the submitted data and are consistent with the known risks of ixekizumab for the treatment of Ps. No new safety signals related to ixekizumab emerged from the PsA studies or from the updated safety data from the Ps studies.

First round recommendation regarding authorisation

Approval of the application to extend the indications of ixekizumab (Taltz) to include the treatment of psoriatic arthritis at the proposed ixekizumab dosage regimens is recommended.

The recommended indication for *psoriatic arthritis* is that proposed by the sponsor, namely:

> *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).*

The sponsor recommends that for *patients with psoriatic arthritis* ixekizumab should be initiated with 160 mg SC (2 x 80 mg injections) at Week 0 followed by 80 mg SC (1 x 80 mg injection every 4 weeks. Based on the submitted data the proposed dosage regimen is recommended. The pooled data from the placebo-controlled period (Weeks 0-24) of Studies RHAP and RHBE showed no clinically significant differences in the efficacy outcomes between ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W. In addition, the 52 week data showed that efficacy outcomes were consistent in patients treated with ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W throughout the 52 week treatment period. There was no evidence of loss of response with continued exposure to ixekizumab Q4W through to Week 52. The safety profiles of the ixekizumab 80 mg Q4W and ixekizumab Q2W dosing regimens were consistent with one another, and with the known safety profile of ixekizumab for the treatment of psoriasis.

The sponsor recommends that for *patients with co-existent psoriatic arthritis and moderate to severe plaque psoriasis* the approved dosing regimen plaque psoriasis should be used (treatment initiated with 160 mg SC (2 x 80 mg injections) followed by 80 mg SC (1 x 80 mg injection) every 2 weeks at Weeks 2, 4, 6, 8, 10 and 12, then 80 mg (1 x 80 mg injection) every 4 weeks).

There were no data in the submission in patients with coexistent PsA and moderate-to-severe plaque Ps treated with exactly the same ixekizumab dosage regimen as that proposed by the sponsor. However, based on the totality of the submitted data the proposed dosage regimen is recommended. In the subset of patients with psoriatic lesions ≥ 3% BSA at baseline in the 'Primary PsA Analysis Set', PASI90/100 response rates at Week 12 were numerically greater in the ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group, although the PASI75 response rate at Week 12 was numerically greater in the ixekizumab 80 mg Q4W group than in the ixekizumab 80 mg Q2W group. At Weeks 16 and 24, the PASI75/90/100 response rates were numerically greater in the ixekizumab 80 mg Q2W group than in the ixekizumab 80 mg Q4W group.

Data from the integrated Ps program in patients with moderate-to-severe plaque psoriasis showed that the difference in PASI75/90/100 response rates between ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W at Week 12 were similar in patients with Ps and in patients with coexistent Ps and self-identified PsA. The integrated Ps data indicated that efficacy was greater in the ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group in patients with Ps and in patients with coexistent Ps and PsA.

No time limit on the duration of treatment with ixekizumab for the treatment of patients with PsA or coexistent PsA and moderate-to-severe plaque Ps has been proposed. No new safety signals relating to ixekizumab emerged from the submitted PsA studies or from the updated safety data from the Ps studies. In clinical practice, the duration of treatment will be governed by response, tolerability and toxicity.

Clinical questions

Pharmacokinetics

No questions.

Pharmacodynamics

1. Please provide a list of the major protocol violations for the PD Study RHCA and discuss the implications of these violations for study outcomes and subject safety.
2. In the appendix to the PD Study RHCA results are provided for post hoc exploratory analyses of the immune response in the ixekizumab and control arms stated to have been requested by regulators. Which regulatory agencies requested the additional post hoc analyses? What were the inferiority margins for each of the analyses? Why were 95% CIs used for the differences in response rates in these analyses rather than 90% CIs, as used for the pre-specified primary analyses?

Efficacy

1. Study RHBE: For a number of pairwise comparisons of efficacy endpoints in the published results of Study RHBE (SPIRIT-2)[16], p-values are given as < 0.0001. However, in the submitted study report for RHBE the p-values for the same pairwise comparisons are given as <0.001 (for example, ACR20 at Week 24 (placebo versus IXEQ4W; placebo versus IXEQ2W)). Please comment on these apparent discrepancies.
2. In both pivotal Phase III studies the majority of patients had a BMI in the overweight/obese/extreme obese category (74.8%, RHAP; 80.4%, RHBE). Please comment on the significance of this observation and the potential impact it might have on extrapolating the efficacy (and safety data) from the two studies to patients with PsA in the Australian community.

Safety

1. The incidence of 'Abnormal URINE protein' (52.3%) appeared to be particular high in the 'All Ps Analysis Set'. However, TEAEs of proteinuria were reported in only 0.4% (n=25) of patients in this analysis set. In addition, *Renal and urinary disorders (SOC)* were reported in only 4.6% (261/5689) of patients in the analysis set. The sponsor is

[16] Nash P, Kirkham B, Okada M et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumor necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 Phase III trial. Lancet 2017;389: 2317-27.

requested to comment on the significance of the high incidence of patients with 'Abnormal URINE protein' (52.3%) reported in the 'All Ps Analysis Set'.

Second round evaluation

Introduction

The sponsor provided a comprehensive response to the first round clinical questions raised. The questions, sponsor's responses and clinical evaluator's comments have been provided below. The sponsor also provided a comprehensive response to the first round comments on the draft PI and Consumer Medicine Information (CMI) these are however beyond the scope of this AusPAR.

Administrative questions

Question 1

It is not entirely clear whether the sponsor has a waiver from the EU specifically relating to psoriatic arthritis studies in the paediatric population. Please clarify the position as regards submission of paediatric psoriatic arthritis studies to the EU.

Sponsor's response

The sponsor has an agreed paediatric investigation plan (PIP) for the treatment of paediatric patients with ixekizumab for the indication of juvenile idiopathic arthritis (JIA) subtypes, including the subtype of juvenile PsA, with the European Union (EU) Paediatric Committee (PDCO). Specifically, this PIP includes the commitment by the sponsor to conduct a single study in the paediatric population (patients aged 2 to 18 years of age). The study is a multicentre, double-blind, randomised, placebo-controlled study to assess the safety, tolerability, pharmacokinetics (PK), and efficacy of subcutaneous ixekizumab in children with JIA subtypes of juvenile PsA, enthesitis-related arthritis (including juvenile-onset ankylosing spondylitis), and systemic JIA (Study I1F-MC-RHCG [Study RHCG]). The completed study report for Study RHCG will be shared with the EMA when available. The sponsor has a waiver from the EU PDCO specifically relating to subjects below the age of 2 years for this PIP for this indication.

Evaluator's comment

The sponsor's response is satisfactory.

Question 2

It is noted that a recently published review of psoriatic arthritis comments that the disease can begin in childhood. Two not mutually exclusive clinical subtypes are described in the review: (1) oligoarticular psoriatic arthritis occurring predominantly in girls with a peak onset at 1 to 2 years of age; and (2) a more frequent subtype characterised by any number of affected joints developing between 6 and 12 years of age with a 1: 1 sex ratio. Please indicate whether the sponsor intends to submit to the TGA psoriatic arthritis studies for Taltz in a paediatric population. If the sponsor does not intend to submit such studies please provide a justification for not doing so.

Sponsor's response

The sponsor does not intend to submit the paediatric study results to TGA in order to update the label. However, as per standard sponsor reporting procedures, the final report will be submitted with the next appropriate Periodic Safety Update Report (PSUR), unless there are new safety findings that change the benefit/risk profile of ixekizumab, in which case appropriate notifications will be made.

It should be noted that the subtype of oligoarticular PsA occurring predominantly in girls with a peak onset of 1 to 2 years of age, will only be studied in Study RHCG in patients ≥ 2 years of age. The second subtype is included in the agreed PIP and will be assessed in Study RHCG.

Evaluator's comment

The sponsor's response is satisfactory.

Pharmacodynamic questions

Question 1

Please provide a list of the major protocol violations for the PD study RHCA and discuss the implications of these violations for study outcomes and subject safety.

Sponsor's response

There were no significant GCP issues or major protocol violations for the pharmacodynamics (PD) Study I1F-MC-RHCA (Study RHCA). The protocol deviations that occurred were reviewed by the sponsor and were considered unlikely to have affected the safety of the subjects or the results or conclusions of the study.

Evaluator's comment

The sponsor's response is satisfactory.

Question 2

In the appendix to the PD study RHCA results are provided for post hoc exploratory analyses of the immune response in the ixekizumab and control arms stated to have been requested by regulators. Which regulatory agencies requested the additional post-hoc analyses? What were the inferiority margins for each of the analyses? Why were 95% CIs used for the differences in response rates in these analyses rather than 90% CIs, as used for the prespecified primary analyses?

Sponsor's response

The post-hoc exploratory analyses in Study RHCA were requested by the US FDA. The non-inferiority margins were 40% for each analysis. The FDA requested that the sponsor use 95% confidence intervals (CIs) for differences in response rates in these analyses.

Evaluator's comment

The sponsor's response is satisfactory.

Efficacy questions

Question 1

Study RHBE: For a number of pairwise comparisons of efficacy endpoints in the published results of Study RHBE (SPIRIT-2) (Nash et al., 2017) p-values are given as < 0.0001.However, in the submitted CSR for RHBE the p-values for the same pairwise comparisons are given as <0.001 (e.g., ACR20 at Week 24 [placebo vs IXEQ4W; placebo vs IXEQ2W]). Please comment on these apparent discrepancies.

Sponsor's response

The statistical analysis plan (SAP) for Study I1F-MC-RHBE (RHBE) states that the sponsor will calculate p-values to 3 decimal places:

> *'P-values that are greater than or equal to 0.001, and less than or equal to 0.999, will be presented to three decimal places. All other p-values which are less than 0.001 will*

be presented as <0.001, while p-values greater than 0.999 will be presented as >0.999.'

The journal (Lancet), where Study RHBE (SPIRIT-2) (Nash et al., 2017)' was published, has a unique requirement to present p-values to 4 decimal places. Due to this unique requirement, the sponsor calculated the p-values to 4 decimal places to satisfy the journal's requirement but continues to follow the SAP for all development, regulatory, and other disclosures.

Evaluator's comment

The sponsor's response is satisfactory.

Question 2

In both pivotal Phase III studies the majority of patients had a BMI in the overweight/ obese/ extreme obese category (74.8%, RHAP; 80.4%, RHBE). Please comment on the significance of this observation and the potential impact it might have on extrapolating the efficacy (and safety data) from the two studies to patients with PsA in the Australian community.

Sponsor's response

The number of patients from Study I1F-MC-RHAP (Study RHAP) and Study RHBE recruited in Australia (n=7) is not large enough to perform a reliable subgroup analysis. While the sponsor did not find published data describing the distribution of BMI in the Australian population of patients with PsA, Page 30 of the attached Australasian Psoriasis Registry Newsletter (Issue 12, October 2017) provides the distribution of BMI in a cohort of 1542 patients with psoriasis. The distribution of BMI from the Primary PsA Placebo-Controlled Integrated Analysis Set (Studies RHAP and RHBE) is consistent with the distribution of BMI in this Australian cohort (see below Table 17).

