Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ixekizumab

Proprietary Product Name: Taltz

Sponsor: Eli Lilly Australia

May 2017

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
ADA	Anti-drug antibody
ADR	Adverse Drug Reaction
AE	Adverse event
AESI	Adverse event of special interest
aPTT	Actived partial thromboplastin time
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
ASA	Australian Specific Annex
AUC	Area under the curve
BMI	Body mass index
CER	Clinical Evaluation Report
CHMP	Committee for Medicinal Products for Human Use
CHMP	Committee for Medicinal Products for Human Use (EU)
CIOMS-IX	Council for International Organizations of Medical Sciences Working Group IX
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximal concentration (steady state)
CMH	Cochran Mantel Haenszel
CNS	Central Nervous System
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough.ss}$	Trough concentration at steady state
CYP	Cytochrome p450 system
DLQI	Dermatology Life Quality Index
EC_{50}	Half maximal effect concentration
ELISA	Enzyme-linked immunosorbent assay

Abbreviation	Meaning
EMA	European Medicines Agency
E_{max}	Maximum possible effect (efficacy)
EU	European Union
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
HLT	High Level Term
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IL	Interleukin
ILD	Interstitial lung disease
ISS	Integrated Summary of Safety
Itch NRS	Itch Numeric Rating Scale
IV	Intravenous
KLH	Keyhole limpet haemocyanin
LOAEL	Lowest observable adverse event level
MACE	Major adverse cardiac event
NAb	Neutralising antibody
NOAEL	No observable adverse event level
NRI	Non-responder imputation
PASI	Psoriasis Area and Severity Index
PCP	Pneumocystis pneumonia
PD	Pharmacodynamic
PI	Product Information

Abbreviation	Meaning
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PMAB	Prescription Medicines Authorisation Branch
pMI	Placebo multiple imputation
PopPK	Population pharmacokinetic
PSAB	Pharmacovigilance and Special Access Branch
PT	Partial thromboplastin
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RA	Rheumatoid arthritis
RMP	Risk Management Plan
RMP	Risk Management Plan
SAE	Serious Adverse Event
SC	Subcutaneous
SmPC	Summary of Product Characteristics
sPGA	Static Physician's Global Assessment
TE-ADA	Treatment-emergent antidrug antibody
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time to maximal serum concentration
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
V_d	Volume of distribution
WBC	White blood cell

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	1 September 2016
Date of entry onto ARTG:	6 September 2016
Active ingredient(s):	Ixekumab
Product name(s):	Taltz
Sponsor's name and address:	Eli Lilly Australia Pty Ltd 112 Wharf Road West Ryde NSW 2114
Dose form(s):	Solution for injection
Strength(s):	80 mg/mL
Container(s):	Glass type I closed syringe or Prefilled pen
Pack size(s):	1, 2, and 3 prefilled syringe(s) 1, 2, and 3 prefilled pen(s)
Approved therapeutic use:	*Taltz is indicated for the treatment of adult patients with moderate‑to‑severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*
Route(s) of administration:	Subcutaneous (SC) injection
Dosage:	160 mg by subcutaneous 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.
ARTG number (s):	253892 (prefilled syringe) 253893 (prefilled pen)

Product background

This AusPAR describes the application by the sponsor to register Taltz (ixekizumab 80 mg/mL solution) for subcutaneous (SC) injection in a prefilled syringe and prefilled pen for the following indication:

'the treatment of adult patients with moderate to severe plaque psoriasis.'

Psoriasis is an inflammatory and hyperplastic condition of the skin, characterised by erythema and scale. It ranges from a few plaques to widespread inflammation with

pustules and systemic symptoms. Psoriasis may present at any age. It is uncommon in children but in infants it often presents as intractable nappy rash or severe cradle cap.

Plaque psoriasis is the most common type. Plaques are well demarcated and pink, with a silvery scale. Common sites are the elbows, knees, sacrum and scalp. Lesions may be single or numerous. Psoriasis is a chronic condition, and its course is often difficult to predict, as its severity can fluctuate. The psychological impact of psoriasis can be marked, but does not always correlate with severity. Psoriasis is strongly familial. It is polygenically inherited but is only activated when specific environmental factors are present. In many patients, no specific trigger is identified.

The Australian prevalence of psoriasis has been reported to be in the range of 2.3% to 6.6% with 20% to 30% of patients having moderate to severe disease. There are 3 primary forms of treatment for psoriasis: topical therapy, phototherapy and systemic therapy. Treatment is chosen on the basis of disease severity, relevant comorbidities, patient preference (including cost and convenience), efficacy, and evaluation of individual patient response.

Topical agents are used for psoriasis are predominantly corticosteroids, salicylic acid, calcipotriol and coal tar preparations. Severe disease requires UV light (such as phototherapy; PUVA) or systemic therapies. The following systemic agents are approved for psoriasis in Australia: cyclosporin, methotrexate, acitretin, and the targeted immunotherapies apremilast (an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), infliximab, etanercept and adalimumab (all TNFα antagonists), ustekinumab (an anti-interleukin (IL)-12/IL-23 agent) and secukinumab (a fully human IgG1 anti-IL-17A agent). Ixekizumab itself is a humanised IgG4 monoclonal antibody with high affinity and specificity to IL-17A. IL-17A is a pro-inflammatory cytokine produced primarily by a subset of CD4+ T cells, called T_h17 cells.

The sponsor's letter of application included a clinical rationale for the development of Taltz. The sponsor commented that psoriasis is a common, life-long and life-shortening chronic inflammatory disease characterised by prototypic red, thick and scaly plaques. Available biologic agents, including adalimumab, etanercept, infliximab and ustekinumab, are generally superior in efficacy to conventional systemic therapies. However, the majority of patients treated with biological agents do not reach high level response of 90% improvement from baseline on the Psoriasis Area and Severity Index (PASI 90), and only a minority attain complete clearance of their psoriatic plaques (PASI 100).[1] Therefore, the sponsor states that considerable need continues to exist for new medicines for the treatment of psoriasis, with new modes of action that can provide rapid onset of effect, attain and maintain high level response, and minimise the impact of the disease, while offering an acceptable safety profile that allows chronic use.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 6 September 2016.

At the time of submission ixekizumab had not been approved by any regulatory agency. Ixekizumab was subsequently approved in the USA in March 2016. Submissions have been made in the USA, Canada, EU, Switzerland and Japan. In each case the indication proposed in those countries was: '*for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy'.* The indication proposed in Australia was abbreviated to remove the specification that patients be

[1] Schmitt J et al. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2014;170(2):274-303.

candidates for systemic or phototherapy. The indications for biological agents approved for treatment of plaque psoriasis in Australia have to date specified use in adults and that the patients who are candidates for phototherapy or systemic therapy. Infliximab was the first biological agent approved for use in plaque psoriasis in Australia and it has the most restrictive indication which states: '*…treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established'.*

There were no paediatric data in this submission. Moderate to severe plaque psoriasis is not frequently seen in children. None of the other biological agents are approved for use in children or adolescents.

Product information

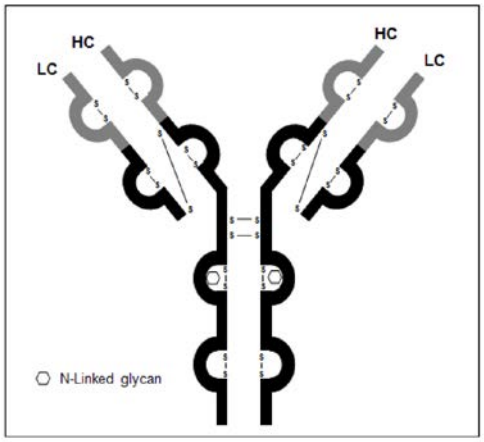
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

Ixekizumab is a humanised immunoglobulin of the IgG4 subtype. It composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains. The overall structure of ixekizumab is depicted in Figure 1 below, showing the disulphide bonding pattern and the location of the N linked glycosylation sites. The constant regions are shown in black and the variable regions are shown in grey.

Figure 1. Ixekizumab immunoglobulin structure



The molecular formula is $C_{6492}H_{10006}N_{1726}O_{2028}S_{46}$ (non-glycosylated). Each heavy chain polypeptide of ixekizumab contains an N-linked glycosylation site at Asn296 which is modified with oligosaccharides. The overall molecular weight of ixekizumab with the predominant forms (G0F/G0F) of the oligosaccharides is 149,049 Dalton.

Ixekizumab is a monoclonal antibody against the pro-inflammatory cytokine IL-17A. It binds to and neutralises IL-17A. The binding affinity (KD) of ixekizumab to IL-17A is < 1 pM at 25°C. Ixekizumab does not bind `Fcγ receptors I, IIa, or IIIa nor to the complement component C1q.

Drug product

All manufacturing processes for the drug product are validated. Pending Good Manufacturing Practice (GMP) clearance there were no issues resulting in objection of approval from quality grounds regarding drug product manufacture.

The proposed shelf life is 24 months when stored at 2°C to 8°C. The real time data submitted support the proposed shelf life.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data shows the product is not photostable.

Biopharmaceutics

Biopharmaceutic studies have not been assessed during the quality evaluation. The company submitted the Phase I study (Study RHAG), which included absolute bioavailability data. The low dose lyophilised formulation produced for Study RHAG along with its CoA was provided and all results are within the specification.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Taltz ixekizumab 80 mg/mL solution for injection prefilled syringe and Taltz ixekizumab 80 mg/mL solution for injection prefilled pending GMP clearance.[2]

Proposed conditions of registration (for clinical delegate)

Batch release testing & compliance with Certified Product Details (CPD)

1. It is a condition of registration that all batches of Taltz (ixekizumab) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Taltz (ixekizumab) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

III. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was good and in general accord with the ICH guideline on nonclinical evaluation of biotechnology derived pharmaceuticals (International Conference on Harmonisation (ICH) guideline S6).[3] All pivotal toxicity studies were conducted according to GLP standards. Ixekizumab is a humanised antibody against human IL-17A and has no affinity for rodent IL-17; thus all toxicity studies were

[2] See VI. Overall conclusions:The sponsor advised in an email dated on 23 May 2016 that GMP applications for four manufacturing sites were submitted between 16 to 20 May 2016 and that approvals are pending.
[3] ICH S6: International Conference on Harmonisation, Preclinical safety evaluation of biotechnology-derived pharmaceuticals

conducted in cynomolgus monkeys, which are responsive to ixekizumab. The sponsor did not conduct any genotoxicity studies, which is acceptable since as a biological substance ixekizumab is not expected to interact with chromosomal material. No carcinogenicity studies were conducted either, which is also generally acceptable; however, the sponsor submitted a carcinogenicity assessment review that evaluated the available evidence on risk of carcinogenicity arising from neutralisation of IL--17 or use of ixekizumab itself.

Ixekizumab is the second therapeutic monoclonal antibody targeting IL-17A that was developed to treat psoriasis. Secukinumab, a fully human anti-human IL-17A monoclonal antibody, was approved by the TGA in January 2015 (as Cosentyx; Zafrez) for a similar indication as that sought for Taltz.

Pharmacology

Ixekizumab is a humanised IgG4 isotype monoclonal antibody designed to bind with high affinity and selectivity to the pro-inflammatory cytokine 17A (IL-17A). IL-17A production by activated CD4+ T cells/T helper (T_h17) cells is implicated in chronic inflammation and tissue damage associated with autoimmune diseases such as psoriasis. The main function of IL-17A is to activate processes that enhance neutrophil recruitment, cytokine production and provide generalised immunity against infectious agents following cell injury. Th17 cells are notably localised in the lungs, the intestinal mucosa and skin, and serve to protect hosts from environmental insults; thus, aberrant IL-17A overproduction in these organs may be considered a viable therapeutic target in autoimmune disorders, such as arthritis, inflammatory bowel diseases and psoriasis.

Pharmacology studies on ixekizumab examined its binding affinity and selectivity for human IL-17A. As the antibody was developed to specifically target human IL-17A, ixekizumab was also examined against a range of species-specific forms of IL-17A. Demonstration of IL-17A neutralisation was mostly done under in vitro conditions; however, one mouse in vivo study was submitted in which the effector response to human IL-17A was monitored in the presence and absence of ixekizumab.

Primary pharmacology

Binding studies confirmed affinity of ixekizumab for human IL-17A and the heteromeric form, IL-17A/F, (K_D < 3 pM for both forms). Ixekizumab did not exhibit affinity for other members of the IL-17 family of cytokines (IL-17B, IL-17C, IL-17D, IL-17E and IL-17F), which share between 20 to 50% homology to IL-17A. Species selectivity was also apparent, with the antibody showing high affinity for monkey IL-17 (K_D 0.8 pM) but considerably lower for rabbit IL-17 (K_D > 1.3 nM) and no binding for rodent IL-17.

Ixekizumab neutralised IL-17 under in vitro conditions, which was demonstrated as dose-dependent attenuation of IL-17A-induced release of cytokine GRO-α by cultured epithelial cells, HT-29 (IC_{50} human IL-17A of 400 pM and monkey IL-17A of 700 pM). Control immunoglobulin IgG4 did not affect IL-17-induced cytokine release. Ixekizumab bound to IL-17A was not displaced by IL-17 receptor (IL-17R), suggesting irreversible binding of ixekizumab to IL-17A and that ixekizumab blocks binding of IL-17A to its receptor, IL-17R.

Epitope mapping studies examined regions of IL-17A important for its interaction with ixekizumab. Native and mutant forms of human IL-17A, including a mutant modelled according to the mouse IL-17 sequence, were applied to mouse 4T1 cells, which respond to human IL-17 to release GRO-α/KC protein, in the presence and absence of ixekizumab. Only the mutant IL-17A modelled to mouse IL-17 was unaffected by ixekizumab (i.e. unable to bind with ixekizumab). Subsequently, it was found that amino acids 80-87 of IL-17A are pivotal to its interaction with ixekizumab. It is possible that this region of IL-17A also governs its interaction with secukinumab, since secukinumab also does not bind to

rodent IL-17. Ixekizumab was developed as an IgG4 type immunoglobulin to minimise Fc-mediated activation of immune functions, as it was claimed that the IgG4 isotype has a lower binding affinity for Fc γ receptors. In vitro binding experiments (by SPR) did not show ixekizumab to have significant affinity for Fc γ receptors I, IIa and IIIa, or for complement component C1q. Repeat dose toxicity studies did not reveal any clinical signs indicative of Fc-mediated reactivity; however, this aspect of ixekizumab pharmacology was not extensively investigated, and affinities of different human IgGs for Fcγ receptors were reported to be similar.[4] In response to a TGA request for information, the sponsor elaborated that because IL-17A is a soluble cytokine immune activation (that is antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity) is not expected to occur and there is also negligible binding between ixekizumab and FcγRI, IIb, IIIa and C1q as discussed above.