In addition, present the efficacy and safety subgroup analyses by baseline BMI category in the Primary PsA Placebo-Controlled Integrated Analysis Set. The frequency of TEAEs, treatment-emergent (TE)-infections and TE-injection site reactions was also analysed by baseline BMI category in the Primary PsA Placebo-Controlled Integrated Analysis Set (Studies RHAP and RHBE). No meaningful difference was detected in the frequencies of these TEAEs in the ixekizumab or placebo groups across the BMI categories.

Therefore, even if the distribution of BMI differed in the present trials compared to the Australian population of patients with PsA, this hypothetical difference should not alter the applicability of the present data to the Australian population.

Table 17: Distribution of BMI primary PsA placebo controlled integrated analysis set (Studies RHAP and RHBE) Australasian psoriasis registry patients

BMI Category	Primary PsA Placebo-Controlled Integrated Analysis Set (Studies RHAP and RHBE) N=679	Australasian Psoriasis Registry Patients N=1542
Distribution of BMI, n (%)		
Underweight (<18.5 kg/m^2)	5 (0.7)	7 (0.5)
Normal (≥18.5 to <25 kg/m^2)	152 (22.6)	321 (20.8)
Overweight (≥25 to <30 kg/m^2)	227 (33.7)	530 (34.4)
Obese (≥30 to <40 kg/m^2)	234 (34.8)	569 (36.9)
Extreme Obese (≥40 kg/m^2)	55 (8.2)	115 (7.5)

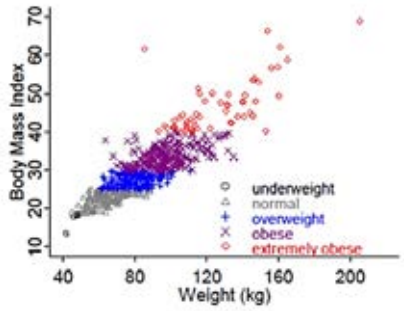
Abbreviations: BMI = body mass index; N = number of patients in the analysis population; n = number of patients in the specified category.

Exposure-response analyses on ACR efficacy

The potential impact of BMI on ACR response was also evaluated with exposure-response analyses. In the current ixekizumab population PK analysis, body weight is a covariate for drug clearance and volume of distribution. Since body weight and BMI are highly correlated (see below Figure 1), BMI has no additional effect when the body weight was already incorporated in the PK model.

In the exposure-ACR response analyses supporting the initial Marketing Authorization Application (MAA) for PsA, body weight was evaluated and not found to be a significant covariate, suggesting that, besides the drug exposure impact on efficacy, there is no additional impact of body weight upon ACR response. Body mass index was not evaluated as a potential covariate in the exposure-ACR response analyses because body weight was already evaluated and there was a strong correlation between body weight and BMI in the pooled Studies RHAP and RHBE dataset (see Figure 1, below).

Figure 1: Correlation between BMI and body weight in patients from Studies RHAP and RHBE

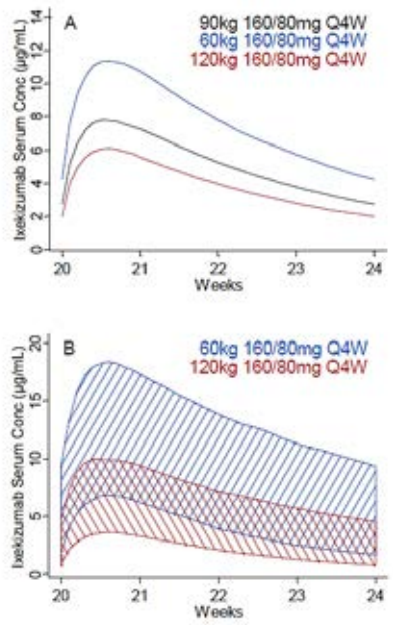


In the present dataset, the median weight (range) for underweight, normal, overweight, obese, and extremely obese patients is 47.2 (41.8 - 49.0) kg, 64.0 (45.1 - 88.5) kg, 81 (61.2 - 111) kg, 96.3 (63.6 - 135) kg, and 123 (85.5 - 206) kg, respectively.

To evaluate the impact of obesity on drug exposure and ACR responses using body weight as a surrogate for the obese condition, simulations were conducted to show the ixekizumab serum concentration profiles for patients with 60, 90, and 120 kg body weight, and ACR responses over the first 24 weeks for patients with 60 and 120 kg body weight, respectively. The 60 kg body weight was chosen because it was close to the median weight of patients in the normal BMI range of the present dataset (64.0 kg). Similarly, patients with 90 kg and 120 kg body weights were chosen to represent the overweight-to-obese and extremely obese groups (median weight: 81.0 kg (overweight), 96.3 kg (obese), 123 kg (extremely obese)), respectively.

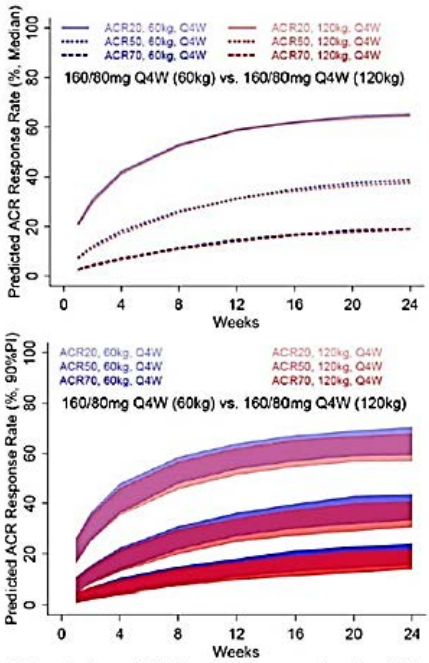
Since ixekizumab CL is approximately proportional to the body weight, steady state exposures in 120 kg or 90 kg patients is estimated to be approximately 50% or 70% of that in 60 kg patients following ixekizumab 80 mg Q4W dosing, respectively (see Figure 2, below). However, since the range of ixekizumab concentration from Studies RHAP and RHBE is near the top plateau of the drug exposure-ACR response curve, response rates of ACR20, ACR50, and ACR70 in patients with PsA weighing 120 kg are expected to be similar to those in patients weighing 60 kg; see Figure 3). Similar ACR response rates are also expected for patients weighing 90 kg (results not shown).

Figure 2: Model predicted steady-state drug concentrations in patients with PsA receiving 160 mg starting dose followed by 80 mg Q4W ixekizumab doses



Abbreviations: 160/80mg = 160 mg starting dose followed by 80 mg repeated doses; Conc = concentration; PI = prediction interval; PK = pharmacokinetic; PsA = psoriatic arthritis; Q4W = every 4 weeks.
The final population PK model was used to simulate the ixekizumab steady-state concentration profiles, assuming thigh injection and negative immunogenicity.
Panel A: median PK profiles; Panel B: overlay of 90% PIs.

Figure 3: Model-predicted time course of ACR response in patients with PsA receiving 160 mg starting dose followed by 80 mg Q4W ixekizumab doses through Week 24



Abbreviations: 160/80mg = 160 mg starting dose followed by 80 mg repeated doses; ACR20 = American College of Rheumatology 20% response rate; ACR50 = American College of Rheumatology 50% response rate; ACR70 = American College of Rheumatology 70% response rate; PI = prediction interval; PK = pharmacokinetic; PsA = psoriatic arthritis; Q4W = every 4 weeks.
The parameters in the final population PK model and those in the final population ACR time course model were used in the simulation. The simulation was based on observed patient demographics (age and sex), dosing events, and immunogenicity incidences in Studies RHAP and RHBE. To predict ACR response rates in light weight patients, 400 simulation iterations of Studies RHAP and RHBE were conducted and the resulting ACR response rates were summarised. In each simulation, the body weight was fixed at 60 kg in all patients, whereas all other patient demographics (age and sex), dosing events, and immunogenicity incidences were retained as observed in Studies RHAP and RHBE. To predict ACR responses in more obese patients, similar simulation iterations were conducted, except that the body weight of all patients was fixed to 120 kg.
Blue lines and shaded areas: patients with 60 kg weight (160 mg starting dose and 80 mg Q4W); Red lines and shaded areas: patients with 120 kg weight (160 mg starting dose and 80 mg Q4W). Left panel: predicted median ACR response rates; Right panel: 90% PIs of ACR response rates.

In summary, the recommended regimen (160 mg starting dose followed by 80 mg Q4W) is expected to result in similar ACR response rates across the patients with normal weight through extreme obesity. These data are consistent with the results from the statistical subgroup analysis results. Therefore, regardless of whether the obese condition of patients with PsA in the Australian community is similar to the patient population in Studies RHAP and RHBE, the ACR efficacy results observed in these 2 Phase III studies are likely applicable.

Evaluator's comment

The sponsor's response is satisfactory.

Safety questions

Question 1

The incidence of 'Abnormal Urine protein' (52.3%) appeared to be particular high in the 'All Ps Analysis Set'. However, TEAEs of proteinuria were reported in only 0.4% (n=25) of

patients in this analysis set. In addition, renal and urinary disorders (SOC) were reported in only 4.6% (261/5689) of patients in the analysis set. The sponsor is requested to comment on the significance of the high incidence of patients with 'Abnormal Urine protein' (52.3%) reported in the "All Ps Analysis Set'.

Sponsor's response

The reported incidence of 52.3% of "Abnormal URINE protein" in the All Psoriasis Ixekizumab Exposures Integrated Analysis Set represents measurement of abnormal urine protein at any time post baseline in the clinical program. Urine protein in the psoriasis (Ps) and PsA clinical trials was measured by urinalysis dipstick, and patients were categorised as having abnormal urine protein if they had any of the following on urinalysis: slight or trace protein in urine (10 to 30 mg/dL), moderate (31 to 100 mg/dL), large (101 to 500 mg/dL), or >500 mg/dL. The urinalysis dipstick was a screening test performed on study participants. Hence, results are cumulative of all patients with abnormal results post baseline.

Several factors could account for the high frequency of abnormal dipstick urine protein reported in the Ps clinical trials and its poor correlation with the frequency of TEAEs of proteinuria and other preferred terms (PTs) in the Renal and urinary disorders System Organ Class (SOC). Albuminuria is usually defined as levels of urinary albumin excretion above 30 mg/day.[17] However, in the Ps program, patients with slight or trace protein (10-30 mg/dL) on dipstick urinalysis, performed at any time post baseline, were all considered to have abnormal urine protein; therefore, the results include a large number of patients who would ordinarily not have been considered to have albuminuria or an abnormal renal function. The urine dipstick test has also been shown to have poor sensitivity and high false positive rates for albuminuria or detection of an albumin: creatinine ratio ≥ 30 mg/g.[18,19] Albuminuria has also been shown to have significant within-person variability, and when repeat assessments are used, estimates of the prevalence of reduced estimated glomerular filtration rate (eGFR) and albuminuria in the population are lower.[20]

Furthermore, review of the abnormal urine protein results in the Primary Psoriasis Placebo-Controlled Integrated Analysis Set indicated that the frequencies of TE-abnormal dipstick urine protein were similar in all groups (31.6% total ixekizumab; 30.9% ixekizumab 80 mg Q4W; 32.3% ixekizumab 80 mg Q2W; 33.4% placebo); there was no clinically meaningful difference between the ixekizumab treatment groups and the placebo group. In the All Psoriasis Ixekizumab Exposures Integrated Analysis Set (reported in the Summary of Clinical Safety for PsA), 0.4% of patients (25/5689) were reported to have a TEAE of proteinuria. Treatment-emergent adverse events of proteinuria in the Ps clinical program were recorded based on patient and/or investigator reports and there was no protocol/case report form (CRF) guidance provided to standardise use of the term. Other objective measures of renal function in the Ps program included measurements of creatinine levels and creatinine clearance; as stated in the Summary of Clinical Safety for Psoriasis, in the analyses of changes from baseline to last observation for measures of renal function, no significant differences between ixekizumab treatment groups and the placebo group were observed for creatinine levels or creatinine clearance.

[17] O'Seaghdha CM, Hwang SJ, Upadhyay A, Meigs JB, Fox CS. Predictors of incident albuminuria in the Framingham Offspring cohort. Am J Kidney Dis. 2010;56(5): 852-860.
[18] Park JI, Baek H, Kim Br, Jung HH. Comparison of urine dipstick and albumin: creatinine ratio for chronic kidney disease screening: A population-based study. PLoS One. 2017;12(2): e0171106.
[19] White SL, Yu R, Craig JC, Polkinghorne KR, Atkins RC, Chadban SJ. Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community. Am J Kidney Dis. 2011;58(1): 19-28.
[20] Selvin E, Juraschek SP, Eckfeldt J, Levey AS, Inker LA, Coresh J. Within-person variability in kidney measures. Am J Kidney Dis. 2013;61(5): 716-722.

In conclusion, the high incidence of abnormal urine protein on the dipstick urinalysis screening is likely due to multiple factors: (a) the inclusion of persons with trace protein in urine, (b) the significant within-person variability of albuminuria, and (c) the poor sensitivity and high false positive rate of the test. The high frequency of abnormal urine protein detected in this fashion on its own is not considered clinically significant due to the above reasons, its lack of correlation with objective measures of renal function, such as creatinine clearance, and the low incidence of TEAEs of proteinuria and other PTs in the Renal and urinary disorders SOC. In addition, no significant differences between ixekizumab treatment groups and the placebo group were observed for any changes from baseline to last observation for relevant measures of renal analytes.

Evaluator's comment

The sponsor's response is satisfactory.

Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits of ixekizumab are unchanged from those identified in the first round.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the benefits of ixekizumab for the proposed usage are unchanged from those identified in the first round.

Second round assessment of benefit-risk benefit

The benefit-risk balance of ixekizumab, given the proposed usage, is favourable for the reasons given in the first round.

Second round recommendation regarding authorisation

Approval of the application to extend the indications of ixekizumab (Taltz) to include the treatment of psoriatic arthritis at the proposed ixekizumab dosage regimens is recommended.

The recommended indication for psoriatic arthritis is that proposed by the sponsor, namely:

> *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.*
>
> *TLZ may be used as monotherapy or in combination with a conventional DMARD (e.g., methotrexate).*

It is recommended that the dosage regimens for ixekizumab for the treatment of *psoriatic arthritis* recommended by the sponsor and provided below be approved for the reasons given in the First round recommendation regarding authorisation:

- 160 mg by SC injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks; and
- For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosing regimen for plaque psoriasis.

VI. Pharmacovigilance findings

Risk management plan (RMP)

The most recently evaluated EU-RMP was version 1 dated 13 April 2015 (data lock point 15 September 2014, 1 October 2014 for Study I1f-MC-RHBA) and Australian Specific Annex (ASA) version 1 to the EU-RMP version 1 dated 22 July 2015 submitted with application the initial registration for the indication moderate to severe plaque psoriasis.

In support of the extended indications, the sponsor has submitted EU-RMP version 5 (date 10 May 2017; DLP 15 September 2016, except for Study I1F-JE-RHAT: 22 SEP 2016, Study I1F-EW-RHBZ: 23 SEP 2016, Study I1F-MC-RHBE: 30 SEP 2016) and ASA version 1.2 to the EU RMP version 5.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 18.

Table 18: Summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Infections	ü	ü	ü	–
	Hypersensitivity	ü	ü	ü	–
	Neutropaenia	ü	–	ü	–
Important potential risks	Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	ü	ü	ü	–
	MACE	ü	ü	–	–
	Malignancies	ü	ü	–	–
Missing information	Long-term safety (such as events with a low frequency and/or long latency)	ü	ü	–	–
	Use in pregnancy and lactation	ü	ü#	ü	–
	Use in very elderly (≥75 years)	ü	ü	ü	–
	Use in paediatrics	ü	ü*	ü	–
	Use in patients with severe hepatic impairment	ü	–	ü	–
	Use in patients with severe renal impairment	ü	–	ü	–
	Use in patients with active infections (human immunodeficiency virus [HIV], hepatitis B, or	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	hepatitis C)				
	Immune response to live and inactive vaccines	–	–	ü	–

[#] Observational United States pregnancy study using electronic medical records.*Paediatric Investigation Plan agreed to with EMA and FDA

Additional pharmacovigilance activities include observational post-authorisation safety registry (CORRONA) and, an observational pregnancy study using electronic medical records, which are conducted in the US. The pharmacovigilance plan is acceptable.

Only routine risk minimisation activities are proposed. Routine risk minimisation measures are considered adequate to address the risks associated with this product.

Outstanding issues after the second round evaluation

There are no outstanding issues from an RMP perspective.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The [Taltz] EU-Risk Management Plan (RMP) (version 5, date 10 May 2017; DLP 15 September 2016), with Australian Specific Annex (version 1.2, date 5 September 2017), included with submission PM-2017-02078-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

VII. Overall conclusion 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 evaluator has recommended approval of Taltz (ixekizumab) for the proposed indication and dosage regimens.

Pharmacokinetics

The PK data included one population PK study report submitted to support the similarity of the PK of ixekizumab in patients with PsA and patients with psoriasis. The data used in this analysis included patients with two phase III studies in psoriatic arthritis (Studies RHAP and RHBE) and psoriasis (Studies RHAG, RHAJ, and RHAZ) and exposure-response analysis in patients with psoriatic arthritis (Studies RHAP and RHBE).

The primary objectives of this analysis were:

- To characterise the PK of ixekizumab in patients with PsA, determine the magnitude of within- and between-patient variability, and identify potential intrinsic and extrinsic factors that impact on the PK of ixekizumab.
- To characterise the exposure-response relationship, including potential covariate effects, for the primary endpoint of the studies: that is, the proportion of patients achieving 20% improvement in American College of Rheumatology Responder Index (ACR20) at Week 24.
- To evaluate the potential impact of anti-ixekizumab antibodies on the efficacy and PK of ixekizumab.

The clinical evaluator reports that the majority of PopPK parameters estimated in the combined PsA/Ps PK model were similar to those estimated in the original Ps PK model. The significant covariates in the updated PsA/Ps PopPK model were body weight (increasing body weight increases both CL and V terms), SC injection via the thigh increases bioavailability compared to other SC injection sites (arm, abdomen, or buttock), and increasing ADA titre increases CL as does positive neutralising (NAb). There appeared to be no additional benefit on response predicted with higher exposures associated with Q2W dosing relative to Q4W dosing in each of the age and sex subgroups tested.

The majority of PsA patients with low titre positive ADA had ixekizumab concentrations similar to patients who were ADA negative.

Based on the available data, TE-ADAs appear in to have no significant impact on the efficacy of ixekizumab as assessed by the ACR20 and/or ACR 50 in patients with PsA.

The PopPK report indicates that the currently accepted linear model appeared to adequately describe the data from the new studies. Combination treatments with methotrexate did not appear to influence the PK of ixekizumab. The sponsor's report did not explore the relationship between weight and the exposure metric of interest.

The available PK-ER report presents the following summary:

- The two proposed dosing regimens for ixekizumab treatment (Q2W versus Q4W) result in a similar ACR response when the Ctrough, 24 weeks was > 5 mg/L.
- Obese patients appear to have lower exposure (trough concentrations below 2.5 to5.0 mg/L). The population PK-ER evaluator thought Q2W dosing could be considered in the obese patients.

- Sex and age were significant covariates in the ACR model. Male patients showed higher response rate than female patients and younger patients showed higher response than older patients. The variable response rate did not appear to be influenced by the dosing regimen.
- The Q2W dosing regimen for ixekizumab treatment results in a higher PASI response.
- Injection site reactions were the only significant safety endpoint identified.

Pharmacodynamics

The PD data from Study RHCA in healthy subjects showed that ixekizumab does not suppress the immune response to inactivated vaccines (tetanus vaccine component of Boostrix and pneumococcal vaccine).

The primary immune response analysis showed that ixekizumab plus vaccines was non-inferior to control (vaccines alone), with the difference in the responder rates at 4 weeks after vaccination being 1.4% (90% CI: -16.6%, 19.2%) for the tetanus vaccine and -0.8% (90% CI: -12.9%, 11.0%) for the pneumococcal vaccine. The results for the pre-specified exploratory and post hoc exploratory immune response analyses supported the findings observed for the primary immune analyses.

Injection of ixekizumab plus vaccines was well tolerated and no significant safety issues were reported during the study.

Efficacy

The sponsor has undertaken no Phase II dose-ranging studies in patients with PsA. Therefore, dose ranging data from Phase II studies of ixekizumab in patients with RA and patients with Ps were used to identify appropriate doses to be evaluated in Phase III studies of ixekizumab in patients with PsA. Population PK data provided in the current submission indicates that the PK of ixekizumab in patients with psoriasis and PsA are similar. The sponsor anticipated that continuous therapy with ixekizumab 80 mg administered SC Q2W and ixekizumab 80 mg administered SC Q4W, each with a 160 mg starting dose, would allow for a robust assessment of safety, efficacy, and benefit/risk profile in the Phase III studies of patients with PsA.

The Study RHBF ongoing Phase III Study RHBF which aims to compare ixekizumab 80 mg Q2W with placebo for the maintenance of treatment response, as measured by the time to relapse during the randomised double-blind withdrawal period in cDMARD-inadequate responders and bDMARD-naive patients with active PsA who meet randomisation criteria. The submission included safety data from RHBF as of the cut-off date for the submission which has been included in an integrated safety analysis of data from all PsA studies reviewed in the clinical evaluation.

Study RHAP SPIRIT-P1

This is a multi-centre, randomised, double-blind, active and placebo-controlled 24 Week study followed by long-term evaluation of efficacy and safety of ixekizumab in biologic disease-modifying anti-rheumatic drug-naive patients with active psoriatic arthritis.

The study included male and female patients who were ≥ 18 years of age, with an established diagnosis of PsA of at least 6 months duration meeting the CASPAR. Patients were also required to have the following: (1) active PsA defined as the presence of at least 3/68 tender and at least 3/66 swollen joints, as determined by the Tender and Swollen Joint Count Assessment Form at Visit 1 (Screening) and Visit 2 (Week 0, baseline); (2) at least 1 disease-related definite joint erosion on hand or foot x-rays as determined by the central reader OR a C-reactive protein (CRP) > 6 mg/L at screening; and (3) active psoriatic skin lesions (plaque) or a documented history of plaque psoriasis.

The majority of the exclusion criteria aimed to reduce the risks by enrolling medically stable, relatively healthy (aside from the disease being studied) patients who were not receiving concomitant therapies that may present a safety risk and/or confound the assessment of safety and/or efficacy of ixekizumab. Patients were excluded from the study if they had received any prior, or were currently receiving, treatment with any bDMARD therapy for PsA or biologic therapy for Ps, including investigational therapies or had received denosumab. Patients were excluded if they had, in the opinion of the investigator, an inadequate response to treatment with ≥ 4 cDMARDs or immune modifiers prescribed alone or in combination for a minimum of 3 months.