No in vivo studies specifically relevant to the indication were conducted as there are no appropriate animal models for psoriasis. However, proof-of-principle demonstration was provided (that is, demonstration of IL-17 neutralisation under in vivo conditions) with mice administered human IL-17 (which mice are responsive to) and IL-17-mediated cytokine (GRO-α/KC/CXCL1) levels monitored in the presence and absence of ixekizumab. Cytokine release was reduced by ixekizumab at 20 μg/animal but not by lower doses (0.02, 0.2 or 2 μg). Due to non-responsiveness of rodent species no other in vivo investigations were conducted using mice or rats. Commercially available antibodies against rodent IL-17 were used in an attempt to develop a mouse or rat model for autoimmune disease for further exploration of pharmacological mechanisms and consequences of neutralising IL-17A; however there were qualitative differences between these and ixekizumab that precluded their use in toxicity assessments (discussed further below).

Secondary pharmacodynamics and safety pharmacology

The sponsor did not submit typical secondary pharmacology studies that examined off-target effects of ixekizumab. Instead a series of studies investigated the physicochemical attributes of two commercially sourced rat anti-mouse IL-17 antibodies, IgG2a and IgG1 (LSN2886817 and LSN2805474, respectively) for the purpose of using these as surrogates for human anti-IL-17A in rodent models of autoimmune disorders. Binding between these antibodies and mouse or rat IL-17 was assessed and both were found to exhibit lower affinity for rodent IL-17 than ixekizumab exhibited for human or monkey IL-17. As well, in a neutralisation assay only one of the tested antibodies, LSN2886817 was effective at neutralising rodent IL-17 and at a higher concentration than ixekizumab against human or monkey IL-17 (1.4 to 6.81 nM compared to 0.4 and 0.7 nM for human and monkey IL-17, respectively). The other antibody, LSN2805474 neutralised only mouse IL-17 (IC_{50} 1.09 nM). Based on these observations, there were no further explorations of rodent models of autoimmune diseases as they were likely to be of limited utility in pharmacological and toxicological characterisations of ixekizumab.

Specialised safety pharmacology studies on ixekizumab were not conducted; however, safety pharmacology parameters were integrated into the protocols of Good Laboratory Practice (GLP) repeat dose toxicity studies (8 and 39 weeks) in cynomolgus monkeys. Acute exposure to ixekizumab was high since both the clinical (subcutaneous) and intravenous routes were employed. No notable changes to central nervous system (CNS) (neurological, behaviour and body temperature), electrocardiographic (heart rate, QT interval duration and corrected QT interval duration) or respiratory parameters were

[4] Guilliams M et al. (2014). The function of Fcγ receptors in dendritic cells and macrophages. Nature Rev Immunology., 14, 94–108.

reported. Thus overall, no effect on functions of CNS, cardiovascular and respiratory systems is predicted with weekly dosing of ixekizumab.

Pharmacokinetics

Pharmacokinetic and toxicokinetic characteristics of ixekizumab were assessed in cynomolgus monkeys. Single dose assessments were conducted following a single 1 mg/kg dose administered by either the intravenous or subcutaneous route, while repeat dose assessments were determined from repeat dose toxicity studies that used weekly subcutaneous doses of ixekizumab (0.5, 5 and 50 mg/kg).

Subcutaneously administered ixekizumab showed slow systemic distribution, reaching maximum serum levels at 72 h post-dose. Bioavailability of ixekizumab was high in monkeys (equivalent to intravenous exposure). Volume of distribution (V_d) was 87 mL/kg (compared with human V_d 7.11 L, approximately 120 mL/kg for a 60 kg adult) and bolus IV ixekizumab was eliminated with a terminal half-life of 156 h (6.5 days), while subcutaneous ixekizumab had a half-life of 246 h (10.3 days, compared with 13 days in humans). Repeat dosing did not uncover differences in exposures of ixekizumab (as are under the curve (AUC)) between male and female animals, which were dose proportional. At the highest dose there was evidence of accumulation by the last sampling day (no accumulation data for the two lower doses tested). This likely reflects the long elimination half-life of ixekizumab which exceeds the dosing interval periods.

No specific studies on distribution were conducted. A tissue cross reactivity study using cryosections of various human and cynomolgus monkey tissues found no evidence of cross-reactivity of ixekizumab with the different cell and tissue types tested. While pharmacology studies suggested low potential for Fc-mediated effects by ixekizumab, placental transfer was demonstrated in the monkey embryofetal development study with a fetal:maternal serum ratio of approximately 0.2, indicating some interaction between ixekizumab and FcRn.

No specific studies on metabolism or excretion were conducted but it is expected that ixekizumab undergoes protein catabolism similarly to other biotechnology-derived pharmaceuticals and is excreted through urine as catabolised protein.

Blood samples were collected in the repeat dose studies to monitor the development of anti-drug (ixekizumab) antibodies (ADAs). Low ADA titres were noted in many of these studies but the assay used to measure anti-ixekizumab ADAs was subject to interference by circulating ixekizumab, thus potential for high rates of false negatives should be considered. Nonetheless, high serum levels of ixekizumab were detected in the toxicity studies during the entire dosing period.

Overall, there were sufficient similarities between the pharmacokinetic profiles of ixekizumab in cynomolgus monkeys and humans to serve as appropriate animal models for toxicity testing.

Pharmacokinetic drug reactions

No specific studies on drug interaction potential of ixekizumab were conducted.

Toxicology

Acute toxicity

Acute toxicity studies were not conducted with ixekizumab. No acute treatment-related findings were noted in the repeat-dose studies in cynomolgus monkeys when either the intravenous or the subcutaneous routes were used with doses of up to 50 mg/kg/week.

Repeat-dose toxicity

The sponsor submitted two repeat dose toxicity studies that were conducted in a responsive species: cynomolgus monkeys. The studies utilised weekly dosing and ixekizumab was administered using the intravenous (8 weeks) and subcutaneous (9 months) routes at weekly doses of 0.5 to 50 mg/kg. Both studies were GLP compliant. Dosing frequency was higher than the clinical dosing regimen (weekly compared to once fortnightly for 12 weeks then once monthly thereafter in patients). Duration of studies was acceptable according to ICH guideline recommendations for non-rodent toxicity tests (ICH S4).[5]

Relative exposure

Exposure ratios were calculated based on animal: human steady state maximal serum concentration ($C_{max,ss)}$ and AUC values. The clinical $C_{max,ss}$ and AUC values predicted by 2-compartment population PK modelling are shown in Table 1 below and are used for exposure comparison. Animal study values represent the highest doses used in the toxicity studies.

Relative exposures based on C_{max} and AUC were high (> 50 fold) when compared either at the induction dose level or at steady state at maintenance dose levels.

Table 1. Relative exposure (ER) in repeat-dose toxicity study findings in cynomolgus monkeys

Study details	Dose mg/kg	C_{max} µg/mL	$AUC_{014days}$ µg day/mL	ER[a] based on C_{max}		ER[a] based on AUC	
				Induct.	Main.	Induct.	Main.
Study No. 6180-918 Repeat dose toxicity: 8 weeks Weekly dosing (Day 57)	50 (IV)	2250	17542	113	105	114	99
Study No. 7608-478 Repeat dose toxicity: 9 months Weekly dosing (Day 267)	50 (SC)	1035	11996	52	48	78	68
Study No. 20003965 Pre-fertility: 90 days;	50 (SC)	1156	13881	58	54	90	78

[5] ICH S4: International Conference on Harmonisation: Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)

Study details	Dose mg/kg	C_{max} µg/mL	$AUC_{014days}$ µg day/mL	ER[a] based on C_{max}		ER[a] based on AUC	
daily dosing (day 85)							
Human: Population PK analyses (2-compartment model)	160 mg induction dose	19.9	154	–	–	–	–
	80 mg main dose (SS)	21.5	177	–	–	–	–

Notes: a) animal : clinical C_{max} or AUC; b) $AUC_{0\text{-}14days}$ at 80 mg Q2W (half the $AUC_{0\text{-}28\ days}$ value of 353)
Abbreviations: induct. = induction, main. = maintenance

Major toxicities

Toxicities associated with ixekizumab treatment were generally minimal. One male in the mid-dose group (5 mg/kg) of the 9-month study was found dead on Day 140, with no clear treatment-related clinical signs, clinical pathology changes or necropsy and histological findings. The cause of death was not determined, but was probably not related to treatment.

Clinical signs were limited to injection site reactions (swelling and scabbing) that persisted in two females from the high dose (50 mg/kg) group during the dosing period in the 9 month study. Treatment-related injection site reactions in other animals were sporadic in nature and generally resolved by the next dosing interval. Histological examination of the injection site showed local inflammation, haemorrhage, necrosis, and vasculitis and were of greater severity at the most recently injected site compared to older injection sites. All signs of injection site reactions were resolved in the recovery groups. The no observable adverse event level (NOAEL) for the 9 month study was 5 mg/kg, due to the severity of injection site reactions at the higher dose level (50 mg/kg). The sponsor's Nonclinical Overview discusses the significance of these findings and contends that the NOAEL/lowest observable event level (LOEL) is more likely to be at the higher dose since the reactions were generally only seen in a single high dose female that also had high anti-ixekizumab antibody titres, the reactions reflect the animal's individual immunogenic response to ixekizumab rather than a clinically relevant toxicological finding. While the injection site reactions are unlikely to reflect a unique toxicity of ixekizumab, the severe injection site reactions were seen and persisted in at least 2 out of the 4 treated females, and injection site reactions were also reported in clinical studies where some subjects had to discontinue their participation although the sponsor did not consider these effects to be severe. Localised reactions in an animal receiving a humanised protein generally have limited clinically predictive value but in this case appear to corroborate the findings from human subjects.

Effects on excreta (liquid or discoloured/reddened faeces) were noted in some of the treatment animals, but due to their sporadic nature were not considered adverse. Neither of the repeat dose studies found evidence of treatment-related effects on body weight gain, ophthalmological parameters, electrocardiographic parameters, respiratory or neurological measures, or changes to organ weights, macroscopic and histopathologic observations (unrelated to injection site reactions).

Serum chemistry analyses did not show clear treatment-related effects, although there were small fluctuations that were not statistically significant (raised cholesterol in mid and high dose groups, decreased potassium in all male treated groups in the 9 month study; slight raises in gamma-glutamyl transferase in male treated groups). The 8 week

study reported significant increases in urinary volume in mid and high dose males (15 and 50 mg/kg, respectively), and decreased urinary pH in mid and high dose females. No changes to urinary parameters were reported in the 9 month study; therefore the observations in the 8 week study are unlikely to be toxicologically significant.

Full haematological assessments did not reveal notable treatment-related changes in either male or female treated animals. Coagulation parameters (partial thromboplastin (PT), activated partial thromboplastin time (aPTT) and platelet counts) were not affected by treatment. Slight but non-significant increases in white blood cell (WBC) counts were noted in males, which appeared to be normalised following the recovery period. More specific analyses of lymphocyte cell types (immunophenotyping), to establish if IL-17A neutralisation altered the population of lymphocytes (CD4 T cells, CD8 T cells, total T cells, B cells, NK cells), found no treatment-related changes following either 8 week or 9 month treatment with ixekizumab. Further characterisation of the effects of ixekizumab on adaptive immunity was conducted by assessing the T-cell dependent antibody response against antigen KLH (keyhole limpet haemocyanin). Neither of the two studies reported any changes in titre levels for anti-KLH IgG or IgM, relative to control group or following recovery period.

Immunogenicity was not prevalent but the assay used to measure ADAs against ixekizumab was reportedly affected by the presence of serum ixekizumab and the likelihood of false negatives is high.

The sponsor did not conduct specific nonclinical studies on susceptibility to infections arising from ixekizumab treatment. Because IL-17A plays a significant role in adaptive immunity to protect against infections, the risk of opportunistic infections arising from chronic neutralisation of IL-17A is high. Neither of the two repeat-dose studies reported observations indicative of opportunistic infections. Clinical studies however did report increases in infections (cellulitis, appendicitis, bronchopneumonia, diverticulitis, erysipelas, pneumonia, *Candida* and urinary tract infections (UTI)) relative to placebo group rates. Most of these were described as mild to moderate in severity. As these are already identified under clinical use conditions, the utility of further characterisation studies in animals is likely to be limited.

Overall, observations in cynomolgus monkeys were mostly benign with toxicity findings limited to injection site reactions in all dose groups.

Genotoxicity

The genotoxic potential of ixekizumab was not examined in dedicated nonclinical studies, which is acceptable for a biotechnology-derived pharmaceutical as per ICH guideline (ICH S6 (R1)).[3]

Carcinogenicity

The carcinogenic potential of ixekizumab was not assessed, which is acceptable under ICH S6 (R1).[3] Conventional carcinogenicity bioassays in rodents are not appropriate since rodents are not responsive to ixekizumab and are also likely to develop antibodies to ixekizumab over time. Life-time carcinogenicity studies in primates are not ethically feasible. Thus it was apparent that such studies would be of limited utility. However, because ixekizumab is used to counter aberrant immune activity it may potentially interfere with tumour immune surveillance mechanisms. For this reason the sponsor submitted a literature review assessing links between IL-17A neutralisation and risk of carcinogenicity.

The review examined the biological role of IL-17A in tumour development and on whether immunosuppression via IL-17A neutralisation enables uncontrolled proliferation. It found

a wide body of literature on the direct tumour promoting properties of IL-17A. IL-17A and IL-17A-generating cells have been found in numerous tumour types, and high circulating levels of IL-17A are correlated to tumour progression in several tumour types.[6,7,8,9,10] As well, IL-17A-mediated release of tumour-promoting and angiogenic factors and cytokines (VEGF, IL-6, IL-8, CXC–1, 5, 6 and 8) is regulated by the transcription factor NF-kB, which is active in malignant cells and assists their ability to evade pro-apoptoptic tumour surveillance mechanisms.[8] Thus, the tumour promoting properties of IL-17A are due to release of pro-angiogenic factors.

The review also explored evidence of tumorigenesis when IL-17A levels are deficient or neutralised. Mice deficient in either IL-17A or IL-17A receptors had reduced tumour growth compared to wild-type mice when either were injected with different tumour cell types (melanoma, bladder carcinoma, lymphoma, prostate carcinoma).[11,12]

However, contrary findings by other authors found tumour growth was higher in IL-17A-deficient mice than in wild type mice following injection of colon adenocarcinoma cells.[13] These contrasting observations were ascribed to the possibility that IL-17A has different signalling roles depending on tumour cell type. Use of IL-17A-neutralising agents was explored in an immune competent mouse model of arthritis, where mice injected with a metastatic breast cancer line developed tumours and metastases, as well as elevations in pro-inflammatory cytokines and angiogenic agents. Treatment with an anti-murine IL-17A antibody reduced expression of pro-inflammatory chemokines and cytokines, and cell extracts from isolated tumour tissues displayed less chemotactic behaviour than lysates from untreated mice.[14]

Overall, the literature indicates that IL-17A is more likely to exert a tumour–promoting influence rather than tumour suppressing effect, depending on tumour type. As well, because of the protein-based nature of ixekizumab, a genotoxic-mediated action is highly unlikely. For these reasons, neutralisation of IL-17A is not expected to generate conditions that promote tumour growth.