The study consisted of 5 periods. Period 1 was the screening period. The Double-Blind Treatment Period (Period 2) involved a comparison of ixekizumab at 2 dose regimens, 80 mg Q2W and 80 mg Q4W, compared with placebo. Adalimumab 40 mg Q2W at the TGA approved dose for PsA was the active control for comparison to placebo. The Extension Period (Period 3) and the ongoing Long-Term Extension Period (Period 4) involve evaluation of longer-term safety and efficacy of ixekizumab. At Week 0 (baseline, Visit 2), patients who met all criteria for enrollment at Visits 1/1A (screening) and 2 (baseline) were randomised (1: 1: 1: 1) to one of the 4 double-blind treatment groups. Patients were stratified by country and cDMARD experience (naive, past use, and current use). The study included a total of 417 randomised patients (comprising the ITT population), of whom 380 (86.3%) completed the double-blind treatment period (Weeks 0-24) and 381 entered the extension-period (Weeks 24-52). The patients in the extension phase were re-assigned into six separate groups. Of the 381 patients who entered the extension period (Weeks 24-52), 191 were included in the IXE80Q4W group (154 completed Week 52) and 190 were included in the IXE80Q2W groups (150 completed Week 52). Period 5 was the post-treatment follow-up from last visit to minimum 12 weeks following that visit.

The mean (SD) age in the total population was 49.5 (11.87) years, with the majority of patients being aged < 65 years (89.4%). The majority of the population were female (54.0%). The mean (SD) BMI of the total population was 30.0 (8.46) kg/m^2, and the majority of patients (74.8%) were categorised as overweight (32.9%), obese (32.9%), or extremely obese (9.0%). The majority of the total population were White (94.0%), with Asian accounting for 3.6% of the total population. There were no Black or African Americans included in the population. The majority of patients were current cDMARD users (64.0%), while 21.3% were past cDMARD uses and 14.6% were cDMARD naïve. Baseline MTX use at randomisation was reported in 54.2% of patients. The mean methotrexate (MTX) dose was 15.8 mg. None of the patients had taken TNF inhibitors. The baseline characteristics (Week 0) of the 381 patients assigned to treatment in the extension period (Weeks 24-52) were similar to the baseline characteristics of the 417 randomised to treatment at Week 0. At baseline, 94.5% of patients had active psoriasis, 58.0% had enthesitis and 37.6% had dactylitis.

The primary efficacy endpoint was the ACR20 response at Week 24. The response rates for the ACR20 at Week 24 in patients in both the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups were statistically significantly greater compared with the placebo group, and the response rates were similar in the two ixekizumab treatment groups. The results for the ixekizumab versus placebo comparisons are summarised in the table below.

Table 19: Study RHAP ACR20 at Week 24, primary efficacy endpoint analysis (NRI), double blind treatment period, ITT population

PBO (n=106)	IXE 80 mg Q4W (n= 107)			IXE 80 mg 2W (n=103)		
Response	Response	Difference vs placebo	p –value	Response	Difference vs placebo	p-value
30.2% (n=32)	57.9% (n=62)	27.8% (95% CI: 15.0, 40.6)	< 0.001	62.1% (n=64)	31.9% (95% CI: 19.1, 44.8)	< 0.001
-	*OR (IXE:PBO) = 3.24 (95% CI: 1.837, 5.721); p < 0.001*			*OR (IXE:PBO) = 3.88 (95% CI: 2.175, 6.913); p < 0.001*		

Source: CSR (amendment), Table RHAP.11.4 and SCE, Table 2.7.3.2. Notes: PBO = placebo; IXE = ixekizumab; Q4W = every 4 weeks; Q2W = every 2 weeks; CI = confidence interval; NRI = non-responder imputation; OR = odds ratio, CI, and p=value are from a logistic regression model using Wald's test with treatment, region and baseline conventional DMARD experience as factors.

The results for the 4 major (multiplicity-controlled) secondary efficacy endpoints in the double-blind treatment period showing statistically significance in both ixekizumab groups compared with the placebo group are as below. The 2 non-statistically significant major secondary efficacy endpoints (multiplicity-controlled) were Change from baseline of LEI score at Week 12 in patients with LEI score > 0 at baseline and Itch NRS at Week 12 in patients with baseline psoriatic lesions ≥ 3%. The results for other secondary efficacy endpoints (non-multiplicity-controlled) generally favoured the two ixekizumab groups compared with placebo.

Change from baseline to Week 24 in HAQ-DI

The LSM reduction in the HAQ-DI score from baseline to Week 24 (NRI) was statistically significantly greater in both ixekizumab groups (0.44 for the IXE80Q4W and 0.50 for the IXE80Q2W group) compared with the placebo group (0.18) with p<0.001. In the adalimumab group, the LSM reduction in the HAQ-DI score from baseline to Week 24 (NRI) was greater than in the placebo group (-0.37 versus -0.18, respectively, p<0.001). The LSM change from baseline to Week 24 (NRI) was numerically similar in the adalimumab and ixekizumab 80 mg Q4W groups and greater in the ixekizumab 80 mg Q2W group than in the other two groups.

Change from baseline to Week 24 in mTSS placebo-controlled period

Progression of structural damage in the peripheral joints was measured using the mTSS The LSM changes from baseline to Week 24 (MMRM) were statistically significantly smaller in both ixekizumab groups (0.17 for the IXE80Q4W and 0.08 for the IXE80Q2W group) compared with the placebo group (0.49) with p<0.01 and p<0.001 respectively. The LSM change from baseline to Week 24 in the adalimumab group was statistically smaller than in the placebo group (0.10 versus 0.49, respectively, p<0.001).

Radiological progression of structural damage based on mTSS cut-off points

The percentage of patients with radiological progression of structural damage ≤ 0.95, ≤ 0.5 and ≤ 0 (no structural damage) at Week 24, based on the mTSS (NRI), was statistically significantly greater in each of the ixekizumab groups (and the adalimumab group) compared with the placebo group.

ACR20 response at Week 12 placebo-controlled period

The ACR20 response rates at Week 12 (NRI) were statistically significantly greater in both ixekizumab groups (57% for the IXE80Q4W and 60.2% for the IXE80Q2W group) compared with placebo (31.1%) with p < 0.001. The ACR20 response rate at Week 12 (NRI) was 51.5% (52/101) in the adalimumab group and 31.1% (33/106) in the placebo groups, with the difference between the two groups being 20.4% (95% CI: 7.2, 33.5), p=0.003.

PASI 75 response at Week 12 (restricted to patients with baseline psoriatic lesion(s) involving ≥3% BSA)

The PASI 75 response rates at Week 12 (NRI) in patients with baseline psoriatic lesions involving ≥ 3% of BSA were statistically significantly greater in both ixekizumab groups (75.3% for the IXE80Q4W and 69.5% for the IXE80Q2W group) and the adalimumab group (33.8%) compared with the placebo group (7.5%), p<0.001.

In the subgroup analysis of ACR 20 response at Week 24, the subgroups (from the Double-Blind treatment period) which showed statistically significant treatment-by-subgroup interactions at p< 0.10 for ACR20 were : (a) baseline weight (<100 kg versus ≥100 kg), p=0.013); and (b) baseline weight (<80 kg versus ≥80 kg to <100 kg versus ≥100 kg), p=0.010). For the subgroup analysis of mTSS, the subgroups which showed statistically significant treatment-by-subgroup interactions at p<0.10 for mTSS were: (a) geographic region (Rest of the World versus Europe), p=0.057; and (b) baseline CRP severity (high sensitivity (assay) C-reactive protein (hs-CRP) ≤6 mg/L versus hs-CRP >6 mg/L), p=0.039. No other treatment-by-subgroup interactions at a significance level of p<0.10 were reported in the CSR, including cDMARD use at baseline. However, the subgroup analyses were not powered to demonstrate a significant effect between categories. The sponsor comments that significance of potential subgroup effects needs to be further investigated in a larger, integrated dataset.

In the extension period (Weeks 24 to 52), efficacy outcomes for the 6 treatment arms were summarised descriptively. The efficacy endpoints of ACR20/50/70, DAS28-CRP, MDA, PsARC, HAQ-DI, BASDAI, LDI-B, LEI, skin and nail disease assessments, and health outcome/quality-of-life assessments were stable or continued to improve (NAPSI) during the extension period in the ixekizumab/ixekizumab groups. The response rates (categorical variables) and improvements (continuous variables) from baseline observed in the placebo/ixekizumab and adalimumab/ixekizumab groups were generally similar to those observed in the ixekizumab/ixekizumab groups at Week 52. The data showed that, for patients initially randomised to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at Week 0 who continued treatment with the same regimen through to Week 52, efficacy achieved in the double-blind period (Weeks 0 to 24) persisted in the extension period (Weeks 24 to 52). In addition, all patients who had been assigned to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W in the extension period (Weeks 24 to 52) maintained efficacy throughout this period.

Study RHBE SPIRIT-P2

Study RHBE is a multinational, multicentre Phase III, randomised, placebo-controlled outpatient study designed to assess the efficacy and safety of ixekizumab in patients with active PsA who are cDMARD and bDMARD experienced and are either inadequate responders to TNFi or intolerant to this class of drugs. The inclusion criteria were male or female patients aged ≥ 18 years with an established diagnosis of active PsA of at least 6 months duration who currently meet the CASPAR criteria. Other key inclusion criteria were: (1) active PsA defined as the presence of at least 3/68 tender and at least 3/66 swollen joints, as determined by the Tender and Swollen Joint Count Assessment Form at Visit 1 (Screening) and Visit 2 (Week 0, baseline); (2) prior treatment with 1 or more cDMARDs (MTX, sulfasalazine, leflunomide, or hydroxychloroquine); (3) prior treatment with at least 1 and not more than 2 TNF inhibitors, and at least 1 TNF inhibitor must have been discontinued due to either an inadequate response (based on a minimum of 12 weeks on therapy) or documented intolerance; and (4) active psoriatic skin lesions (plaque) or a documented history of plaque psoriasis. The key exclusion criteria were: (1) current treatment with bDMARD; (2) prior treatment with cDMARDs other than MTX, sulfasalazine, leflunomide, or hydroxychloroquine; (3) discontinued MTX or sulfasalazine within 8 weeks prior to baseline, hydroxychloroquine within 12 weeks prior to baseline, or leflunomide within 4 weeks prior to baseline; (4) if taking MTX, leflunomide,

sulfasalazine, or hydroxychloroquine must have been treated for at least 12 weeks prior to baseline and on a stable dose for at least 8 weeks prior to baseline; (5) use of oral corticosteroids at average daily doses of >10 mg/day of prednisone or its equivalent, or use of variable doses of any oral corticosteroids, within 4 weeks prior to baseline (Week 0, Visit 2).