Reproductive toxicity

Reproductive toxicity was evaluated in pre-fertility, embryofetal development and pre/post-natal development studies in cynomolgus monkeys. Animals received weekly subcutaneous doses of ixekizumab of up to 50 mg/kg/week. In the embryofetal development study dosing covered the period of organogenesis (gestation day 20 to 139), while the pre/postnatal development study ceased dosing at parturition (started from gestation day 20). The embryofetal and pre/post-natal development studies also included measurement of ixekizumab in serum (maternal, fetal and infant), placental and milk, as

[6] Tartour E et al., (1999) Interleukin 17, a T-cell-derived cytokine promotes tumourigenicity of human cervical tumours in nude mice. Cancer Res., 59(15), 3698–3704.
[7] Kato T et al., (2001) Expression of IL-17 mRNA in ovarian cancer. Biochem Biophys Res Comm., 282(3), 735-738.
[8] Li J et al. (2011). Interleukin 17A promotes hepatocellular carcinoma metastasis via NF-kB induced matrix metalloproteinases 2 and 9 expression. PLoS One, 6(7), e21816.
[9] Xu M et al. (2013). IL-17A stimulates the progression of giant cell tumours of bone. Clin Cancer Res, 19(17), 4697–4705.
[10] Wu D et al., (2013) Interleukin-17: a promoter in colorectal cancer progression. Clin Dev Immunol. 2013, 1–7.
[11] He D et al., (2010) IL-17 promotes tumour development through the induction of tumour promoting microenvironments at tumour sites and myeloid-derived suppressor cells. J Immunol., 184(5), 2281–2288.
[12] Wang L et al., (2009) IL-17 can promote tumour growth through an IL-6-Stat3 signalling pathway. J. Exp. Med., 206(7), 1457-1464.
[13] Krycek I et al., (2009) Endogenous IL-17 contributes to reduced tumour growth and metastatsis. Blood, 114(2), 357-359.
[14] Das Roy L et al., (2009) Breast cancer-associated metastasis is significantly increased in a model of autoimmune arthritis. Breast Cancer Res., 11(4), R56.

well as assessment of ADA development; however, toxicokinetic parameters were not determined. The study designs were generally acceptable in view of the limitations associated with relying on primate animal models. Choice of doses was based on the doses used in the chronic toxicity studies. Timing and duration of dosing was also acceptable and appropriate for primate models.

Toxicokinetic parameters were not available for the reproductive toxicity studies; however, as the same doses used in the repeat dose studies were also used in embryofetal development and pre/postnatal development studies, exposure comparisons can be based on those shown in Table 1 (above). Exposure ratios based on maximum serum concentration (C_{max}) and AUC values were high (> 50).

Placental transfer was demonstrated in cynomolgus monkeys, with ixekizumab detected in fetal serum and amniotic fluid. Fetal to maternal serum ratios were in the order of 25% and 18% for 5 and 50 mg/kg dose groups, respectively, suggesting that rate of transfer may be relatively low but in view of the slow elimination half-life the likelihood of ixekizumab levels persisting in the fetal circulation is high. This may also explain the relatively high exposure of infant to ixekizumab, which showed time-dependent increases in infant to maternal ixekizumab serum ratios (0.5 to 1.2) even though the ixekizumab concentration in milk was low (< 0.2% of maternal serum level). The possibility of infant exposure from milk exists; however since measurements were made at time points at least 14 days post-ixekizumab dosing, more likely placental transfer of ixekizumab and its long elimination half-life explains the relatively high infant serum levels of ixekizumab.

A pre-fertility study examined parameters relevant to reproductive function (menstrual cycling, sperm parameters and histological assessments of reproductive organs) following weekly treatment with ixekizumab (50 mg/kg SC) for a 3 month period. For sperm count parameters there were significantly lower counts per ejaculate in the treated group in week 13 relative to vehicle controls. However, the pre-treatment values were generally low for the treated group males, the mean value in week 13 was comparable to the pre-treatment value and in view of the fact that the other parameters were comparable, and thus the difference between the treated and vehicle control group was probably not related to treatment. Minimal grade hypocellularity of the germinal epithelium noted in two treated males was considered incidental since it has been occasionally seen in untreated monkeys from their test facility, although they did not provide historical control reports to confirm this is the case. Nevertheless, there were no overt changes to reproductive organs at the gross, histological or functional level to anticipate any ixekizumab-related changes to fertility.

The embryofetal development study tested two doses of ixekizumab (5 and 50 mg/kg), administered weekly through the SC route during the period of organogenesis, with caesarean section conducted on gestation day 140. There were no maternal treatment-related changes or mortalities and fetal effects seen in the treated groups were overall comparable to the vehicle group, with no evidence of embryofetal toxicity or malformations. There appeared to be higher incidences of extranumerary ribs (13 lumbar ribs) in the treatment groups relative to controls (3/11 compared with 1/10) but as a skeletal variation the difference was small and considered incidental. As with the other chronic treatment studies, very low number of animals was found positive for anti-ixekizumab ADAs, but as mentioned above there is the likelihood that false negatives might be high because of assay interference by ixekizumab. Nevertheless, there were no treatment-related effects on embryofetal development in cynomolgus monkeys. The NOAEL was ≥ 50 mg/kg/week.

For the pre/post-natal development study pregnant females received weekly ixekizumab injections (two treatment groups of 5 and 50 mg/kg) from the period of organogenesis to parturition. Infants were observed for a further 6 months after birth. No adverse effects on maternal health were reported and rates of fetal loss were comparable between the

treated and vehicle control groups. Overall length of gestation was not affected by treatment and total number of infants delivered was similar between groups. External assessments found no overall difference in morphometric measurements (crown to rump length, chest circumference, femur length, anogenital distance) of infants from treatment groups compared with vehicle group. There were no treatment-related effects on neurobehavioural parameters (including various reflexes, general behaviour, proprioceptive positioning, muscle tone and eye reactions), ophthalmology assessments or heart rate measurements. Infant immune functions were also not affected by ixekizumab exposure, as shown by the lack of effect on NK-mediated cytolytic activity, no changes to lymphocyte subsets between treatment groups, and no effects on primary humoral responses to KLH antigen.

It is noted, however, that a number of infants from the ixekizumab-treated groups died or were euthanised within 6 days of birth. One infant from the 5 mg/kg group displayed visceral abnormalities (ani atresia/rectovaginal fistula) and was euthanised early. This was not considered treatment-related since it was an isolated observation and only occurred in the lower dose ixekizumab group. Although overall gestation length was not significantly affected by ixekizumab treatment, one infant from the low dose group and 2 from the high dose group were delivered early, which likely contributed to their failure to thrive and subsequent euthanasia. A further three infants of the high dose group experienced maternal neglect and because of their failure to thrive, these animals were also euthanised early during the observation period. Overall there were a total of 2 infant losses in the low dose group and 5 in the high dose group, with none in the vehicle group. Although all infant losses were seen only in the ixekizumab treated groups, the sponsor did not regard these to be treatment related and maintained that rates of maternal neglect were within the range of historical control data. Historical control data were not initially included in the study to confirm the validity of this claim; however the sponsor submitted this data in response to a TGA request for further information. Circumstances for infant loss were variable in historical control studies with a few being due to maternal neglect (1 or 2 out of an average of 13 infants (range 10 to 17) born per study and a total of 9 out of 161 (5.6%; range 0 to 16.7% per study)). Citing this variability, the sponsor also referred to a study in which a statistical simulation on pregnancy outcomes generated a method for determining infant loss numbers relative to maternal group size that would indicate statistical significance.[15] According to this analysis, for a group size of 18 the total number of surviving infants that would indicate a statistically significant (and treatment-related) effect is 8 or lower. In the ixekizumab postnatal development study the lowest number of live infants was 9 out of 18 for the high dose group (50 mg/kg/week), with a total of 14 infants delivered live and 3 lost due to maternal neglect. Infant losses were only seen in the treated groups, which suggested a treatment-related effect. The sponsor argued that this was consistent with historical control data in which no infant loss was noted in 3 out of 12 studies, indicating some level of randomness in the incidence of infant loss. However, relative to the historical control data, the 50 mg/kg/week treated group had infant loss incidences caused by maternal neglect above the historical control range (21.4% compared with 0 to 16.7%). There were no adverse maternal clinical signs reported that could shed light on why some females from the ixekizumab groups rejected their infants, although first-time mothers tend to have a higher chance of infant neglect. Ixekizumab treatment at 50 mg/kg/week as the cause of infant losses cannot be excluded. The NOAEL is considered to be 5 mg/kg/week. The remainder of the infants from the treatment groups did not show any other differences relative to infants born to control group monkeys. With the exception of infant losses seen only in the treatment groups, there were no other indications of an adverse effect of ixekizumab on neonatal development.

[15] Jarvis P et al., (2010) The cynomolgus monkey as a model for developmental toxicity studies: variability of pregnancy losses, statistical power estimate, and group size considerations. Birth Defects Res Pt B, 89, 175–187.

The investigative scope of pre/post-natal development studies in primates is more limited than that of rodent studies; however the overall design of the submitted study was sound for the circumstances allowed and the findings generally suggest no adverse effect on neonatal development in infant monkeys.

Pregnancy classification

The sponsor proposed Pregnancy Category B1 for ixekizumab.[16] A B1 category is not considered appropriate for this product. Although there were no treatment-related changes to immune responses or effects on lymphocytes observed in neonates exposed in utero to ixekizumab in the pre/post-natal development study, there is still a theoretical risk of compromised neonatal immunity due to its pharmacological action. Placental transfer was demonstrated to occur with ixekizumab and in view of its long elimination half-life, fetal exposure is likely to be extended. Considering the potential risk of compromised neonatal immunity based on the pharmacological action of ixekizumab, a more appropriate category is Pregnancy Category C, which is also consistent with the pregnancy category for secukinumab.[17]

Local tolerance

The sponsor did not conduct specific local tolerance studies on ixekizumab. Observations from the two repeat-dose toxicity studies indicated treatment-related injection site reactions. As discussed in the Repeat-dose toxicity section, these reactions were characterised by mostly mild to moderate swelling and scabbing with signs of local inflammation and haemorrhage. One male and female each from the 5 mg/kg group exhibited local signs of necrosis, while one high dose female (50 mg/kg) had vasculitis. At the end of the 16 week recovery period, most of the signs of local reaction had resolved and only inflammation evident in a few animals from the high dose group.

Paediatric use

The sponsor did not provide specific studies in juvenile animals and have not proposed a paediatric indication for ixekizumab.

Nonclinical summary and conclusions

- The submitted dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines (ICH S6).[3] The overall quality of the nonclinical studies was generally high. All safety-related studies were GLP compliant.
- Ixekizumab has high affinity for human IL-17A and its heteromeric form, IL-17A/F (K_D < 3 pM for both). Affinity for monkey IL-17A was high (K_D 0.8 pM) but absent for rodent IL-17A. Ixekizumab neutralised IL-17A under in vitro conditions (IC_{50} human IL-17A: 400 pM; monkey IL-17A: 700 pM). Ixekizumab did not have significant affinity for Fc γ receptors I, IIa and IIIa, or for complement component C1q. No in vivo studies specifically relevant to the indication were conducted as there are no appropriate animal models for psoriasis.

[16] TGA Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
[17] TGA Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

- Ixekizumab did not exhibit any cross-reactivity when tested against a panel of different human and monkey tissue types. Safety pharmacology parameters were assessed in the GLP repeat dose toxicity studies. No notable changes to CNS (neurological, behaviour & body temperature), electrocardiographic (heart rate, QT interval duration and corrected QT interval duration) or respiratory parameters were reported. Thus, no effect on functions of CNS, cardiovascular and respiratory systems is predicted with weekly dosing of ixekizumab.
- In monkeys ixekizumab showed slow systemic distribution (time to maximum serum concentration (T_{max}) approximately 72 h), a long elimination half-life (246 h) and high bioavailability when administered by the clinical route (SC). Serum levels were dose proportional, and repeat dosing resulted in accumulation, which likely reflected the long $t_{½}$. Human pharmacokinetic parameters were similar to those noted in cynomolgus monkeys (T_{max} approximately 4 to 7 days; $t_{½}$ approximately 13 days), showing first order absorption profile and slow clearance with steady state attained by Week 8 of fortnightly dosing (80 mg, Q2W). There were sufficient similarities to the human ixekizumab pharmacokinetic profile to indicate that monkeys serve as the appropriate animal model for toxicity testing.
- Two repeat dose toxicity studies (ixekizumab 0.5, 5, 50 mg/kg/week) by the intravenous (8 weeks) and clinical (SC, 9 months) routes were conducted in monkeys. Treatment related effects were minimal. Injection site reactions were the main effect but generally resolved by the next dosing interval. Ixekizumab treatment did not affect T-cell dependent antibody responses against antigen KLH (keyhole limpet haemocyanin), nor did it affect lymphocyte (and subsets) populations. Studies to assess adaptive immunity and susceptibility to infections were not conducted; however, clinical use identified a heightened risk of infections following ixekizumab use. Note that although low titres of anti-ixekizumab antibodies were reported for toxicity studies, the assay used was affected by ixekizumab and the possibility of false negatives should be considered. Nonetheless, high serum levels of ixekizumab were detected in the toxicity studies during the entire dosing period.
- No genotoxicity or carcinogenicity studies were conducted which is acceptable for a biotechnology–derived pharmaceutical. A literature review on the role of IL-17A neutralisation on carcinogenesis concluded that since IL-17A has a tumour promoting influence, its neutralisation by ixekizumab is not expected to generate conditions that are likely to promote tumour growth.
- Ixekizumab was found to cross the placenta (fetal:maternal serum ratio approximately 0.2) in monkeys. Milk transfer studies showed a low amount of ixekizumab excreted in the milk (< 0.2%). Ixekizumab had no effect on menstrual cycling, sperm parameters or caused histological changes to reproductive tissues in monkeys, and is not anticipated to affect fertility. There were also no effects on embryofetal development (NOAEL ≥ 50 mg/kg/week).
- Although there were no treatment-related changes to immune responses or lymphocyte populations in neonates, there is a theoretical risk of compromised neonatal immunity and the Pregnancy Category C is considered appropriate based on the pharmacological action of ixekizumab.
- A pre/postnatal development study reported no adverse effects on maternal health, no effect to length of gestation, infant morphometric measurements, neurobehavioural parameters, ophthalmology assessments, heart rate assessments, NK-mediated cytolytic activity, humoral responses to KLH antigen and lymphocyte subset populations. A number of infants from ixekizumab treated groups died or were euthanised within 6 days of birth (2 from mid-dose group; 5 from the high dose group

out of a total of 18 infants). The predominant cause was maternal neglect, and an association to ixekizumab could not be excluded.

- Primary pharmacology studies provided sufficient evidence of ixekizumab affinity and selectivity for human and monkey IL-17A, as well as neutralisation of its actions.
- Treatment-related effects associated with weekly injections were minimal and limited to injection site reactions which resolved by the next dosing interval.
- Pregnancy Category C is considered appropriate.
- Overall, there are no nonclinical objections to the registration of ixekizumab (Taltz).
- Amendments to the draft PI were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor's letter of application included a clinical rationale for the development of Taltz. The sponsor commented that psoriasis is a common, life-long and life-shortening chronic inflammatory disease characterised by prototypic red, thick and scaly plaques. The Australian prevalence of psoriasis has been reported to be in the range of 2.3% to 6.6%.[18] It has been estimated that approximately 20% to 30% of patients with psoriasis suffer from moderate to severe disease. There are 3 primary forms of treatment for psoriasis, namely, topical therapy, phototherapy and systemic therapy. Conventional systemic therapies, including methotrexate, cyclosporine and acitretin, are stated by the sponsor to rarely provide a high level response in patients with moderate to severe psoriasis. While these treatment options may be effective in some patients, most patients will need to transition to other therapies over time to achieve appropriate treatment goals. Available biologic agents, including tumour necrosis factor alpha (TNFα) antagonists (adalimumab, etanercept, infliximab) and anti-IL-12/IL-23 agents (ustekinumab), are generally superior in efficacy to conventional systemic therapies. However, the majority of patients treated with biological agents do not reach high level response of 90% improvement from baseline on the Psoriasis Area and Severity Index (PASI 90), and only a minority attain complete clearance of their psoriatic plaques (PASI 100).[19] Therefore, the sponsor states that considerable need continues to exist for new medicines for the treatment of psoriasis, with new modes of action that can provide rapid onset of effect, attain and maintain high level response, and minimise the impact of the disease, while offering an acceptable safety profile that allows chronic use.

The sponsor's clinical rationale for development of Taltz is acceptable. The Therapeutic Goods Administration (TGA) recently registered secukinumab (Cosentyx), a fully human IgG1 antibody that selectively binds to and neutralises IL-17A, for the treatment of

[18] Parisi R et al. Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-385.
[19] Schmitt J et al. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2014;170(2):274-303.

moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The ARTG start date for Cosentyx was 12 January 2015. The mode of action of Taltz and Cosentyx appear to be identical. However, Cosentyx is a first in class fully human monoclonal antibody of the IG1 type while Taltz is a humanised monoclonal antibody of the IgG4 type produced in Chinese hamster ovary cells (CHOK1SV cells).

Guidance

The sponsor states that the ixekizumab clinical development program includes scientific advice from the European Union (EU) Committee for Medicinal Products for Human Use (CHMP) obtained before completion of the Phase II studies, and complies with the CHMP 'Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis'. The relevant CHMP guidelines relating to the treatment of psoriasis (CHMP/EWP/2454/02 corr., London 18 November 2004) have been formally adopted by the TGA.

Contents of the clinical dossier

The relevant clinical information provided in the dossier is summarised below:

- Three pivotal Phase III studies evaluating efficacy and safety in adult patients for the proposed indication (Studies RHAZ, RHBA and RHBC).
- One Phase III study evaluating efficacy and safety in adult Japanese patients with plaque, pustular, and erythrodermic psoriasis (Study RHAT); one Phase II study evaluating dose-ranging and efficacy in patients with moderate to severe plaque psoriasis (Study RHAJ).
- One Phase I study evaluating pharmacokinetics (PK), multiple-doses and tolerability in patients with chronic plaque psoriasis (Study RHAG); one Phase III study evaluating PK following administration using the PFS and autoinjector (AI) device in patients with chronic plaque psoriasis (Study RHBL).
- One Population PK (PopPK) and Pharmacodynamics (PD) Report based on data from Study RHAJ; one Population and Exposure Response Report based on pooled data from Studies RHAG, RHAZ, RHAJ; one Observed Exposure Response Analyses based on pooled data from Studies RHAZ, RHBA, RHBC; one Exposure Response Analysis Plan based on pooled data from Studies RHAZ, RHBA, RHBC.
- One study comparing the PK of EU and the United States (US) Food and Drug Administration (FDA) approved etanercept in healthy subjects.
- Five studies in patients with rheumatoid arthritis (Studies RHAF, RHAK, RHAL, RHAM, RHAP).
- Two in-vitro human biomaterial reports relating to the effect if IL-17 on cytochrome P450 isoforms in human hepatocytes.
- Four in vitro bioanalytical reports relating to the validation of the enzyme-linked immunosorbent assay (ELISA) used to detect human antibodies against ixekizumab in human serum and validation of an anti-ixekizumab neutralising antibody assay.
- Literature References

Paediatric data

No paediatric data were submitted supporting the proposed indication. The sponsor indicated that it had not submitted paediatric data for the proposed indication to either

the EU or the US (FDA) regulatory authorities. The sponsor indicated that it has an agreed Paediatric Investigation Plan (PIP) with the EU. The sponsor indicated that it has a waiver from the US (FDA) to have a Paediatric Plan for patients younger than 6 years '*on the basis that the majority of paediatric patients with psoriasis experience mild-to-moderate symptoms that can be managed with topical and/or phototherapies, with fewer than 10% of paediatric patients experiencing severe manifestations of the disease. Therefore, treatment with ixekizumab would not likely offer a meaningful therapeutic benefit over risk for this age group compared with existing therapies, and is unlikely to be used in this age group*'.

Comment: The EMA waiver of 29 May 2012 (obtained from the EMA website) indicates that the PIP waiver for ixekizumab solution of injection for the 'treatment of psoriasis vulgaris' applies to the paediatric population from birth to less than 6 years on the grounds that the product does not represent a significant therapeutic benefit over existing treatments. The PIP indicates that a 'multicentre, double-blind, randomised, active- and placebo-controlled study to evaluate safety, tolerability, and efficacy of Ixekizumab in patients from 6 to less than 18 years of age with plaque psoriasis' is to be undertaken. The date given for completion of the PIP, which includes treatment of both chronic idiopathic arthritis and psoriasis vulgaris, is 'by October 2025'. The sponsor is requested to outline its plan regarding the submission of studies to the TGA investigating the efficacy and safety of ixekizumab for the treatment of children and adolescents with moderate to severe plaque psoriasis (see Section 12 of this document).

Good clinical practice

The sponsor states that studies included in the dossier have been performed in compliance with the principles of good clinical practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2 (below) gives a summary of clinical studies providing pharmacokinetic data.

Table 2. Clinical studies providing PK, PopPK, and PK/PD data in patients with moderate-severe psoriasis

Study ID	Relevant PK and PD data	Ixekizumab Dosing Regimen
RHAG Phase I	Single-dose PK; PopPK; PD (histology) SC bioavailability PK/PD (exposure-response/efficacy)	Q2W given on 3 occasions: 5, 15, 50, 150 mg SC, 15 mg IV All data were available to Week 16 N = 46 randomised; N = 37 exposed to ixekizumab; N = 9 exposed to placebo
RHAJ Phase II	PopPK Report; PK/PD (exposure response/efficacy) Immunogenicity	Part A: SC injections of 10, 25, 75, and 150 mg at 0, 2, 4, 8, 12, and 16 weeks; Final PK dataset = 114 patients/651 concentrations; Final PD dataset = 142 patients/1445 PASI scores

Study ID	Relevant PK and PD data	Ixekizumab Dosing Regimen
RHBL Phase III	Single-dose PK (up to Day 14 after 160 mg starting dose) Biopharmaceutics PFS versus AI Effect of intrinsic and extrinsic factors on PK	PFS and AI SC 160 mg starting dose, 80 mg Q2W first 12 weeks Optional safety extension 80 mg Q4W; N = 204 randomised and exposed to ixekizumab
Primary PopPK, exposure response analyses	PopPK (RHAG; RHAJ; RHAZ) Exposure-response (RHAJ to Week 16, RHAZ to Week 60) Immunogenicity (RHAJ to Week 32, RHAZ to Week 60) Safety data (RHAZ to Week 60)	RHAG, as above RHAJ (Part A): SC 10, 25, 75 and 150 mg at 0, 2, 4, 8, 12 and 16 weeks RHAZ induction = starting dose of 160 mg SC then 80 mg Q2W or Q4W for up to 12 weeks; maintenance = 80 mg SC Q4W or Q12W from Week 12 to Week 60
Secondary exposure response analyses	Observed data from studies RHAZ, RHBA, RHBC Exposure-response/efficacy/safety Effect of immunogenicity on PK RHAZ data through Week 60; RHBA data through Week 36 in all patients and Week 60 in a subset; RHBC data through Week 12	RHAZ, as above RHBA, induction = starting dose 160 SC, then 80 mg SC Q2W or Q4W up to Week 12; maintenance = 80 mg SC Q4W or Q12W from Week 12 up to Week 60 RHBC, induction = starting dose 160 mg SC then 80 mg SC Q2W or Q4W up to Week 12
RHAT	Descriptive PK data up to Week 52 in Japanese patients	Induction = starting dose 160 mg SC then 80 mg SC up to Week 12; Maintenance = 80 mg SC Q4W from Week 12 to Week 52 N = 91 entered study and exposed to ixekizumab

The key PK and exposure-response data for ixekizumab presented in the submission were derived from the Primary PopPK and Exposure-Response Analyses based on data from three studies in 1399 patients with psoriasis (Study RHAG (Phase I); Study RHAJ (Phase II); and Study RHAZ (Phase III)). These analyses were undertaken to characterise the PK of ixekizumab, to model the relationship between ixekizumab exposure and both efficacy and safety outcomes, and to evaluate the effect of potential covariates on the PK of ixekizumab and on the exposure-efficacy models. Exposure-response analyses were performed by correlating efficacy with model-predicted exposure estimates at Week 12 (end of the induction dosing period and time of the primary efficacy endpoint assessment) and at Week 60 (end of the maintenance dosing period). In addition, a time course model over the 60 week duration was developed for sPGA scores. Data from these analyses were used to support the proposed commercial dosing regimen.

Secondary Exposure-Response Analyses were conducted by using observed concentration data (trough concentrations) from the three pivotal Phase III studies (Studies RHAZ, RHBA, and RHBC). Analyses were performed at Week 12 (end of the induction dosing period and time of the primary efficacy endpoint assessment) and at Week 60 (end of the maintenance dosing period). Data from the Secondary Exposure-Response Analyses were used to confirm the results of the Primary Exposure-Response Analyses.

The approach to the evaluation of the PK data presented in this Clinical Evaluation Report (CER) has been, firstly, to individually review Studies RHAG, RHAJ, RHBL, and RHAT, and the Primary PK and Exposure-Response Analyses (RHAZ, RHBA, RHBC) and, secondly, to summarise the PK of ixekizumab based on the data from the studies.

In addition to the clinical studies providing PK and/or PD data, the submission also included 4 in vitro reports detailing the bioanalytical methods and analytical methods used to detect antibodies against ixekizumab in human serum, and 2 in vitro human biomaterial reports relating to the effects of IL-17 on hepatic cytochrome p450 (CYP) isoforms. The evaluation of these in vitro reports is primarily a matter for the quality, biological and non-clinical evaluators. However, the data from the 2 in vitro human biomaterial reports have been briefly presented in the text of this CER relating to drug-drug interactions.

Evaluator's conclusions on pharmacokinetics

The PK of ixekizumab administered by SC injection in patients with moderate to severe plaque psoriasis has been reasonably well characterised. The Primary Population PK and Exposure-Response Analyses were performed using data from 3 studies (Phase I, Study RHAG; Phase II, Study RHAJ; and Phase III, Study RHAZ) in 1399 patients with psoriasis.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included exposure-response data from the Primary PopPK and Exposure Response Analyses (data from Studies RHAG, RHAJ, RHAZ) supported by data from the Secondary Exposure-Response Analyses (data from Studies RHAZ, RHBA, and RHBC). In addition to efficacy and safety exposure-response analyses for both efficacy and safety endpoints, both of the primary and secondary analyses also included an assessment of the relationship between ixekizumab exposure and immunogenicity.

Evaluator's conclusions on pharmacodynamics

Analyses of exposure-response relationships (efficacy and safety)

The PD profile of ixekizumab was primarily explored through exposure-response (PK/PD) relationships relating to efficacy, safety and immunogenicity. The goal of the analyses was to determine the optimal benefit-risk balance for the registration and commercialisation of ixekizumab for the treatment of patients with moderate to severe plaque psoriasis. The exposure-response relationships were described in the Primary Exposure-Response Analyses Report (Primary PopPK and Exposure-Response Analyses) and Secondary Exposure-Response Analyses Report (Secondary Exposure-Response Analyses).

The Primary Exposure-Response Analyses were performed using data from three studies (Study RHAG (Phase I); Study RHAJ (Phase II) and Study RHAZ (Phase III)) in 1399 patients. In the primary analyses, modelling used trough concentrations at steady state ($C_{trough.ss}$) estimates derived from the PopPK model as the exposure parameter and observed parameters as the outcome parameters (efficacy, safety and immunogenicity). The Secondary Exposure-Response Analyses were performed using data from three Phase III studies (Studies RHAZ, RHBA and RHBA). In the secondary analyses, modelling used observed $C_{trough.ss}$ levels as the exposure parameter and observed outcomes parameters as the response parameters (efficacy, safety and immunogenicity). The methods used in the Secondary Exposure-Response Analyses were largely based on the methods used in the

Primary Exposure-Response Analyses, but data used to derive the exposure estimates for the primary analyses were more extensive than for the secondary analyses.

The exposure-response data derived from the Secondary Exposure-Response Analyses are considered by the sponsor to provide supportive data for the Primary Exposure-Response Analyses.

The exposure-response relationships (efficacy and safety) discussed below relate primarily to results reported in the Primary Exposure-Response Analyses. The exposure-response relationships (efficacy and safety) reported in the Secondary Exposure-Response Analyses were consistent with those reported in the Primary Exposure-Response Analyses and support the conclusions derived from the primary analyses.

The overall objective of the Primary Exposure-Response Analyses was to correlate steady-state exposure of ixekizumab to key efficacy outcomes in the Phase II Study RHAJ and the Phase III Study RHAZ. Efficacy data from the Phase I Study RHAG were not included in the primary analyses due to the short duration of the study and absence of relevant covariate data. The exposure-response model (efficacy) developed for the primary exposure-response analyses explored the relationship between PopPK model-predicted $C_{trough.ss}$ estimates and measurements of efficacy (Static Physician's Global Assessment (sPGA) and PASI scores). Single-time points measurements (Week 12 and Week 60) were assessed for sPGA and PASI, while time course modelling was also used to assess the sPGA.

The primary efficacy analyses in the Phase III clinical studies were sPGA (score of 0 or 1) and PASI 75 outcomes at Week 12. In the Primary Efficacy-Response Analyses, the response rates predicted by the exposure-response models were higher for the 80 mg Q2W regimen compared to the 80 mg Q4W regimen for both the sPGA (score of 0 or 1) model (87% versus 83%, respectively) and the PASI 75 model (94% versus 90%, respectively). The model predicted estimates were similar to the observed data for the two efficacy outcomes. For the efficacy endpoints associated with the higher measures of response (PGA (0), PASI 90 and PASI 100) the predicted response rates were greater with the 80 mg Q2W regimen compared to the 80 mg Q4W regimen. Overall, the results indicate that the more frequent induction dosing regimen of 80 mg Q2W provides additional benefits compared to the 80 mg Q2W regimen, with increases in the predicted percentage of responders being in the range of 4% to 7%. The higher range of predicted concentration exposures for patients in the 80 mg Q2W group resulted in the majority of patients being on or close to the plateau of the exposure response curve, while the range of predicted concentration exposures for patients in the 80 mg Q4W group was lower and encompassed more of the slope of the curve resulting in fewer patients predicted to achieve a response.