The study consisted of a double-blind placebo controlled period of 24 weeks. A long term extension period (Weeks 24-156) is planned but no data from this period was included in the current submission. A total of 474 patients signed informed consent and entered Study RHBE. Prior to randomisation (Week 0), 111 patients had discontinued from the study. In total, 363 patients were randomised to 1 of 3 treatment groups as the ITT Population (122 to ixekizumab 80 mg Q4W, 123 to ixekizumab 80 mg Q2W, and 118 to placebo). A total of 86.5% (314/363) of randomised patients completed the double-blind treatment period. At the time of the database lock, none of the 318 patients had completed the extension period, 68 (21.9%) patients had discontinued and 242 (78.1%) were ongoing. Treatment in the Extension Period (Period 3) included ixekizumab 80 mg Q2W or ixekizumab 80 mg Q4W for all patients. The major reason for study treatment discontinuation in the extension period was lack of efficacy (18.4%, n=57).

The mean (SD) age of the total population was 51.9 (12.00) years, with the majority of patients being aged < 65 years (82.9%). The majority of the total population were female (53.4%). The majority of the total population were White (91.7%), with most of the remaining population being Asian (5.8%). There was only 1 (0.3%) Black or African Americans included in the total population. At baseline, the median time since PsA diagnosis was 8.2 years, 93.4% of patients had active psoriasis, 75.2% had enthesitis, and 23.7% had dactylitis, as assessed by the investigator. The majority of patients were current cDMARD users (51.0%). MTX use at baseline was reported by 41.0% of patients. The mean MTX dose was 16.1 mg in Study RHBE was comparable across the four treatment groups. Inadequate response to 1 TNF inhibitors was reported in 56.2% of patients, inadequate response to 2 TNF inhibitors was reported in 35.3% of patients and intolerance to a TNF inhibitor was reported in 8.5% of patients.

The primary efficacy endpoint was the ACR20 response at Week 24 (NRI). There were a statistically significantly greater proportion of patients in the ITT population with an ACR20 response in both ixekizumab groups compared with placebo. The results are summarised below in Table 20 below. The time-course data showed that onset of action was at about 1 week after initiation of treatment, with ACR20 response rates remaining relatively constant from Week 12 through to Week 24.

Table 20: Study RHBE ACR20 at Week 24 (NRI), primary efficacy endpoint analysis, double blind treatment period ITT population

PBO (n=118)	IXE 80 mg Q4W (n= 122)			IXE 80 mg 2W (n=123)		
Response	Response	Difference vs placebo	p –value	Response	Difference vs placebo	p-value
19.5% (23/118)	53.3% (65/122)	33.8% (95% CI: 22.4, 45.2)	< 0.001	48.0% (59/123)	28.5% (95% CI: 17.1, 39.8)	< 0.001
	OR (IXE:PBO) = 4.7 (95% CI: 2.7, 8.5); p < 0.001			OR (IXE:PBO) = 3.8 (95% CI: 2.1, 6.8); p < 0.001		

Source: CSR, Table RHAP.11.2. Notes: PBO = placebo; IXE = ixekizumab; Q4W = every 4 weeks; Q2W = every 2 weeks; CI = confidence interval; NRI = non-responder imputation; OR = odds ratio, CI, and p-value are from a logistic regression model using Wald's test with treatment, region and TNFi experience as factors in the model. Response rate based p-value based on Fisher's exact test.

Results for the multiplicity-controlled secondary efficacy endpoints

Statistically significant treatment differences between the two ixekizumab groups and placebo in favour of ixekizumab were observed for 4 of the 5 major multiplicity controlled secondary efficacy endpoints (HAQ-DI score change from baseline at Week 24; ACR20 response at Week 12; PASI 75 response at Week 12 in patients with baseline psoriatic lesions involving ≥ 3% BSA; and Coates criteria for MDA (E6)). However, for the 5th major

multiplicity controlled secondary efficacy outcome of complete resolution of enthesitis (LEI (0)) at Week 24 in patients with baseline enthesitis (LEI ≥ 1) there was no statistical significance in the response rate between either of the two ixekizumab groups compared with the placebo group.

Nominal statistically significant superiority in both ixekizumab groups compared with the placebo group in the double-blind treatment-period were observed for the following non-multiplicity controlled secondary efficacy endpoints, individual components of the ACR Core Set, BASDAI, CPDAI, Itch NRS and the secondary health outcomes endpoints of Fatigue NRS and health-related quality-of-life outcomes as assessed by the SF-36 PCS and MCS. There were no data relating to the effect of treatment on radiographic progression of joint damage. There were no efficacy data for patients treated for more than 24 weeks. Study RHBE is ongoing and the sponsor states that long-term efficacy and safety data from the extension period (Weeks 24 to 156) will be summarised in future CSRs.

The ACR20 endpoint at Week 24 was examined for a number of subgroups. Both ixekizumab doses were statistically significantly greater compared with placebo in all subgroups on the ACR20 endpoint at Week 24. Two subgroups showing statistically significant ($p<0.10$) treatment-by-subgroups interactions were gender (male versus female (ixekizumab more effective in males)) and hs-CRP severity (≤ 6 mg/mL versus > 6 mg/mL (ixekizumab more effective in the greater severity group)). No treatment-by-subgroup interactions were observed for concomitant therapy, including cDMARD use at baseline or prior TNFi experience. The subgroup analyses were conducted with small subgroup sizes and without control for Type I error. The sponsor comments that significance of potential subgroup effects needs to be further investigated in a larger, integrated dataset.

The submission included an analysis of pooled data from Studies RHAP and RHBE from the placebo-controlled double-blind treatment period (Weeks 0-24). The analysis included a total of 679 patients (placebo (n=224); IXE80Q4W (n=229); IXE80Q2W (n=226)). It was considered that the two patient populations from the two studies were sufficiently similar to allow the efficacy data to be pooled, although all patients in Study RHAP were TNFi naïve while all patients in Study RHBE were TNFi experienced. The pooled analysis was not specified in the protocol. The pooled efficacy data were consistent with the efficacy data from each of the two individual studies for the comparisons between the two ixekizumab groups and the placebo group, and comparison of efficacy outcomes between the two ixekizumab groups identified no marked differences between the two groups. However, no formal statistical testing of heterogeneity between the two studies was undertaken. Significant treatment-by-subgroup interactions were seen for ACR20 for:

- *Weight (80 kg and 100 kg cut-offs):* Treatment differences were greater in the middle weight subgroup (≥ 80 to < 100 kg) than in either the higher- or lower-weight subgroups. The Q4W group had significantly greater response rates compared with placebo in all weight groups, while the Q2W group had significantly greater response rates compared with placebo in both the <80 kg and ≥80 to <100 kg subgroups but only a numerically greater response rate in the ≥100 kg subgroup.
- Treatment differences (ixekizumab versus placebo) were greater in males. Both ixekizumab dose groups had significantly greater response rates compared with placebo in both males and females. Treatment differences were greater in the CRP > 6 mg/L subgroup and in the subgroup of patients with duration of disease ≥ 5-year.

Patients with PsA and coexistent baseline moderate to severe plaque psoriasis

The sponsor is proposing a dosage regimen for patients with PsA and co-existent moderate to severe plaque psoriasis which is same as currently approved for treatment of patients with plaque psoriasis: 160 mg (2 x 80 mg) starting dose followed by 80 mg every

2 weeks at Weeks 2, 4, 6, 8, 10 and 12 and then 80 mg every 4 weeks. This dosing regimen has not been tested in Studies RHAB or RHBE.

Efficacy in patients with active PsA and active moderate to severe PsA for Studies RHAP and RHBE

In the pooled data for RHAP and RHBE (Week 0 to 24), 83 of the patients randomised to ixekizumab or placebo had PsA and coexistent moderate-to-severe plaque psoriasis at baseline. Of the 83 patients, 27 had been randomised to placebo, 32 to ixekizumab 80 mg Q4W and 24 to ixekizumab 80 mg Q2W. The results for the efficacy endpoints of PASI 75/90/100, sPGA (0) response rate and percent improvement in PASI total score at Weeks 12 and 24 for patients with moderate-to-severe baseline psoriasis were presented, showing the outcomes were statistically significantly greater in both ixekizumab groups compared with the placebo group. The pairwise comparisons between the ixekizumab groups numerically favoured the ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group for most of the selected efficacy outcomes.

Supportive data from the integrated clinical program in patients with psoriasis and data from Studies RHAP and RHBE

The sponsor provided data for PASI 75/90/100 response rates at Week 12 in patients with psoriasis treated with ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W in different populations to demonstrate the effect of coexistent Ps and PsA on response. In the subpopulation of patients with moderate-to-severe plaque Ps with coexistent self-reported PsA in the Phase III Ps program, the PASI 75/90/100 response rates at Week 12 were 8.6%, 8.5%, and 2.4% higher, respectively, in the ixekizumab 80 mg Q2W group compared with the IXE80Q4W group. It was a similar pattern of PASI response rates in patients with Ps. The sponsor concluded that results from the analyses support the use of the ixekizumab 80 mg Q2W regimen approved for patients with Ps for the treatment of patients with coexistent PsA and Ps.

Safety

The safety of ixekizumab in PsA was characterised in 1118 patients with active PsA exposed to least 1 dose of ixekizumab, representing 1050.6 patients-years of exposure (Studies RHAP, RHBE, and RHBF). The safety data were provided in three separate integrated analysis sets comprising the 'Primary PsA Analysis Set' (pooled data from Studies RHAP an RHBE from Weeks 0 to 24), the 'All PsA Analysis Set' (pooled data from Studies RHAP, RHBE, and RHBF for all treatment periods from Week 0 through to last visit before the database lock), and the 'All Ps Analysis Set' (pooled updated data from 11 studies in patients with Ps). In this overview, only the safety data from the two analysis sets in patients with PsA treated with ixekizumab or placebo is reviewed. In the 'Primary PsA Analysis Set', the proportion of patients with PsA who had been treated for ≥ 120 days was greater in both the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups (83.2% versus 86.3%, respectively) compared with the placebo group (62.3%). In the 'All PsA Analysis Set', a total of 1118 patients with PsA received at least 1 dose of ixekizumab, comprising 365 patients in the ixekizumab 80 mg Q4W group and 752 patients in the ixekizumab 80 mg Q2W group.

TEAEs (all causality)

In the 'Primary PsA Analysis Set', the proportion of patients with at least 1 TEAE (all causality) was statistically significantly greater ($p<0.05$) in both ixekizumab groups compared with the placebo group (66.8%, 80Q4W versus 69.3%, 80Q2W versus 56.7%, placebo). The proportion of patients in this analysis set was similar in both ixekizumab groups, and the majority of TEAEs in both groups were mild or moderate in severity. TEAEs (irrespective of causality) reported in ≥ 5% of patients in the ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W groups compared with the placebo group were,

respectively, injection site reaction (9.6% versus 14.2% versus 0.4%), upper respiratory tract infection (7.0% versus 6.7% versus 7.1%), injection site erythema (3.9% versus 7.6% versus 0%), and nasopharyngitis (6.6% versus 3.1% versus 4.0%). In the 'All PsA Analysis Set', the proportion of patients with at least 1 TEAE (all causality) in the pooled ixekizumab group was 65.7% (incidence rate = 69.9 per 100 person-years). In this analysis set, TEAEs reported in ≥ 5% of patients were injection site reaction (11.8%), upper respiratory tract infection (8.0%), nasopharyngitis (6.8%) and injection site erythema (4.5%).