When the Week 12 data were evaluated by body weight (< 100 kg versus ≥ 100 kg), lighter weight patients had higher predicted response rates compared to heavier weight patients, particularly for the higher clinical response measures. A higher percentage of patients in each weight group consistently achieved increased predicted response rates of up to 12% for the 80 mg Q2W dosing regimen compared to the 80 mg Q4W dosing regimen across all sPGA and PASI endpoints.

In the Primary Exposure-Response Analyses, the Week 60 (end of the maintenance dosing period) sPGA time course model demonstrated sustainability of response. Exposures in patients on the 80 mg Q4W dosing regimen at Week 60 were associated with a 25% to 27% higher predicted sPGA (score of 0 or 1) and sPGA (0) response rate than exposures in patients on the 80 mg Q12W dosing regimen. In the sPGA time course model, the 80 mg Q2W dosing regimen in the induction dosing period was projected to achieve an 80% response rate by Week 12, whereas the 80 mg Q4W dosing regimen in the induction period was projected to achieve an 80% response rate by Week 19 (demonstrating faster onset of response with the 80 mg Q2W induction dosing regimen).

In the Primary ER Analyses, in the Week 12 sPGA models significant patient predictors (covariates) of exposure were palmoplantar psoriasis and body weight. Patients with palmoplantar psoriasis had a 13% lower maximum possible effect (E_{max}) compared to patients with no palmoplantar involvement, resulting in a reduced probability of achieving a sPGA (score of 0 or 1) score at Week 12. Heavier patients had a lower E_{max} and thus a lower probability of achieving a sPGA (score of 0 or 1) score at Week 12 compared to lighter patients. The effect of weight was in addition to the effect of weight previously identified in the PopPK model, where an increase in weight was associated with a decrease in exposure. In the Week 60 endpoint analyses (Primary Exposure-Response Analyses), no covariates significantly affected the sPGA. In the time course model for sPGA (Primary Exposure-Response Analyses), previous use of a biologic agent increased the EC_{50} resulting in a decreased probability of achieving sPGA (score of 0 or 1) compared to no previous use of a biologic agent, and palmoplantar psoriasis reduced the drug effect on sPGA (score of 0 or 1) by 1.9% compared to no palmoplantar psoriasis.

In the Week 12 PASI 75 model (Primary Exposure-Response Analyses), no covariates were found to significantly affect exposure. In the Week 90 model (Primary Exposure-Response Analyses), patients with higher baseline PASI scores had higher E_{max} levels and an increased probability of achieving this endpoint, while patients previously treated with biologic agents had higher EC_{50} values and a reduced probability of achieving this endpoint. In the Week 12 PASI 90 and PASI 100 models (Primary Exposure-Response Analyses), both patients with palmoplantar psoriasis and patients with higher body weight had lower E_{max} values compared to both patients without palmoplantar psoriasis and patients with lower body weight, resulting in reduced probabilities of achieving these endpoints in both patients with palmoplantar psoriasis and higher body weight. In the Week 60 endpoint analyses (Primary Exposure-Response Analyses), no covariates significantly affected the PASI scores (75, 90 or 100).

In the Primary Exposure-Response Analyses, exposure-response relationships were explored for a number of safety outcomes of special interest based on data from the Phase III Study RHAZ. The only safety outcomes of special interest that showed exposure-response relationships were injection site reactions, with higher incidences being observed at higher ixekizumab concentrations in both the induction and maintenance periods. In the Secondary Exposure-Response Analyses, the same safety outcomes of special interest as those assessed in the Primary Exposure-Response Analyses plus additional outcomes were explored in the integrated data from the three Phase III Studies RHAZ, RHBA and RHBC. Consistent with the Primary Exposure-Response Analyses, the secondary analysis showed the same exposure-response relationship for injection site reactions. In addition, in the Secondary Exposure-Response Analyses the incidence of neutropaenia Grade 2 and the incidence of *Candida* infections both increased with exposure, but only in the induction period.

Immunogenicity

In the induction dosing period, 11.2% (256/2293) of the evaluable ixekizumab-treated patients were treatment-emergent ADA positive at Week 12 and 1.0% (24/2293) were neutralising antibody (NAb) positive. In the treatment-emergent ADA positive patients, 61.3% (157/256) had low ADA titres (< 1:160). More frequent administration of ixekizumab was associated with lower rates of immunogenicity, with the incidence of treatment-emergent ADA positive patients being 9.0% in the 80 mg Q2W group and 13.4% in the 80 mg Q4W group.

In the maintenance dosing period, 21.4% (141/659) of patients were treatment-emergent ADA positive and 0.8% (5/659) were NAb positive in the efficacy evaluable patients who were ixekizumab-treated sPGA (score of 0 or 1) responders during the induction period and remained on ixekizumab through to Week 60. Of the treatment-emergent ADA positive patients, 90.8% (128/141) had low ADA titres (< 1:160). In patients who were

sPGA (score of 0 or 1) responders to ixekizumab at Week 12 and re-randomised in the maintenance period, the incidence of treatment-emergent ADA positive patients at Week 60 was 17.3% in those re-randomised to 80 mg Q4W, 25.5% in those re-randomised to 80 mg Q12W and 24.2% in those re-randomised to placebo.

In patients initially randomised to placebo in the induction period who were non-responders at Week 12 and subsequently received ixekizumab 80 mg Q4W during the maintenance period, the incidence of treatment-emergent ADA positive patients was 13.6% (74/543) and the incidence of NAb positive patients was 2.4% (13/543).

In ixekizumab-treated patients, in the pooled data from the three pivotal studies (Studies RHAZ, RHBA and RHBC) the proportion of patients achieving an sPGA (score of 0 or 1) response at Week 12 was lower in treatment-emergent ADA positive patients compared to treatment-emergent negative patients (65.6% (168/256) versus 81.1% (1652/2037)), as was the proportion of patients achieving a PASI 75 (72.7% (186/256) versus 87.9% (1791/2037)). These results are considered to be clinically meaningful and suggest that consideration should be given to testing ixekizumab ADA status in patients not responding to the drug during the induction dosing period. In general, patients who were NAb positive had reduced ixekizumab concentrations and responded poorly or not at all to treatment with ixekizumab. In the maintenance period, the incidence of patients achieving or maintaining an sPGA (score of 0 or 1) or PASI 75 was similar in the treatment-emergent ADA positive and treatment-emergent ADA negative groups. The safety profile of ixekizumab was similar in treatment-emergent ADA positive and treatment-emergent ADA negative patients.

Skin histopathology

An exploratory evaluation of the impact of ixekizumab on skin histopathology was conducted during the Phase I study RHAG. At all dose levels tested (15 mg IV and 5, 15, 50, and 150 mg SC), there was a dose-related trend toward decreased epidermal thickness, number of patients with K16+ cells, numbers of CD3+ cells, and CD11c+ cells from baseline to Day 43, reflecting disease improvement. Significant reductions in epidermal thickness, CD3+ cells, and CD11c+ cells from baseline were most persistent at the 15 mg IV dose level and at the 50 mg SC and 150 mg SC dose levels.

Dosage selection for the pivotal studies

The results from the Phase I dose range Study RHAG (5 to 150 mg; 3 doses Q2W) informed the dose-ranging selection for the Phase II dose-ranging Study RHAJ. In view of the 150 mg dose in Study RHAJ being associated with higher responses by Week 2 compared to the lower doses studied (10 mg, 25 mg, and 75 mg), a 160 mg starting dose (two 80 mg injections) was selected for evaluation in the Phase III studies to allow for steady state to be achieved earlier and to obtain a more rapid onset of clinical response. Simulations of dosing regimens using the PopPK model developed from the Study RHAJ data showed that 80 mg Q4W and 80 mg Q2W regimens with a 160 mg starting dose reached steady-state ixekizumab concentrations earlier than regimens without a 160 mg starting dose. Based on Phase I and II data, the sponsor considered that once an initial response was achieved during the induction dosing period, less frequent dosing would be needed to maintain that response during longer-term therapy. Therefore, an 80 mg Q4W regimen was chosen to determine if the response achieved at Week 12 could be maintained with this regimen during the maintenance dosing period (Weeks 12 to 60). In addition, to determine whether even less frequent dosing would maintain the response an 80 mg Q12W dose was also evaluated. These 2 dosing regimens (80 mg Q4W and 80 mg Q12W) were expected to result in distinct exposures, allowing for adequate comparison of the 2 dosing frequencies for maintenance therapy. It was predicted that the 80 mg Q12W dosing regimen would

provide exposures similar to the 25 mg Q4W dosing regimen evaluated in the Phase II study, RHAJ.

In Study RHAJ, no clinically significant dose-related safety concerns had been noted in patients with moderate to severe plaque psoriasis treated with multiple ixekizumab doses up to 150 mg at Weeks 0, 2, 4, 8, 12 and 16. Additionally, there had been no major dose-related safety concerns detected up to the maximum dose of 2 mg/kg IV Q2W for 10 weeks (Study RHAF) and 180 mg SC Q2W for 12 weeks (Study RHAK) in patients with rheumatoid arthritis. The 2 mg/kg IV dose used in Study RHAF in a 100 kg patient is approximately equivalent to a 370 mg SC dose (bioavailability of SC administration is 54%). In addition, the sponsor reported an approximate 113 fold margin of safety for the maximum anticipated steady state exposure at 80 mg Q2W relative to the lowest observable adverse event level (LOAEL) exposure in the 9 month monkey toxicology study. Therefore, based on the totality of the data, neither the proposed induction treatment regimens of 80 mg Q2W and 80 mg Q4W nor the maintenance treatment regimens of 80 mg Q4W and 80 mg Q12W raised significant safety concerns.

Comment: The sponsor's rationale for selecting the ixekizumab doses used in the pivotal Phase III studies is considered to be acceptable.

Efficacy

Studies providing efficacy data

The submission included 3 pivotal, Phase III clinical efficacy and safety studies (Studies RHAZ, RHBA, and RHBC); see Table 3, below. Each of the three pivotal studies included a placebo control group, while two of the studies (Studies RHBA and RHBC) also included an etanercept active control group. In each of the three studies, the primary efficacy analysis was based on the Week 12 data (that is, at the end of the induction dosing period), while Studies RHAZ and RHBA also included and efficacy analysis based on the Week 60 data (that is, at the end of the maintenance dosing period). In addition to the efficacy data from each of the three individual pivotal Phase III studies, the submission also included an integrated efficacy assessment for the induction and maintenance dosing periods based on pooled data from the pivotal Phase III studies. The individual efficacy data from each of the three pivotal Phase III studies and the integrated analysis of efficacy based on pooled data have been evaluated in this clinical evaluation.

Comment: The three pivotal studies are referred to in the PI as UNCOVER-1 (RHAZ), UNCOVER-2 (RHBA) and UNCOVER-3 (RHBC). The 12-week data from UNCOVER-2 (RHBA) and UNCOVER-3 (RHBC) comparing ixekizumab to etanercept and placebo have been published (*Griffiths et al., 2015*).

It was noted that the Statistical Analysis Plans (SAPs) for the three pivotal studies stated that additional Australian specific efficacy analyses will be conducted to meet Pharmaceutical Benefits Advisory Committee (PBAC) criteria. Specifically, the sPGA (0,1), sPGA (0), PASI 75, PASI 90 and PASI 100 at Week 12 (NRI) and Week 60 (NRI) will be analysed using PBAC induction dosing period and maintenance dosing period populations. The PBAC induction dosing period population is a subset of the ITT population and is defined as all randomised patients with a PASI score > 15 at baseline. The PBAC maintenance dosing period population is a subset of the maintenance dosing period primary population and is defined as patients with a PASI score > 15 at baseline.

Integrated efficacy analysis

Introduction

The submission included a pre-specified integrated efficacy analysis (IEA) including:

- placebo-controlled data from three Phase III psoriasis studies (Studies RHAZ, RHBA, RHBC) from screening through Week 12 (the primary psoriasis placebo-controlled integrated analysis set);
- placebo- and active-controlled data from two Phase III psoriasis studies (Studies RHBA and RHBC) from screening through Week 12 (secondary integrated analysis set); and
- data from maintenance dosing periods from two Phase III studies (Studies RHAZ and RHBA) for patients randomised to ixekizumab at Week 0 who met sPGA (score of 0 or 1) response criteria at Week 12 (NRI) and were re-randomised to maintenance treatment from Week 12 to Week 60. The maintenance dosing period starts at the first injection of study treatment at Week 12 and ends prior to the first injection of study treatment at Week 60 or the date of the early termination visit or the date of the visit where the patient meets relapse criteria (that is, sPGA ≥ 3).

The results of the IEA were presented in a Summary of Clinical Efficacy.

Table 3. Design features of the three, pivotal Phase III studies

	RHAZ N=1296 Placebo-Controlled, Efficacy and Safety Study with LTE	**RHBA N=1224** Active Comparator (Etanercept) and Placebo-Controlled, Efficacy and Safety Study with LTE	**RHBC N=1346** Active Comparator (Etanercept) and Placebo-Controlled, Efficacy and Safety Study with LTE
Population	Adults with moderate-to-severe plaque psoriasis; candidates for phototherapy or systemic therapy		
Disease Activity	BSA ≥10%; PASI ≥12; sPGA ≥3		
Induction Treatment Groups (Weeks 0-12)	160-mg starting dose, then 80 mg Q2W 160-mg starting dose, then 80 mg Q4W Placebo (Randomization ratio: 1:1:1)	160-mg starting dose, then 80 mg Q2W 160-mg starting dose, then 80 mg Q4W Placebo Comparator (etanercept) (Randomization ratio: 2:2:1:2)	
Maintenance Treatment Groups: Maintenance Dosing Period Primary Population[a] (Weeks 12-60)	80 mg Q4W 80 mg Q12W Placebo (Randomization ratio: 1:1:1, re-treatment with 80 mg Q4W upon relapse)		NA
Maintenance Treatment Groups: Maintenance Dosing Period Secondary Population[b] (Weeks 12-60)	80 mg Q4W (nonresponders to any treatment at Week 12)[c] Placebo (responders to placebo or etanercept at Week 12, re-treatment with 80mg Q4W upon relapse)		NA
Treatment Groups (LTE Phase)	80 mg Q4W 80 mg Q12W Placebo		80 mg Q4W
Co-Primary Endpoints	PASI 75 and sPGA (0,1) at 12 weeks		
Duration Blinded	60 weeks		12 weeks
Efficacy/Health Outcome Data Included in This Submission[d]	All data up to 60 weeks	Data up to 60 weeks (based on an interim analysis performed when the final patient completed 36 weeks)	All data up to 12 weeks

Notes: a) Ixekizumab-treated patients who responded to treatment, that is, who achieved sPGA (score of 0 or 1), during the period; b) Patients randomised to either placebo or etanercept at Week 0 or ixekizumab-treated patients who did not respond to therapy (achieve sPGA 0/1) during the induction period; c) etanercept non-responders received placebo for a 4-week washout period, before commencing treatment with ixekizumab 80 mg Q4W at Week 16; d) For the maintenance period, efficacy data reported are from patients who completed Week 60, discontinued prior to Week 60, or relapsed prior to Week 60.