TEAEs (treatment-related)

In the 'Primary PsA Analysis Set', the proportion of patients with at least 1 TEAE (treatment related) was greater in both ixekizumab groups compared with the placebo group (29.3%, 80Q4W versus 39.6%, 80Q2W versus 18.3%, placebo). The proportion of patients in this analysis set with TEAEs (treatment-related) was higher in the ixekizumab 80 mg Q2W group than in the ixekizumab 80mg Q4W group (39.6% versus 29.3%, respectively). TEAEs (treatment-related) reported in ≥ 2% of patients in the ixekizumab 80 mg Q4W group or the 80 mg Q2W ixekizumab group compared with placebo were, respectively, injection site reaction (9.2% versus 13.8% versus 0.4%), injection site erythema (7.6% versus 3.9% versus 0%), upper respiratory tract infection (3.1% versus 3.1% versus 1.3%), and injection site hypersensitivity (0.4% versus 2.7% versus 0%). In the 'All PsA Analysis Set', TEAEs (treatment-related) reported in ≥ 1% of patients in the pooled ixekizumab group were injection site reaction (11.6%), injection site erythema (4.4%), upper respiratory tract infection (2.4%), nasopharyngitis (1.0%) and diarrhoea (1.0%).

There were no deaths in the 'Primary PsA Analysis Set', and 2 (0.2%) deaths in the 'All PsA Analysis Set'. The 2 deaths in the 'All PsA Analysis Set' were due to a cerebrovascular accident in a male with cardiovascular risk factor at study entry (initially randomised to adalimumab and subsequently re-randomised to ixekizumab 80 mg Q4W), and pneumonia in another male randomised to ixekizumab 80 mg Q2W. In the 'Primary PsA Analysis Set', SAEs were reported more frequently in patients in both ixekizumab groups compared with the placebo group (3.9%, 80Q4W versus 4.9%, 80Q2W versus 2.7%, placebo). SAEs were reported in a comparable proportion of patients in the two ixekizumab groups. No individual SAEs were reported in more than 1 patient in either of the two ixekizumab groups. In the 'All PsA Analysis Set', 6.5% (n=73) of patients in the pooled ixekizumab group experienced at least 1 SAE. SAEs reported in ≥ 2 patients were pneumonia (n=3, 0.3%), lower respiratory tract infection (n=2, 0.2%), carotid artery stenosis (n=2, 0.2%), cerebrovascular accident (n=2, 0.2%), fall (n=2, 0.2%), acute myocardial infarction (n=2, 0.2%), cholecystitis acute (n=2, 0.2%), cholelithiasis (n=2, 0.2%), coronary artery disease (n=2, 0.2%), and osteoarthritis (n=2, 0.2%). In the 'Primary PsA Analysis Set', discontinuation of the study drug due to AEs was reported in a numerically higher proportion of patients in the ixekizumab 80 mg Q2W group than in either the ixekizumab 80 mg Q4W group or the placebo group (5.3% versus 3.1% versus 3.6%, respectively). No particular pattern in the AEs leading to discontinuation of the study drug was observed in two ixekizumab groups, apart from a small number of discontinuations due to clustered injection site related events. In the 'All PsA Analysis Set' (n=1118), 5.7% of patients in the pooled ixekizumab group had an AE resulting in discontinuation of the study drug. Overall, AEs leading to discontinuation of the study drug didn't appear to be significant risk for patients with PsA treated with ixekizumab.

Infections

In the 'Primary PsA Analysis Set', the proportion of patients with ≥ 1 infection-related TEAE was numerically higher in both ixekizumab groups compared with the placebo group (33.6%, 80Q4W versus 32.0%, 80Q2W, versus 27.7%, placebo), while the proportion of patients with ≥ 1 infection-related SAE was small in each of the three

treatment groups (0.4%, 80Q4W versus 2.2%, 80Q2W versus 0%, placebo) as was the proportion of patients discontinuing the study drug due to infection-related AEs (0.9%, 80Q4W versus 0.4%, 80Q2W versus 0.4%, placebo). In the 'All PsA Analysis Set' (n=1118), 37.2% of patients in the pooled ixekizumab group experienced at least 1 infection-related TEAE, 1.3% of patients experienced ≥ 1 infection related SAE, and 1.3% of patients discontinued the study drug due to an infection-related AE. The only Infection-related AE resulting in discontinuation of the treatment drug reported in ≥ 2 (≥ 0.2%) patients in the pooled ixekizumab group was latent tuberculosis (0.5%, n=6). No patients were reported to have active tuberculosis.

Cytopaenias

In the 'Primary PsA Analysis Set' the proportion of patients with treatment-emergent laboratory values < LLN at any time post-baseline for both leukocytes and neutrophils was statistically significantly greater in each of the two ixekizumab groups compared with the placebo group, while the values for lymphocytes and platelets did not differ significantly across the three treatment groups. There was only one patient (0.4%) with Grade 3 or 4 worsening of the count which was with TE-lymphopaenia. In the 'All PsA Analysis Set', the proportion of patients in the pooled ixekizumab group with ≥ 1 TE-low laboratory value was 14.2% for leukocytes (153/1075), 12.5% for neutrophils (136/1092), 13.4% for lymphocytes (131/979), and 5.0% for platelets (54/1082). TE-neutropaenia Grade 3 or 4 was seen in 3 (0.3%) patients, leukopaenia in 1 (0.1%), lymphopaenia in 4(0.4%) and thrombocytopaenia in none of the patients. Cytopaenias (TEAEs SMQ) (neutropaenia, leukopaenia, lymphopaenia, and thrombocytopaenia) occurred infrequently in both ixekizumab groups and in the placebo group.

Allergic reactions/hypersensitivities

In the 'Primary PsA Analysis Set', the proportion of patients with ≥ 1 allergic reaction/hypersensitivity TEAE was higher in the both ixekizumab groups than in the placebo group (6.2%, 80Q2W versus 4.4%, 80Q4W versus 1.8%, placebo). There were no SAEs reported in ixekizumab or placebo groups. In this group 5.1% (23/447) of patients in the total ixekizumab group were TE-ADA positive, and 4 (0.9%) of these patients were NAb positive. None of the TE-ADA positive patients had events that were considered to be potential anaphylaxis TEAEs.In the 'All PsA Analysis Set', in the pooled ixekizumab group the proportion of patients with ≥ 1 allergic reaction/hypersensitivity TEAE was 5.4% and the proportion of patients with ≥ 1 SAE was 0.1% (1x angioedema). In this group 85 (8.5%) patients in the pooled ixekizumab group were TE-ADA positive, including 4 (4.7%) patients reporting non-anaphylaxis allergic reactions/ hypersensitivity TEAEs. No patients in this analysis set had events that were considered to be potential anaphylaxis TEAEs. Overall, the available data do not support an association between TE-ADA status and allergic reaction/hypersensitivity TEAEs.

Injection site reactions

In the 'Primary PsA Analysis Set', injection site reactions occurred notably more frequently in both the ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups (17.5% versus 25.3%) compared with the placebo group (4.5%). There were no patients in the ixekizumab or placebo groups with a SAE injection site reaction. In the 'All PsA Analysis Set', injection site reactions were reported 18.9% (n=211) of patients in the pooled ixekizumab group. There were no patients in the ixekizumab or placebo groups with a SAE injection site reaction.

Malignancies

In the 'Primary PsA Analysis Set', TEAE malignancies were reported infrequently in the ixekizumab and placebo groups. TEAE malignancies were also reported infrequently in the 'All PsA Analysis Set'.

Hepatic events

In the 'Primary PsA Analysis Set', no clinically significant differences in hepatic function laboratory abnormalities or hepatic TEAEs were observed in the ixekizumab and placebo groups. No patients in either of the analysis sets met Hy's law criteria for drug induced liver injury.

Cerebro-cardiovascular events

In the 'Primary PsA Analysis Set', cerebro-cardiovascular TEAEs, including MACE, were reported infrequently in the ixekizumab and placebo groups. In the 'All PsA Analysis Set', there were 12 (1.1%) patients with ≥ 1 CEC-confirmed cerebro-cardiovascular event, including MACE; all were SAEs and 4 (0.4%) patients discontinued due to an event.

Inflammatory bowel disease (IBD)

In the 'Primary PsA Analysis Set', no patient had TEAEs of IBD and in the 'All PsA Analysis Set', 1 (0.1%) patient in the pooled ixekizumab group had an IBD TEAE (ulcerative colitis).

Renal and urinary tract disorders (SOC)

The data in patients with PsA indicated a small increase in the number and percentage of patients with reductions in serum creatinine levels associated with ixekizumab treatment. However, the changes from baseline are not considered to be clinically significant. There is no evidence that ixekizumab is associated with clinically meaningful renal toxicity.

Vital signs and ECG findings

The data on patients with PsA raise no significant clinical concerns relating to changes in vital signs or ECG findings associated with ixekizumab treatment.

Risk management plan

The RMP evaluation stated that, 'In *support of the extended indications, the sponsor has submitted the EU Risk Management Plan for Taltz (ixekizumab), version 5 (date10 May 2017; DLP 15 September 2016, except for Study I1F-JE-RHAT: 22 SEP 2016, Study I1F-EW-RHBZ: 23 SEP 2016, Study I1F-MC-RHBE: 30 SEP 2016) and ASA version 1.2 to the EU RMP version 5.'*

The RMP evaluator has confirmed in the second round RMP evaluation report that there are no outstanding issues from an RMP perspective.

Risk-benefit analysis

Delegate's considerations

In monoarticular or oligoarticular PsA disease, NSAIDs and intra-articular corticosteroid injections are often used first line; DMARDs are used for resistant or progressive cases. The DMARDs used are conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), Biological disease-modifying anti-rheumatic drugs (bDMARDs) and Targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs).[21]

[21]Therapeutic Guidelines: https: //tgldcdp.tg.org.au/viewTopic?topicfile=spondyloarthritides-including-psoriatic-arthritis&guidelineName=Rheumatology#toc_d1e1152

Efficacy

The efficacy of ixekizumab (80 mg Q4W and 80 mg Q2W) in adult patients with active PsA (>3 swollen and tender joints) has been satisfactorily demonstrated with placebo up to 24 weeks in two pivotal Phase III studies (Studies RHAP and RHBE) and was maintained in the open-extension phase through to Week 52. These studies are representative of the intended target patient population in Australia. The design and the efficacy parameters used are broadly consistent with other similar studies and the EU Guideline on treatment of PsA, and are considered acceptable.

A treatment dose of ixekizumab SC 160 initially (2 x 80 mg injections) followed by 80 mg Q4W or Q2W was used in the pivotal studies to achieve the primary objective of the studies, with statistically significantly higher proportion of subjects with PsA achieving an ACR 20 response at Week 24 compared with placebo.

In the pivotal Study RHAP, 4 of the 6 major secondary efficacy endpoints (multiplicity-controlled) were statistically significant in both ixekizumab groups compared with the placebo group (mTSS at Week 24, HAQ-DI at Week 24, ACR20 at Week 12, and PASI 75 at Week 12 in patients with baseline psoriatic lesions ≥ 3%). In the study, efficacy data for the extension period (Weeks 24 to 52) were provided for a total of 381 patients. Overall, in Study RHAP, efficacy at Week 52 was observed for patients remaining on ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W or switching to ixekizumab 80 mg Q4W or ixekizumab 80 mg Q2W at Week 24 from placebo or adalimumab 40 mg Q2W for all key endpoints. In the other pivotal Study RHBE, 4 of the 5 major secondary efficacy endpoints (multiplicity controlled) were statistically significant in both ixekizumab groups compared with the placebo group (HAQ-DI at Week 24, ACR20 at Week 12, PASI 75 at Week 12 in patients with baseline psoriatic lesions ≥ 3%, and MDA at Week 24). There were no efficacy data in patients treated with ixekizumab for longer than 52 weeks in either Study RHAP or RHBE. However, it appears that both studies are ongoing and that the sponsor intends to submit long-term efficacy data at a future date.