Evaluator's conclusions on efficacy

- The proposed treatment regimen is ixekizumab administered by SC injection at a starting dose of 160 mg followed by 80 mg Q2W (that is, Weeks 2, 4, 6, 8, 10 and 12) and then 80 mg Q4W (maintenance treatment every 4 weeks). This treatment regimen was assessed in the three Pivotal Phase III studies (Studies RHAZ, RHBA and RHBC), and was compared with ixekizumab induction/maintenance regimens of 80 mg Q2W/Q12W, 80 mg Q4W/Q4W, and 80 mg Q4W/Q12W, with each regimen being initiated with a starting dose of 160 mg.
- The submitted data demonstrated that treatment with ixekizumab 80 mg Q2W in the induction dosing period (Weeks 0 to 12) was significantly more efficacious than both placebo and etanercept. In addition, in the induction dosing period the ixekizumab 80 mg Q2W treatment regimen was consistently more efficacious than the ixekizumab 80 mg Q4W treatment regimen. The submitted data also showed that ixekizumab 80 mg Q4W in the maintenance dosing period (Weeks 12 to 60) was significantly more efficacious than placebo. In addition, the submitted data showed that ixekizumab 80 mg Q4W was more efficacious in the maintenance dosing period (Weeks 12 to 60) than ixekizumab 80 mg Q12W, and that the induction/maintenance regimen of ixekizumab 80 mg Q2W/ Q4W was more efficacious than ixekizumab 80 mg Q2W/Q12W. Furthermore, data showed that at Week 60 the induction/maintenance regimen of ixekizumab 80 mg Q2W/Q4W was more efficacious than the induction/maintenance regimen of ixekizumab 80 mg Q4W/Q4W.
- The efficacy of ixekizumab has been satisfactorily demonstrated in the three, pivotal Phase III studies in adult patients with moderate-to-severe plaque psoriasis (Studies RHAZ, RHBA and RHBC). In each of the three studies, all patients were required to be candidates for systemic therapy or phototherapy, with a ≥ 6-month history of plaque psoriasis, a sPGA score of ≥ 3, a PASI 75 score of ≥ 12 and percentage BSA involvement of ≥ 10% at baseline and screening. Patients were excluded if they had pustular, erythrodermic, and/or guttate forms of psoriasis.
- In pivotal studies, all primary and major secondary efficacy endpoints were met in the induction dosing period (Weeks 0 to 12) and the maintenance dosing period (Weeks 12 to 60). The statistical methods used to analyse the primary and major secondary efficacy endpoints were extensively described in the submission and are considered appropriate. In order to adjust for the multiple pairwise comparisons undertaken in the studies to assess efficacy, a gatekeeping strategy was used to control the family-wise type 1 error rate at a 2-sided alpha level of 0.05. Missing data were handled using appropriate imputation methods.
- In the pivotal studies, the co-primary efficacy endpoints were the proportion of patients achieving a sPGA (score of 0 or 1) and PASI 75 at Week 12. Both of these endpoints are considered to be clinically appropriate for the assessment of treatment of patients with moderate to severe plaque psoriasis. In each of the pivotal studies, the same ixekizumab SC treatment regimens were used in the induction dosing period (Weeks 0 to 12), consisting of a starting dose of 160 mg followed by 80 mg Q2W or 80 mg Q4W. In each of the pivotal studies, the proportion of patients achieving each of the co-primary efficacy endpoints was significantly greater ($p < 0.001$) in the two ixekizumab groups (80 mg Q2W, 80 mg Q4W) than in the placebo group.
- In each of the pivotal studies, the proportion of patients with a co-primary efficacy response at Week 12 was numerically higher in patients treated with ixekizumab 80 mg Q2W compared to ixekizumab 80 mg Q4W. In two of the three pivotal studies, the higher response rates for the co-primary efficacy endpoints in the ixekizumab Q2W group were nominally statistically significant compared to ixekizumab Q4W ($p \leq 0.05$, ad hoc comparison, Studies RHAZ and RHBA). In the primary psoriasis placebo-

controlled set (Studies RHAZ, RHBA and RHBC), the pre-specified integrated analysis showed that the Week 12 response rates for sPGA (score of 0 or 1), PASI 75, PASI 90, sPGA (0) and PASI 100 were statistically significantly greater in the ixekizumab Q2W group compared to the ixekizumab Q4W group ($p \leq 0.05$).

- In the pre-specified integrated analysis (Studies RHAZ, RHBA and RHBC), both ixekizumab treatment regimens (80 mg Q2W, 80 mg Q4W) showed significantly greater response rates than placebo for both co-primary efficacy endpoints as early as Week 1 (first visit) of the 12-week induction dosing period, and the difference in response rates increased throughout the remaining induction dosing period (primary psoriasis placebo-controlled integrated analysis set, ITT population).
- In the two pivotal studies that included an etanercept group in the 12-week induction dosing period (Studies RHBA and RHBC), the proportion of patients achieving each of the co-primary efficacy endpoints was significantly greater ($p < 0.001$) in the two ixekizumab groups (80 mg Q2W, 80 mg Q4W) compared to the etanercept group. In addition, pre-specified non-inferiority testing using fixed-margin and retention rate approaches showed that both ixekizumab treatment regimens were non-inferior (and superior) to etanercept, based on Week 12 co-primary endpoint response rates.
- In Studies RHAZ and RHBA, patients responding to treatment with ixekizumab (Q2W or Q4W) in the induction period (sPGA (score of 0 or 1); PASI 75) and re-randomised to continued treatment with ixekizumab (80 mg Q4W or Q12W) at Week 12 were more likely to maintain response at Week 60 compared to patients who had been re-randomised to placebo. In the maintenance dosing period, the sPGA (score of 0 or 1) and PASI 75 response rates at Week 60 were almost 2-fold higher in patients treated with ixekizumab 80 mg Q4W compared to ixekizumab 80 mg Q12W in both Studies RHAZ and RHBA. In both Studies RHAZ and RHBA, responders to ixekizumab 80 mg Q2W in the induction dosing period who were re-randomised at Week 12 to ixekizumab 80 mg Q4W in the maintenance dosing period (Q2W/Q4W) had numerically higher sPGA (score of 0 or 1) and PASI 75 response rates at Week 60 compared to responders to ixekizumab 80 mg Q4W in the induction dosing period who were re-randomised at Week 12 to ixekizumab 80 mg Q4W regimen in the maintenance dosing period (Q4W/Q4W), indicating that the more frequent induction regimen (Q2W) was associated with improved long-term patient outcomes.
- In both Studies RHAZ and RHBA, high-level sPGA (0), PASI 90 and PASI 100 endpoints at Week 60 were observed significantly more frequently with both ixekizumab maintenance regimens (80 mg Q12W and 80 mg Q4W) compared to placebo ($p < 0.001$), with the greatest response rates for each of the high-level outcomes being observed with the Q2W/Q4W regimen. Other secondary efficacy endpoints of itch NRS, DLQI, and NAPSI significantly favoured both ixekizumab maintenance regimens (80 mg Q12W and 80 mg Q4W) compared to placebo ($p < 0.001$), with the greatest response rates for each of the high-level outcomes being observed with the Q2W/Q4W regimen.
- The large number of subgroup analyses in the induction and maintenance dosing periods consistently showed that ixekizumab was superior to placebo based on sPGA (score of 0 or 1) and PASI 75.

Safety

Studies providing safety data

The submitted data included an Integrated Summary of clinical Safety (ISS). The safety data in the ISS were derived from 11 clinical trials (7 in patients with psoriasis and 4 in

patients with rheumatoid arthritis). The ISS was conducted in accordance with the methods detailed in the pre-specified program safety analysis plan (PSAP). A copy of this plan was included in the submitted data.

Of the 4736 patients included in the ISS dataset, the majority (88.8%, n = 4204) were from 7 psoriasis studies, and the remainder (11.2%, n = 532) were from 4 rheumatoid arthritis studies. The sponsor commented that the safety conclusions derived from the ISS were primarily driven by the three pivotal studies in patients with moderate to severe psoriasis, comprising the induction dosing period primary placebo-controlled analysis set (Studies RHAZ, RHBA and RHBC) and the maintenance dosing period maintenance analysis set (Studies RHAZ and RHBC).

In this clinical evaluation, the evaluation of the safety of ixekizumab for the proposed indication is based on the data included in the ISS, in particular on the data from the three pivotal Phase III studies (Studies RHAZ, RHBA and RHBC). The safety data included in the ISS is considered to be an accurate representation of the relevant data from the individual studies contributing to the integrated analysis sets.

The integrated safety data from the 4 studies assessing ixekizumab for the treatment of rheumatoid arthritis have been examined, but have not been considered in detail in this CER. The sponsor stated that data from the psoriasis and rheumatoid arthritis studies were not combined because the 2 populations were sufficiently different to justify separate safety profile characterisations. The sponsor's decision to assess the safety profiles of the two diseases separately is considered to be appropriate.

Patient exposure

In total, 4736 patients have been studied in 11 clinical trials of psoriasis and rheumatoid arthritis (7 psoriasis and 4 rheumatoid arthritis (RA) studies). In the 7 psoriasis studies, 4204 patients have been exposed to ixekizumab (as of 15 September 2014), representing 4729.7 patients-years of exposure, with over 2190 patients treated with any dose regimen for at least 1 year. The exposure data for patients with psoriasis meets the TGA adopted guideline (CPMP/ICH/375/95) relating to the extent of population exposure required to assess clinical safety for non-life threatening conditions (that is, > 1500 patients exposed in total, 300 to 600 patients exposed for 6 months, and > 100 patients exposed for 1 year). In the 4 RA studies, 532 patients have been exposed to ixekizumab representing 533.5 patient-years of exposure. Exposure in the ISS data sets are summarised below in Table 4.

Table 4. Study drug exposure in the ISS datasets

Treatment Period	Integrated Analysis Dataset	Treatment	No. of Patients[a]	Median [min, max] Patient-Days of Exposure	Patient-Years
Induction Dosing Period	Primary Ps Placebo Controlled	Placebo	791	85.0 (8, 183)	180.0
		Ixe 80 mg Q4W	1161	85.0 (1, 197)	265.9
		Ixe 80 mg Q2W	1167	85.0 (8, 116)	268.6
		Total Ixe 80 mg	2328	85.0 (1, 197)	534.5
	Ps Placebo and Active Controlled	Placebo	360	85.0 (11, 146)	83.2
		Ixe 80 mg Q4W	729	85.0 (1, 197)	167.6
		Ixe 80 mg Q2W	734	85.0 (8, 116)	168.9
		Total Ixe 80 mg	1463	85.0 (1, 197)	336.5
		Etanercept	739	85.0 (7, 217)	169.2
Maintenance Dosing Period	Ps Maintenance [b]	Placebo	402	152.0 (20, 423)	184.1
		Ixe 80 mg Q12W	408	267.0 (1, 361)	269.5
		Ixe 80 mg Q4W	416	336.0 (24, 370)	326.7
		Total Ixe 80 mg	824	316.0 (1, 370)	596.2
All Treatment Periods	All Ps Ixekizumab Exposures	Total Pooled Ixe	4204	366.0 (1, 1591)	4729.7
	All RA Ixekizumab Exposures	Total Pooled Ixe	532	418.0 (1, 599)	533.5

Notes: a) Note that the exposure numbers for the induction period, maintenance period, and overall categories at any time (that is, all psoriasis (Ps) and all RA) cannot be summed across categories; b) 1226 patients who were responders to treatment during the Induction Period (as measured by sPGA (score of 0 or 1) at Week 12 and were then re-randomised in the Maintenance Period were included in the Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA).

The ixekizumab exposure data based on the number of exposure days for the 4 datasets including patients treated with psoriasis are summarised below in Table 5. The table does not include data for the comparator placebo or etanercept treatment groups. However, the relevant exposure data for placebo were:

- 791 patients in the primary psoriasis placebo controlled analysis set (12 weeks) representing 180.0 patient-years of exposure;
- 360 patients in psoriasis placebo and active controlled analysis set (12 weeks), representing 83.2 patient-years of exposure; and
- 402 patients in the psoriasis maintenance analysis set (48 weeks) representing 184.1 patient-years of exposure.

The relevant exposure data for etanercept were 739 patients in the psoriasis placebo and active controlled analysis set (12 weeks), representing 739 patient-years of exposure.

Table 5. Ixekizumab exposure data from the four analysis sets in patients with psoriasis

Analysis Set	Primary Ps Placebo-Controlled (12 Weeks)			Ps Placebo- and Active-Controlled (12 Weeks)			Ps Maintenance (48 Weeks)			All Ps IXE Exposures				
Studies Included	RHAZ, RHBA, RHBC			RHBA, RHBC			RHAZ, RHBA			RHAZ, RHBA, RHBC, RHAT, RHBL, RHAJ, RHAG				
Treatment Group	IXE 80 Q4W	IXE 80 Q2W	Total IXE	IXE 80 Q4W	IXE 80 Q2W	Total IXE	IXE 80 Q12W	IXE 80 Q4W	Total IXE	IXE 80 Q4W[a]	IXE 80 Q4W/ Q4W[b]	IXE 80 Q2W/ Q4W[c]	IXE 80 Q2W or Q4W[d]	IXE (All Doses Pooled)
N	1161	1167	2328	729	734	1463	408	416	824	3798	729	1010	4030	4204
Days, n														
≥84	1019	1027	2046	655	656	1311								
≥90							349	392	741	3493	712	974	3569	3972
≥183							275	364	639	2964	684	944	3151	3536
≥365							0	1	1	1574	391	578	1845	2190
≥548										695	189	193	809	1070
≥730										147	64	67	202	378
Patient-years[e]	265.9	268.6	534.5	167.6	168.9	336.5	269.5	326.7	596.2	3616.4	836.7	1094.7	3950.9	4729.7

Note: Grey shading indicates that a value was not calculated or not applicable; a) data from patients who received at least one dose of ixekizumab 80 mg Q4W in Studies RHAT, RHAZ, RHBA, RHBC and RHBL; b) data from patients who received 80 mg Q4W/Q4W treatment in Studies RHAZ, RHBA and RHBC; c) data from patients who received 80 mg Q2W/Q4W treatment in Studies RHAT, RHAZ, RHBA, RHBC and RHBL; d) data from patients who started 80 mg Q2W or Q4W and either switched or remained on 80 mg Q4W in Studies RHAT, RHAZ, RHBA, RHBC and RHBL; e) total patient-years are calculated as sum of duration of exposure in days (for all patients in treatment group)/365.25.