An analysis of pooled data from Studies RHAP and RHBE showed the pooled efficacy data to be consistent with that of the two individual studies. It is considered that the two patient populations from the two studies are sufficiently similar to allow the efficacy data to be pooled, although all patients in Study RHAP were TNFi naïve while all patients in Study RHBE were TNFi experienced. However, no formal statistical testing of heterogeneity between the two studies was undertaken. Significant subgroup interactions for ACR20 response at Week 24 were observed for gender (efficacy favoured males), weight (efficacy favoured patients in the ≥ 80 to < 100 kg group and patients in the ≥ 50th to < 75th percentile), baseline CRP (efficacy favoured patients with higher baseline CRP of > 6 mg/mL), and duration of disease (efficacy favoured patients with a disease duration of ≥ 5 years). There were no significant subgroup interactions for ACR20 response at Week 24 for baseline cDMARD or MTX use. There no subgroup interactions for ACR20 response at Week 24 based on age.

The population PK evaluator has stipulated that considering that the obese patients appear to have lower exposure (trough concentrations below 2.5 to 5.0 mg/L) they would be expected to have lower ACR response and hence the Q2W dosing should be considered. However, the clinical evaluator has recommended the sponsor's proposed dosing without any distinction for the obese patients based on the submitted data. The clinical evaluator's recommendation appears acceptable because this PK analysis is not confirmatory as the relationship between the weight and the exposure has not been established and the subgroup analysis from the pooled analysis showed that the Q4W group had significantly greater response rates compared with placebo in all weight groups, while the Q2W group had significantly greater response rates compared with placebo in both the <80 kg and ≥ 80 to <100 kg subgroups but only a numerically greater response rate in the ≥100 kg subgroup. This data from the subgroup analysis does not favour the Q2W dose for the

highest weight subgroup. Also, the current PsA indication for ixekizumab does not have any weight based dosing. The US PI states that Taltz may be administered alone or in combination with a conventional disease-modifying anti-rheumatic drug (cDMARD) (such as methotrexate) and the European Summary of Product Characteristics (SmPC) mentions that Taltz can be used alone or in combination with methotrexate for the treatment of PsA in adult patients without any weight based dosing.

The proportion of patients using MTX at randomisation was higher in Study RHAP compared with Study RHBE (54.2% versus 41.0%), as was current cDMARD use (54.0% versus 51.0%). In accordance with the protocol no patients in RHBE were cDMARD naïve, while 14.6% of patients in RHAP were cDMARD naïve (no current use or no history of use). In accordance with the protocol all patients in Study RHAP were TNFi naïve, while in Study RHBE inadequate response to 1 or 2 TNFi was reported in 91.5% of patients and intolerance to TNFi in 8.5% of patients. In the pivotal Phase III studies the ACR 20 responses were higher with SC ixekizumab (80 mg Q4W and 80 mg Q2W) as compared to placebo irrespective of concomitant non-biologic DMARD treatment (multiple cDMARDs considered including methotrexate). Hence, the efficacy of the proposed ixekizumab SC doses appears to have been demonstrated both as monotherapy and in combination with non-biologic DMARDs in patients with active PsA. The US PI states that Taltz may be administered alone or in combination with a conventional disease-modifying anti-rheumatic drug (cDMARD) (such as methotrexate) and the European SmPC mentions that Taltz can be used alone or in combination with methotrexate for the treatment of PsA in adult patients. However, the statement in the proposed indication '*Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g., methotrexate)'* is more appropriate to be positioned under the 'Dosage and Administration' section of the PI rather than being part of the indication.

The sponsor's proposed dosage regimen for patients with PsA and co-existent moderate to severe plaque psoriasis (which is same as currently approved for treatment of patients with plaque psoriasis): 160 mg (2 x 80 mg) starting dose followed by 80 mg every 2 weeks at Weeks 2, 4, 6, 8, 10 and 12 and then 80 mg every 4 weeks appears acceptable. This dosing regimen has not been tested in the RHAB or RHBE studies. However, in the subset of patients with psoriatic lesions ≥ 3% BSA at baseline in the 'Primary PsA Analysis Set' the pairwise comparisons between the ixekizumab groups numerically favoured the ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group for most of the selected efficacy outcomes. The integrated Ps data indicated that efficacy was greater in the ixekizumab 80 mg Q2W group compared with the ixekizumab 80 mg Q4W group in patients with Ps and in patients with coexistent Ps and PsA.

Safety

The safety profile of SC ixekizumab in the PsA population appeared consistent with the known safety profile of SC ixekizumab for the treatment of Ps. No new safety signals relating to ixekizumab emerged from the submitted PsA studies or from the updated safety data from the Ps studies. The risk profile of the pooled ixekizumab group in the 'All PsA Analysis Set' was similar to the risk profiles of the two ixekizumab groups in the 'Primary PsA Analysis Set'. Treatment with ixekizumab for PsA does not appear to be associated with an increased risk of death. Overall, AEs leading to discontinuation of the study drug are not considered to be a significant risk for patients with PsA treated with ixekizumab. No increase in the incidence of malignancies or opportunistic infections was seen in both the PsA studies.

RMP

An acceptable RMP has been provided with no outstanding issues from an RMP perspective.

Overall

The Delegate considers the efficacy and safety of ixekizumab at the dose requested to be satisfactorily established for the new indication for the treatment of active psoriatic arthritis (PsA) in adults pending further advice from the TGA's Advisory Committee on Medicines (ACM) and the PI changes requested herein.

Data deficiencies

There were no data in the PsA pivotal Phase III studies (Studies RHAB and RHBE) in patients with coexistent PsA and moderate-to-severe plaque Ps treated with exactly the same ixekizumab dosage regimen as that proposed in the PI.

Conditions of registration

The following are proposed as conditions of registration:

- *The [Taltz] EU-Risk Management Plan (RMP) (version 5, date 10 May 2017; DLP 15 September 2016), with Australian Specific Annex (version 1.2, date 5 September 2017), included with submission PM-2017-02078-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Questions for the sponsor

The sponsor is requested to address the following issues in the pre ACM response:

1. Please clarify the reference source for the 'ACR50 and PASI 100' data in Table 4 of the PI.
2. Please clarify if Phase III Study RHBF is part of the RMP.

The statement in the proposed indication '*Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g., methotrexate)'* is more appropriate to be positioned under the 'Dosage and Administration' section of the PI rather than being part of the indication. Please clarify.

Summary of issues

The primary issue with this submission is as follows with further information in the Discussion section:

- The significant covariate in the updated PsA/Ps PopPK model was body weight (increasing body weight increases both CL and V terms). Obese patients appear to have lower exposure (trough concentrations below 2.5 to 5.0 mg/L).

- The proposed dosage regimen for patients with PsA and co-existent moderate to severe plaque psoriasis has not been tested in the PsA pivotal Phase III studies (Studies RHAB and RHBE).

The statement in the proposed indication '*Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g., methotrexate)'* is more appropriate to be positioned under the 'Dosage and Administration' section of the PI rather than being part of the indication.

Proposed action

The Delegate had no reason to say, at this time, that the application for Taltz should not be approved for registration.

Request for ACM advice

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

1. Does the ACM consider that the proposed dosing appropriate for the obese patients?
2. Does the ACM consider the proposed dosing appropriate for patients with co-existent psoriatic arthritis and moderate to severe plaque psoriasis?
3. Does the ACM consider the statement '*Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g., methotrexate)*'appropriate as part of the proposed indication*?* The committee is 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.

Response from Sponsor

The text that follows contains the sponsor's written response to TGA's request for ACM advice dated 1 May 2018. This response will focus on the 3 questions submitted for advice from the ACM and the 3 questions addressed to the sponsor.

Sponsor's responses to the specific issues on which the Delegate requests the committee's advice

1. Appropriate Dosing for Obese Patients

Summary of Issue: '*The significant covariate in the updated PsA/Ps PopPK model was body weight (increasing body weight increases both CL and V terms). Obese patients appear to have lower exposure (trough concentrations below 2.5 to 5.0 mg/L).*'

Advice Sought: 'Does the ACM consider that the proposed dosing appropriate for the obese patients?'

Sponsor's response

The sponsor previously responded to a similar question in the sponsor's response to TGA's request for further information. Below, the sponsor has briefly summarised the response.

The recommended ixekizumab dosing regimen (160 mg starting dose followed by 80 mg every 4 weeks (Q4W)) is expected to result in similar American College of Rheumatology (ACR) response rates across patients with normal weight through extreme obesity.

Based on the data from Studies I1F-MC-RHAP (Study RHAP) and I1F-MC-RHBE (Study RHBE), body weight and BMI are highly correlated. To evaluate the impact of obesity on drug exposure and ACR responses using body weight as a surrogate for the obese condition, simulations were conducted to show the ixekizumab serum concentration

profiles for patients with 60, 90, and 120 kg body weight, and ACR responses over the first 24 weeks for patients with 60 and 120 kg body weight, respectively. The 60 kg body weight was chosen because it was close to the median weight of patients in the normal BMI range of the RHAP/RHBE exposure response analysis dataset (64.0 kg). Similarly, patients with 90 kg and 120 kg body weights were chosen to represent the overweight-to-obese and extremely obese groups (median weight: 81.0 kg (overweight), 96.3 kg (obese), 123 kg (extremely obese)), respectively.

Since ixekizumab CL is approximately proportional to the body weight, steady state exposures in 120 kg or 90 kg patients is estimated to be approximately 50% or 70% of that in 60 kg patients following ixekizumab 80 mg Q4W dosing, respectively. Although with differences in drug exposures, based on the simulation, response rates of ACR20, ACR50, and ACR70 in patients with PsA weighing 120 kg are expected to be similar to those in patients weighing 60 kg because the range of ixekizumab concentration from Studies RHAP and RHBE is near the top plateau of the drug exposure-ACR response curve. Similar ACR response rates are also expected for patients weighing 90 kg.

These conclusions from the exposure response analysis are consistent with the results from the statistical subgroup analysis. Therefore, regardless of the obese condition of patients with PsA, the ACR efficacy results observed in these 2 Phase III studies are likely applicable.

2. *Proposed dosing regimen in patients with co-existent moderate-to-severe plaque psoriasis*

Summary of Issue: 'The proposed dosage regimen for patients with PsA and co-existent moderate to severe plaque psoriasis has not been tested in the PsA pivotal phase 3 studies (RHAB, RHBE).'

Advice Sought: 'Does the ACM consider the proposed dosing appropriate for patients with co-existent psoriatic arthritis and moderate to severe plaque psoriasis?'

Sponsor's response

The proposed dosing regimen for patients with PsA and co-existent moderate-to-severe plaque psoriasis (Ps) (160 mg at Week 0, followed by 80 mg every 2 weeks (Q2W) for 12 weeks, followed by 80 mg Q4W) has not been tested in the PsA pivotal Phase III studies (Studies RHAP, RHBE), but it is the approved dosing regimen for the treatment of moderate-to-severe plaque Ps.

Patients who have PsA and co-existent moderate-to-severe plaque Ps could be considered, and hence treated, either as a subset of PsA patients (with co-existent moderate-to-severe plaque Ps) or as a subset of moderate-to-severe plaque Ps patients (with co-existent PsA). The available evidence suggests that the dosing regimen approved for moderate-to-severe plaque Ps should be used in this population.

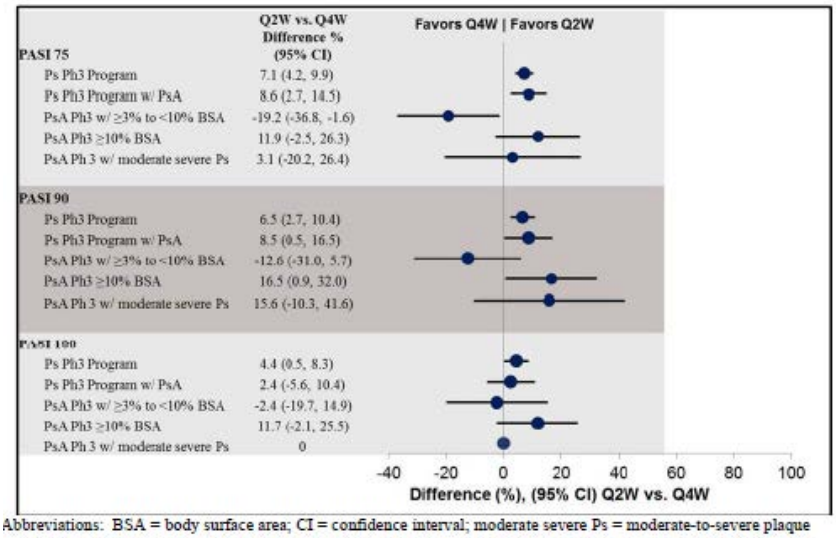
The regulatory trial definition of moderate-to-severe plaque Ps is very stringent (Psoriasis Area and Severity Index (PASI) ≥12, sPGA ≥3, and body surface area (BSA) ≥10%). As a result, moderate-to-severe plaque Ps represents a major burden for affected patients, justifying in itself the use of the dosing regimen that was proven most effective and approved for this condition (160 mg at Week 0, followed by 80 mg Q2W for 12 weeks, followed by 80 mg Q4W), even in patients who have co-existent PsA.

In addition, and as outlined by the TGA Delegate, continuous Q2W dosing tended to be more effective on plaque Ps symptoms than continuous Q4W dosing (without meaningful differences in safety) in patients with higher levels of skin involvement (patients with BSA ≥ 10% and patients with co-existent moderate-to-severe plaque Ps) within the ixekizumab PsA Phase III trials, as presented in the sponsor's Clinical Overview and included as Figure 4 (below) of this response document for convenience.

In the ixekizumab PsA Phase III trials, the safety and the efficacy on PsA-related endpoints (such as, ACR20, tender joint count, swollen joint count and so on) of continuous ixekizumab Q2W dosing were comparable to those of continuous ixekizumab Q4W dosing. Since the dosing regimen for moderate-to-severe plaque Ps is intermediate in overall exposure between continuous Q4W dosing and continuous Q2W dosing, it can be inferred that the efficacy of the Ps dosing regimen on PsA-related endpoints and safety are also comparable to that of continuous Q4W or Q2W dosing.

In conclusion, the available evidence supports the use of the approved label dose for moderate-to-severe plaque Ps in patients with both PsA and moderate-to-severe plaque Ps.

Figure 4: PASI 75/90/100 response rates at Week 12 for ixekizumab 80 mg Q4W versus 80 mg Q2W in patients with psoriasis with or without PsA and in patients with PsA and psoriasis



Abbreviations: BSA = body surface area; CI = confidence interval; moderate severe Ps = moderate-to-severe plaque psoriasis at baseline (PASI total score ≥12, sPGA ≥3, BSA ≥10%); PASI 75/90/100 = Psoriasis Area and Severity Index 75%/90%/100% response rate; Ph = phase; Ps = psoriasis; PsA = psoriatic arthritis; Q2W = ixekizumab 80 mg every 2 weeks; Q4W = ixekizumab 80 mg every 4 weeks.

3. Location of Dosage and Administration text in the PI

Summary of Issue: 'The statement in the proposed indication 'Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g., methotrexate)' is more appropriate to be positioned under the Dosage and Administration section of the PI rather than being part of the indication.'

Advice Sought: 'Does the ACM consider the statement 'Taltz may be used as Monotherapy or in combination with a conventional DMARD (e.g., methotrexate)' appropriate as part of the proposed indication?

Sponsor's response

The sponsor considers it appropriate to include the statement '*Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g., methotrexate)*' in the proposed Indications section.

The efficacy of the proposed ixekizumab SC doses has been demonstrated both as monotherapy and in combination with non-biologic DMARDs in patients with active PsA.

Positioning this statement in the Indications section provides guidance to the prescriber on the appropriate product usage of Taltz in the population, for which it is indicated; that is, those patients who may receive monotherapy or combination therapy for PsA. The sponsor does not consider it appropriate to include it in the Dosage and Administration section of the Product Information (PI).

No dosage adjustment of Taltz, or additional monitoring, is required in patients receiving Taltz as monotherapy or combination therapy.

This approach is consistent with the labelling in the company core datasheet and the Taltz EU SmPC. It is also consistent with Australian labelling for similar products indicated for rheumatoid arthritis and/or PsA (such as baricitinib, adalimumab, ustekinumab, etanercept, and certolizumab). In addition, the sponsor considers that relocating this text to the Dosage and Administration section could potentially confuse prescribers accustomed to locating this information in the Indications section of the PI.

Sponsor's responses to the questions for the sponsor

1. Source for ACR50 and PASI 100 Data

'*Please clarify the reference source for the 'ACR50 and PASI 100' data in Table 4 of the PI.'*

Sponsor's response

The reference source for the 'ACR50 and PASI 100' data in Table 4 of the PI is located in the sponsor's Clinical Overview and is included as Table 21 (below) for convenience.

Table 21: ACR50/PASI 100 (assessed in patients with BSA ≥3% at Baseline; NRI) at Weeks 12, 16, and 24 by pivotal study

Study	RHAP				RHBE		
Treatment Group	ADA N=101	PBO N=106	80 mg Q4W N=107	80 mg Q2W N=103	PBO N=67	80 mg Q4W N=68	80 mg Q2W N=68
ACR50/PASI 100 (%)							
Week 12	8.8	0	17.8	20.3	1.5	7.4	11.8 [b]
Week 16	11.8	3.0	23.3 [b]	22.0 [b]	1.5	11.8 [c]	11.8 [c]
Week 24	13.2 [c]	1.5	28.8 [b]	32.3 [a]	0	17.6 [a]	14.7 [b]

Abbreviations: 80 mg Q2W = ixekizumab 80 mg every 2 weeks; 80 mg Q4W = ixekizumab 80 mg every 4 weeks; ACR50/PASI 100 = American College of Rheumatology 50% plus Psoriasis Area and Severity Index 100% response rate; ADA = adalimumab 40 mg every 2 weeks; BSA = body surface area; N = number of patients in the analysis population; NRI = nonresponder imputation; PBO = placebo.

[a] p<.001 versus PBO.
[b] p<.01 versus PBO.
[c] p<.05 versus PBO.

2. Study I1F-MC-RHBF and the RMP

'Please clarify if Phase III Study RHBF is part of the RMP.'

Sponsor's response

The RMP includes data from 3 ixekizumab PsA clinical trials (Studies RHAP, RHBE and I1F-MC-RHBF (RHBF)). Patient safety data from ongoing Study RHBF, specifically the patient safety data from the Open-Label Period, was included in the following RMP tables:

- Table SIII.7 (Duration of Exposure)
- Table SIII.8 (Exposure by Dose)
- Table SIII.9 (Exposure by Age Group and Gender)
- Table SIII.10 (Exposure by Racial Origin)
- Table SVI.2 (Medication Errors during Clinical Trial Program)
- Table SVII.1 (Important Identified and Potential Risks from Clinical Development)

3. Location of Dosage and Administration text in the PI

'The statement in the proposed indication 'Taltz may be used as monotherapy or in combination with a conventional DMARD (eg methotrexate)' is more appropriate to be

positioned under the 'Dosage and Administration' section of the PI rather than being part of the indication. Please clarify.'

Sponsor's response

Please refer to sponsor's response to point 3 under *Sponsor's responses to the specific issues on which the Delegate requests the committee's advice*.

Advisory Committee Considerations[22]

The ACM taking into account the submitted evidence of efficacy and safety, agreed with the delegate and considered Taltz Injection prefilled pen and injection prefilled syringe containing 80 mg/mL solution for injection prefilled pen and 80 mg/mL solution for injection prefilled syringe of ixekizumab to have an overall positive benefit-risk profile for the indication:

> *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).*

In providing this advice the ACM

- Noted that although the population pharmacokinetic data suggested obese patients would have lower exposures of ixekizumab due to increases in clearance and volume of distribution, no clinical benefit was observed from twice weekly (Q2W) dosing when compared to 4 weekly (Q4W) dosing in the Phase III studies.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACM advised the following in response to the delegate's specific questions on the submission:

1. Does the ACM consider that the proposed dosing appropriate for the obese patients?

In the subgroup analysis from the pooled data of the two Phase III studies, the Q4W group had significantly greater response rates compared to placebo in all weight groups, while the Q2W group only had significantly larger responses to placebo in the < 80 kg and 80 to 100 kg group. There were only a numerically greater response in the >100 kg group.

The committee was of the view that the proposed dosing is appropriate for obese patients based on the current data available, but noting the limitations of post hoc subgroup analysis of pooled data from a heterogeneous study population.

[22] 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.

2. *Does the ACM consider the proposed dosing appropriate for patients with co-existent psoriatic arthritis and moderate to severe plaque psoriasis?*

Many patients who present with psoriatic arthritis may also have some degree of skin involvement. Although the proposed dose regime for patients with both moderate to severe plaque psoriasis and active psoriatic arthritis were not studied, the committee was of the view that current dosage regime for moderate to severe plaque psoriasis is appropriate for patients with co-existing conditions.

3. *Does the ACM consider the statement 'Taltz may be used as monotherapy or in combination with a conventional DMARD (e.g., methotrexate)' appropriate as part of the proposed indication?*

The statement described the place in therapy of ixekizumab rather than dosage direction, thus it belongs in the Indication section rather than the Dosage and Administration of the PI. By including the statement in the Indication section, clinicians can quickly determine the place in therapy for ixekizumab. The committee is of the view that the statement should be a part of the indication.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Taltz containing ixekizumab 80 mg/mL prefilled syringe and prefilled pen subcutaneous injection for the new 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).*

Specific conditions of registration applying to these goods

- Taltz (ixekizumab) is to be included in the Black Triangle Scheme. The PI and CMI for Taltz must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

  The ixekizumab EU-Risk Management Plan (EU-RMP), version 5, date 10 May 2017; DLP 15 September 2016), with Australian Specific Annex (version 1.2, date 5 September 2017), included with submission PM-2017-02078-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

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>.

Therapeutic Goods Administration

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