Safety issues with the potential for major regulatory impact

Special safety topics and adverse events of special interest were addressed individually by the clinical evaluator. These included infections, cytopaenias, allergic reactions and hypersensitivities, injection site reactions, cerebro-cardiovascular events, malignancies, hepatic adverse events, depression and suicide or self-injury, autoimmune disease (including Crohn's disease and ulcerative colitis) and pneumocystis pneumonia and interstitial lung disease.

Postmarketing data

There was no post-marketing experience with ixekizumab at the date of the submission.

Evaluator's conclusions on safety

Exposure

The safety of ixekizumab for the treatment of patients with moderate to severe plaque psoriasis has been satisfactorily established in the submitted data. In the all psoriasis ixekizumab exposures integrated analysis set, 4204 patients were exposed to ixekizumab at various doses and for various dosing periods, representing 4729.7 patients-years of exposure, with 2190 patients treated for ≥ 365 days and 1070 patients treated for ≥ 548 days and 378 patients treated for ≥ 378 days. Based on the 'rule of threes', 4204 patients should be adequate to reliably detect adverse drug reactions occurring with ixekizumab with an incidence of up to 1 in 1401 patients.

Induction dosing period (week 0 to week 12), pivotal studies

In the induction dosing period (pooled data from pivotal studies), 2328 patients were exposed to ixekizumab (1167 to 80 mg Q2W; 1161 to 80 mg Q4W), 791 patients were exposed to placebo and 739 patients were exposed to etanercept. The proposed maintenance dose in the induction period is 80 mg Q2W (following a starting dose of 160 mg). Overall, the safety profiles of ixekizumab and etanercept were inferior to

placebo, while the safety profiles of ixekizumab and etanercept were similar. The safety profiles of ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W were similar.

In the primary psoriasis placebo-controlled integrated analysis set (Studies RHAZ, RHBA and RHBC), treatment emergent adverse events (TEAE) were reported notably more frequently in patients in the total ixekizumab group compared to the placebo group (58.6% (n = 1364) versus 46.8% (n = 370); $p < 0.05$). There were no deaths in the ixekizumab or placebo groups. Serious adverse events (SAE) were reported in a similar proportion of patients in the total ixekizumab and placebo groups (2.0% (n = 46) versus 1.5% (n = 12), respectively). TEAEs leading to discontinuation of the study drug were reported infrequently in patients in the total ixekizumab and placebo groups (2.1% (n = 49) versus 1.1% (n = 9), respectively). TEAEs considered by the investigator to be possibly related to the study drug were reported notably more frequently in patients in the total ixekizumab group compared to the placebo group (27.1% (n = 632) versus 13.0% (n = 103); $p < 0.05$).

Adverse events of special interest (AESI) reported notably more frequently in the total ixekizumab group than in the placebo group included, infection-related TEAEs (including *Candida* infections), allergic/hypersensitivity reactions, reductions in laboratory assessed leukocyte, neutrophil and platelet counts, injection-site reactions, and autoimmune disorder-related TEAEs. There was an imbalance in patients reporting attempted suicide between patients in the total ixekizumab group compared to the placebo group (0.1% (n = 2) versus 0%).

AESI reported in a similar proportion of patients in the total ixekizumab and placebo groups included treatment-emergent elevated ALT and AST levels, and shifts from baseline to post-baseline higher ALT, AST, ALP and total bilirubin levels.

AESI reported infrequently and in a similar proportion of patients in the total ixekizumab and placebo groups included, cytopaenia-related TEAEs, adjudicated Major adverse cardiac events (MACE) and non-MACE CV events, malignancy-related TEAEs, hepatic-related TEAEs; depression (excluding suicide/self-injury), and interstitial lung disease. There were no cases of pneumocystis pneumonia (PCP) in either the total ixekizumab or the placebo group.

In the psoriasis placebo and active controlled integrated analysis set (Studies RHBA and RHBC), TEAEs were reported in a similar proportion of patients in the total ixekizumab and etanercept groups (57.6% (n = 483) versus 54.0% (n = 399), respectively). There were no deaths in the ixekizumab or etanercept groups. SAEs were reported in the same proportion of patients in the total ixekizumab and etanercept groups (1.9% (n = 20) versus 1.9% (n = 14), respectively). TEAEs leading to discontinuation of the study drug were reported infrequently in both the total ixekizumab and etanercept groups (2.0% (n = 29) versus 2.0% (n = 9), respectively). TEAEs considered by the investigator to be possibly related to the study drug were reported in a similar proportion of patients in the total ixekizumab and placebo groups (26.9% (n = 394) versus 23.8% (n = 176); $p < 0.05$). Overall, the observed differences in the safety profiles of the total ixekizumab group and the etanercept group are considered to be clinically insignificant.

Maintenance dosing period (week 12 to week 60), pivotal studies

In the maintenance dosing period (pooled data from pivotal Studies RHAZ and RHBA), 1226 responders to treatment during the induction dosing period (sPGA (score of 0 or 1) at Week 12) were re-randomised to ixekizumab or placebo and included in the psoriasis maintenance integrated analysis set. In this integrated analysis set, 416 patients were randomised to ixekizumab 80 mg Q4W (326.7 patient-years of exposure), 408 patients were randomised to ixekizumab 80 mg Q12W (269.5 patient-years of exposure), and 402 patients were randomised to placebo (184.1 patient-years of exposure). The total number of patients randomised to ixekizumab was 824 (596.1 patient-years of exposure). The

proposed maintenance dose of ixekizumab is 80 mg Q4W. There was only 1 patient in the total ixekizumab group exposed for more than 1 year.

The proportion of patients completing the maintenance dosing period was notably higher in in the ixekizumab 80 mg Q2W group compared to the ixekizumab 80 mg Q12W and placebo groups (64.4% (n = 268) versus 39.2% (n = 160) versus 8.2% (n = 33), respectively). The proportion of patients reported as relapsing and being censored from the psoriasis maintenance analysis set was notably higher in the ixekizumab 80 mg Q12W and the placebo groups compared to the ixekizumab 80 mg Q4W group (44.4% (n = 181) versus 81.8% (n = 329) versus 4.4% (n = 60), respectively).

The TEAE exposure-adjusted incidence rate in patients in the total ixekizumab group was significantly lower than in the placebo group (103.0 versus 125.5 per 100 patient-years, respectively; $p < 0.05$). The TEAE exposure-adjusted incidence rate in patients the ixekizumab 80 mg Q4W group was numerically lower than in the ixekizumab Q12W group (97.9 versus 109.1 per 100 patient-years, respectively), and significantly lower ($p < 0.05$) than in the placebo group.

There were 2 deaths reported in the psoriasis maintenance analysis set, both occurring in the ixekizumab 80 mg Q4W group (0.6 per 100 patient-years). The SAE (including death) exposure-adjusted incidence rates was the same in patients in the total ixekizumab and placebo groups (8.1 per 100 patient years), and were similar in patients in the ixekizumab 80 mg Q4W and 80 mg Q12W groups (7.7 versus 8.5 per 100-patient years, respectively).

The exposure-adjusted incidence rates for discontinuation from the study drug due to TEAEs were similar in patients in the total ixekizumab and placebo groups (3.5 versus 4.3 per 100 patient-years, respectively), and in patients in the ixekizumab 80 mg Q4W and 80 mg Q12W groups (3.7 versus 3.3 per 100 patient-years, respectively).

The exposure-adjusted incidence rates for TEAEs considered by investigators to be possibly related to the study drug was lower in patients in the total ixekizumab group compared to the placebo group (36.2 versus 44.0 per 100 patient-years, respectively), and higher in patients in the ixekizumab 80 mg Q4W group compared to the ixekizumab 80 mg Q12W group (39.5 versus 32.3 per 100 person years, respectively).

Adverse events of special interest reported with a higher exposure-adjusted incidence rate per 100 patient-years in patients the total ixekizumab group compared to the placebo group were (respectively), *Candida* infections (3.7 versus 2.2), non-anaphylaxis allergic/hypersensitivity related TEAEs (7.9 versus 6.5), injection site reaction related TEAEs (9.7 versus 4.3), malignant related TEAEs (0.8 versus 0.5), depression and suicide self-injury (broad) (1.2 versus 1.1), and suicide attempt (broad) (0.2 versus 0).

Adverse events of special interest reported with a lower (or the same) exposure-adjusted incidence rate per 100 patient-years in patients in the total ixekizumab group compared to the placebo group were (respectively), infection-related (72.1 versus 77.1), cytopaenia TEAEs (1.2 versus 1.6), adjudicated MACE events (0.5 verus 0.5), adjudicated non-MACE CV events (0.8 versus 1.0), hepatic related TEAEs (4.9 versus 4.9), autoimmune disorder related TEAEs (0.5 versus 1.6), PCP (0 versus 0), and ILD (0 versus 0).

Overall, in both the induction and maintenance dosing periods, the observed differences in laboratory parameters (haematology, clinical chemistry, and urinalysis), vital signs, and ECG changes (including QTc interval prolongation) between the total ixekizumab group and the placebo group are unlikely to be clinically significant. In addition, observed differences between the total ixekizumab group and the placebo group based on age, sex, and weight are unlikely to be clinically significant. However, the safety profile in patients aged ≥ 65 years should be interpreted cautiously due to the relative small number of patients in this age group compared to patients aged < 65 years. The numbers of patients in racial groups other than 'White' are too small to draw meaningful conclusions regarding

safety across the racial groups. There are no safety data on patients with hepatic or renal impairment, but based on the pharmacokinetics of ixekizumab it is unlikely that the safety of the drug will significantly differ in patients with these conditions compared to patients without these conditions.

First round benefit-risk assessment

First round assessment of benefits

The benefits of the sponsor's proposed treatment regimen of ixekizumab administered by SC injection at a starting dose of 160 mg followed by 80 mg Q2W in the induction dosing period (that is, Weeks 2, 4, 6, 8, 10 and 12) and then maintenance treatment with 80 mg Q4W (that is, every 4 weeks) have been satisfactorily demonstrated in the three pivotal Phase III studies. The submitted data have established that the proposed treatment regimen (Q2W/Q4W) is superior to the other treatment regimens tested in the pivotal studies (Q4W/Q4W, Q2W/Q12W and Q4W/Q12W). The benefits of the proposed treatment regimen (Q2W/Q4W) for the proposed indication are considered to be favourable. The benefits of treatment of the proposed treatment regimen (Q2W/Q4W) for the proposed indication are described below.

- The two co-primary efficacy endpoints in the three pivotal studies were sPGA (score of 0 or 1) and PASI 75 at Week 12 of the induction dosing period (Weeks 0 to 12). The response rates for both co-primary efficacy endpoints observed with the 80 mg Q2W treatment regimen in the induction dosing period were significantly greater compared to placebo in each of the three pivotal studies, and significantly greater compared to etanercept in the two pivotal studies that included this active control. The results are summarised below in Table 6.

Table 6. Induction dosing period, co-primary efficacy endpoints at Week 12 (NRI); ITT population

Study	Endpoint	Placebo	Etanercept	IXE 80 mg Q2W	IXE versus PBO	IXE versus ETN
RHAZ	sPGA (score of 0 or 1)	3.2% (14/431)	-	81.8% (354/433)	p < 0.001	-
RHBA	sPGA (score of 0 or 1)	2.4% (4/168)	36.0% (129/358)	83.2% (292/351)	p < 0.001	p < 0.001
RHBC	sPGA (score of 0 or 1)	6.7% (13/193)	41.6% (159/382)	80.5% (310/385)	p < 0.001	p < 0.001
RHAZ	PASI 75	3.9% (17/431)	-	89.1% (386/433)	p < 0.001	-
RHBA	PASI 75	2.4% (4/168)	41.6% (149/358)	89.7% (315/351)	p < 0.001	p < 0.001

Study	Endpoint	Placebo	Etanercept	IXE 80 mg Q2W	IXE versus PBO	IXE versus ETN
RHBC	PASI 75	7.3% (14/193)	53.4% (204/382)	87.3% (336/385)	p < 0.001	p < 0.001

Notes: sPGA (score of 0 or 1) = complete clearance of plaques (0), minimal plaque severity (1); PASI 75 at least 75% improvement from baseline in PASI.

- In the primary psoriasis placebo-controlled integrated analysis set (RHAZ, RHBA, RHBC), the response rates at Week 12 (NRI) for ixekizumab 80 mg Q2W versus placebo were 81.8% (956/1169) versus 3.9% (31/792) for sPGA (score of 0 or 1), and 88.7% (1037/1169) versus 4.4% (35/792) for PASI 75 (p < 0.001 for both comparisons; ITT populations). Based on the absolute difference in response rates between ixekizumab 80 mg Q2W and placebo for the co-primary efficacy endpoints it can be estimated that the number of patients needed to be treated with ixekizumab order to achieve an sPGA (score of 0 or 1) or PASI 75 is two (that is, numbers needed to treat (NNT) = 2, both endpoints). The results indicate that the proposed ixekizumab induction dosing regimen of 80 mg Q2W is highly efficacious.
- The results from the primary psoriasis placebo-controlled integrated analysis set (Study RHAZ, RHBA and RHBC) demonstrated that the benefits of treatment with ixekizumab 80 mg Q2W compared to placebo for both co-primary efficacy endpoints were observed as early as Week I after initiation of treatment with ixekizumab 160 mg. The data also showed that the benefits of treatment with ixekizumab 80 mg Q2W compared to placebo continued to increase throughout the remainder of the induction dosing period (that is, through to Week 12).
- In the induction dosing period (pivotal studies), high-level responses (sPGA (0), PASI 90, and PASI 100) at Week 12 (NRI) were observed significantly (p < 0.001) more frequently in patients treated with ixekizumab 80 mg Q2W than with placebo or etanercept (see Table 7, below).

Table 7. Induction dosing period, high-level response rates at Week 12 (NRI); ITT population

Study	Endpoint	Placebo	Etanercept	IXE 80 mg Q2W	IXE versus PBO	IXE versus ETN
RHAZ	PASI 90	0.5% (2/431)	-	70.9% (307/418)	p < 0.001	NA
RHBA	PASI 90	0.6% (1/168)	18.7% (67/358)	70.7% (248/351)	p < 0.001	p < 0.001
RHBC	PASI 90	3.1% (6/193)	25.7% (98/382)	68.1% (262/385)	p < 0.001	p < 0.001
RHAZ	PASI 100	0% (0/431)	-	35.3% (153/433)	p < 0.001	NA
RHBA	PASI 100	0.6%	5.3%	40.5%	p < 0.001	p < 0.001

Study	Endpoint	Placebo	Etanercept	IXE 80 mg Q2W	IXE versus PBO	IXE versus ETN
		(1/168)	(19/358)	(142/351)		
RHBC	PASI 100	0% (0/193)	7.3% (28/382)	37.7% (145/385)	p < 0.001	p < 0.001
RHAZ	sPGA (0)	0% (0/431)	-	37.0% (160/433)	p < 0.001	NA
RHBA	sPGA (0)	0.6% (1/168)	5.9% (21/358)	41.9% (147/351)	p < 0.001	p < 0.001
RHBC	sPGA (0)	0% (0/193)	8.6% (33/382)	40.3% (155/385)	p < 0.001	p < 0.001

Notes: sPGA (0) = complete clearance of plaques; PASI 90 = at least 90% improvement from baseline in PASI; PASI 100 = 100% improvement from baseline PASI.

In the induction dosing period (ITT population), the response rates for Itch NRS, DLQI (score of 0 or 1), and DLQI total score at Week 12 (NRI) were statistically significantly greater in the ixekizumab 80 mg Q2W group compared to the placebo group in each of the three pivotal studies ($p < 0.001$) as shown below in Table 8. Similarly, the response rates for Itch NRS, DLQI (score of 0 or 1), and DLQI total score at Week 12 (NRI) were statistically significantly greater in the ixekizumab 80 mg Q2W group compared to the etanercept group in each of the two pivotal studies testing the active control ($p < 0.001$). However, the response rates for NAPSI (0) were statistically significantly greater in the ixekizumab 80 mg Q2W groups than in the placebo groups in Studies RHAZ and RHBC ($p < 0.001$), but not for the ixekizumab 80 mg Q2W versus placebo comparison in Study RHBA ($p = 0.121$). Similarly, the response rate for NAPSI (0) was statistically significantly greater in the ixekizumab 80 mg Q2W group compared to the etanercept group in Study RHBC ($p = 0.009$), but not in Study RHBA ($p = 0.152$). The results for Itch NRS, DLQI (score of 0 or 1), DLQI total score and NAPSI (0) for the relevant treatment comparisons in the pivotal studies are summarised below in Table 8. The quality of life outcomes at Week 12, as measured by reduction in Itch and improvement in DLQI outcomes, are markedly improved in patients treated with ixekizumab 80 mg Q2W compared to both placebo and etanercept.

Table 8. Induction dosing period, selected secondary efficacy endpoint responses at Week 12 (NRI); ITT population

Study	Endpoint	Placebo	Etanercept	IXE 80 mg Q2W	IXE versus PBO	IXE versus PBO
RHAZ	Itch NRS	15.5% (58/374)	-	85.9% (336/391)	p < 0.001	-
RHBA	Itch NRS	14.1% (19/135)	57.8% (177/306)	85.1% (258/303)	p < 0.001	p < 0.001
RHBC	Itch NRS	20.9% (33/158)	64.1% (200/312)	82.5% (264/320)	p < 0.001	p < 0.001

Study	Endpoint	Placebo	Etanercept	IXE 80 mg Q2W	IXE versus PBO	IXE versus PBO
RHAZ	DLQI (score of 0 or 1)	4.6% (20/431)	-	66.3% (287/433)	p < 0.001	-
RHBA	DLQI (score of 0 or 1)	6.0% (10/168)	33.8% (121/358)	64.1% (225/351)	p < 0.001	p < 0.001
RHBC	DLQI (score of 0 or 1)	7.8% (15/193)	43.7% (167/382)	64.7% (249/385)	p < 0.001	p < 0.001
RHAZ	DLQI total score	25.3% (95/375)	-	89.6% (345/385)	p < 0.001	-
RHBA	DLQI total score	32.2% (46/143)	69.6% (218/313)	91.8% (280/305)	p < 0.001	p < 0.001
RHBC	DLQI total score	32.7% (56/171)	73.0% (233/319)	87.6% (283/323)	p < 0.001	p < 0.001
RHAZ	NAPSI (0)	3.5% (10/283)	-	16.9% (48/284)	p < 0.001	-
RHBA	NAPSI (0)	8.8% (10/113)	10.5% (24/229)	15.3% (32/209)	p = 0.121	p = 0.152
RHBC	NAPSI (0)	4.3% (5/116)	10.2% (24/236)	17.5% (40/229)	p < 0.001	p = 0.009

Notes: Itch NRS (itch numeric rating scale) = proportion of patients with Itch NRS score of ≥ 4 point reduction from baseline in patients with Itch NRS score ≥ 4 at baseline at Week 12. DLQI (score of 0 or 1) (dermatology life quality index) = proportion of patients with DLQI (score of 0 or 1) scores at Week 12 (representative of psoriasis having no effect on HRQoL). DLQI total score (dermatology life quality index) = proportion of patients with DLQI total score ≥ 5 improvement from baseline in patients with DLQI total score ≥ 5 at baseline at Week 12 (clinically relevant improvement). NAPSI (0) (Nail psoriasis severity index) = proportion of patients with fingernail involvement at baseline with NAPSI total score of 0 at Week 12 for patients (no nail involvement).

In the two pivotal studies that examined the maintenance effect of ixekizumab (RHAZ, RHBA), the benefits of treatment with ixekizumab 80 mg Q2W observed in responders at Week 12 were maintained with 80 mg Q4W administered from Week 12 through Week 60 (maintenance dosing period). Responders were defined as ixekizumab-treated patients who achieved a sPGA (score of 0 or 1) at Week 12. This responder criterion was sufficiently stringent to ensure that only those patients who achieved a clinically meaningful clinical response were re-randomised at Week 12.

The results for sPGA (score of 0 or 1) and PASI 75 at Week 60 (NRI) show that the proportion of patients maintaining response through to Week 60 was significantly higher ($p < 0.001$) for both endpoints in the 80 mg Q2W/Q4W group than in the placebo group (see Table 9, below).

Table 9. Maintenance dosing period, sPGA (score of 0 or 1) and PASI 75 responses at Week 60 (NRI); maintenance dosing period primary population (Study RHAZ) and maintenance dosing period primary population efficacy evaluable patients (Study RHBA)

Study	Endpoint	IXE 80 mg Q2W/PBO	IXE 80 mg Q2W/80 mg Q4W	IXE versus PBO
RHAZ	sPGA (score of 0 or 1)	7.7% (9/117)	74.8% (89/119)	p < 0.001
RHBA	sPGA (score of 0 or 1)	7.0% (6/86)	75.8% (47/62)	p < 0.001
RHAZ	PASI 75	9.4% (11/117)	78.2% (93/119)	p < 0.001
RHBA	PASI 75	5.8% (5/86)	85.5% (53/62)	p < 0.001

Notes: sPGA (score of 0 or 1) = complete clearance of plaques (0) of minimal plaque severity (1); PASI 75 at least 75% improvement from baseline in PASI

In the maintenance dosing period, high-level responses (that is, sPGA (0), PASI 90, and PASI 100) at Week 60 (NRI) were observed significantly more frequently in the ixekizumab 80 mg Q2W/Q4W group than in the 80 mg Q2W/placebo group in the relevant pivotal studies (see Table 10, below).

Table 10. Maintenance dosing period, high-level response rates at Week 60 (NRI); maintenance dosing period primary population (Study RHAZ) and maintenance dosing period primary population efficacy evaluable patients (Study RHBA)

Study	Endpoint	IXE 80 mg Q2W/PBO	IXE 80 mg Q2W/80 mg Q4W	IXE versus PBO
RHAZ	PASI 90	5.1% (6/117)	72.3% (86/119)	p < 0.001
RHBA	PASI 90	3.5% (3/86)	75.8% (47/62)	p < 0.001
RHAZ	PASI 100	3.4% (4/117)	52.1% (62/119)	p < 0.001
RHBA	PASI 100	2.3% (2/86)	56.5% (35/62)	p < 0.001
RHAZ	sPGA (0)	3.4% (4/117)	54.6% (65/110)	p < 0.001
RHBA	sPGA (0)	2.3% (2/86)	56.5% (35/62)	p < 0.001

Notes: sPGA (0) = complete clearance of plaques; PASI 90 = at least 90% improvement from baseline in PASI; PASI 100 = 100% improvement from baseline PASI.

The results for the proportion of patients with change from baseline at Week 60 (NRI) for selected secondary efficacy endpoints for the ixekizumab 80 mg Q2W/Q4W and the 80 mg Q2W/placebo groups are summarised below in Table 11. In both studies, all pairwise comparisons for the selected endpoints significantly favoured the ixekizumab 80 mg Q2W/Q4W group compared to the 80 mg Q2W/placebo group (p < 0.001).

The results indicate that the quality of life at Week 60, as measured by the reduction in Itch NRS and improvement in DLQI outcomes, are markedly improved in patients treated

with ixekizumab 80 mg Q2W/Q4W compared to patients treated with ixekizumab 80 mg Q2W/PBO.

Table 11. Maintenance dosing period, selected secondary efficacy endpoint responses at Week 60 (NRI); maintenance dosing period primary population (Study RHAZ) and maintenance dosing period primary population efficacy evaluable patients (Study RHBA)

Study	Endpoint	IXE 80Q2W/PBO	IXE 80Q2W/80Q4W	IXE/IXE versus IXE/PBO
RHAZ	Itch NRS	8.6% (9/105)	72.3% (73/101)	p < 0.001
RHBA	Itch NRS	3.9% (3/77)	82.4% (42/51)	p < 0.001
RHAZ	DLQI (score of 0 or 1)	6.8% (8/117)	67.2% (80/119)	p < 0.001
RHBA	DLQI (score of 0 or 1)	4.7% (4/86)	69.4% (43/62)	p < 0.001
RHAZ	DLQI total score	10.5% (11/105)	78.1% (82/105)	p < 0.001
RHBA	DLQI total score	5.2% (4/77)	83.7% (41/49)	p < 0.001
RHAZ	NAPSI (0)	0 (0/77)	50.0% (38/76)	p < 0.001
RHBA	NAPSI (0)	2.0% (1/50)	57.9% (22/38)	p < 0.001

Notes: Itch NRS (itch numeric rating scale) = proportion of patients with Itch NRS score of ≥ 4 point reduction from baseline in patients with Itch NRS score ≥ 4 at baseline at Week 60. DLQI (score of 0 or 1) (dermatology life quality index) = proportion of patients with DLQI (score of 0 or 1) scores at Week 60 (psoriasis had no effect on HRQoL). DLQI total score (dermatology life quality index) = proportion of patients with DLQI total score ≥ 5 improvement from baseline in patients with DLQI total score ≥ 5 at baseline at Week 60 (clinically relevant improvement). NAPSI (0) (Nail psoriasis severity index) = proportion of patients with fingernail involvement at baseline with NAPSI total score of 0 at Week 60 for patients (no nail involvement).

Of the patients responding to treatment with ixekizumab 80 mg Q2W at Week 12 (that is, those achieving sPGA (score of 0 or 1)), relapse (defined as sPGA ≥ 3) was reported during the maintenance period in 84.7% (172/203) of patients re-randomised to placebo, 47.8% (88/184) of patients re-randomised to ixekizumab 80 mg Q12W and 14.4% (26/181) of patients re-randomised to ixekizumab 80 mg Q4W (psoriasis maintenance integrated analysis set efficacy evaluable patients (Studies RHAZ and RHBA)). The median time to relapse in the maintenance dosing period for the three re-randomised treatment groups was 164 days for the placebo group, 340 days for ixekizumab 80 mg Q12W group and could not be calculated for the ixekizumab 80 mg Q4W group as too few patients in this group had relapsed by Week 60. The results show that the maintenance treatment with 80 mg Q4W is highly efficacious in preventing relapse.

Of the patients not responding to treatment with ixekizumab 80 mg at Week 12 (that is, those who did not achieve sPGA (score of 0 or 1)), switching to ixekizumab 80 mg Q4W during the maintenance dosing period resulted in 25.8% (16/62) of patients achieving an

sPGA (score of 0 or 1) and 51.6% (32/62) of patients achieving a PASI 75 at Week 60 (NRI). The results suggest that, after initial non-response in the induction dosing period (Weeks 0 to 12) to ixekizumab 80 mg Q2W, continuing treatment with ixekizumab 80 mg Q4W in the maintenance dosing period (Weeks 12 to 60) achieved a clinically meaningful improvement. However, the non-responder data need to be interpreted cautiously due to the absence of a comparator placebo control group in the maintenance dosing period.

In the subgroup analyses, superior efficacy of ixekizumab compared to placebo and etanercept at Week 12 was consistent across all subgroups of age, race, body weight, geographical region, disease severity, previous exposure to systemic psoriasis therapy, and or failure of previous systemic psoriasis therapy (including anti-TNF and other biologics). In addition, greater response were observed with ixekizumab 80 mg Q2W in almost every subgroup compared to ixekizumab 80 mg Q4W.

First round assessment of risks

The proposed ixekizumab SC dosing regimen for the proposed indication is a starting dose of 160 mg followed by 80 mg Q2W though to and including Week 12, with subsequent maintenance doses of 80 mg Q4W. No limitations have been proposed on the duration of treatment with ixekizumab for moderate to severe plaque psoriasis, but due to the chronic nature of the condition, it can be anticipated that in the absence of loss of efficacy or adverse events treatment will continue indefinitely.

The assessment of the risks of ixekizumab for the proposed indication primarily focuses on the data from the pivotal studies for the ixekizumab 80 mg Q2W regimen (n = 1167) in the induction dosing period (Weeks 0 to 12) and the ixekizumab 80 mg Q4W (n = 416) regimen in the maintenance dosing period (Weeks 12 to 60). The pivotal studies included only 1 patient treated with ixekizumab for ≥ 365 days (1 x 80 mg Q4W). Consequently, there are no pivotal safety data in patients with moderate to severe plaque psoriasis treated with the proposed regimen for longer than 1 year.

The main risks associated with ixekizumab were infections, injection site reactions, and allergic reactions/hypersensitivity events. The majority of these events were categorised as mild to moderate in intensity and did not result in discontinuation of the study drug. The most commonly observed infections were nasopharyngitis and upper respiratory tract infections. *Candida* infections were also observed (primarily oral candidiasis), while the only other fungal infections seen in the pivotal studies were associated with tinea. There were no invasive fungal infections observed in the pivotal studies. There were no active cases of TB associated with ixekizumab. The most commonly reported allergic reactions reported were urticaria. No confirmed anaphylactic reactions were observed in the pivotal studies.

In general, incidence rates for MACE events, cytopaenias, hepatic TEAEs including shifts in hepatic enzyme levels, malignancies, and auto-immune disorders were low in patients treated with ixekizumab and did not markedly differ from placebo. There was no increased risk of PCP or ILD in patients treated with ixekizumab. There were no pivotal long-term (> 1 year) safety data and, consequently, an association with conditions with long latency periods such as malignancy cannot be excluded.

Suicide attempts were observed in patients with a previous history of self-harm treated with ixekizumab, but there did not appear to be an increased risk of depression associated with the drug. The drug should not be used in patients with a history of self-harm or in patients considered to be at risk of self-harm.

In general, the risk of the treatment with ixekizumab was higher in the first 12 weeks of treatment (induction dosing period) than in the subsequent 48 weeks of treatment (maintenance dosing period).

An association between treatment-emergent ADA positive status and TEAEs including allergic/hypersensitivity reactions was not observed in the pivotal clinical studies.

For details of the *Induction dosing period, psoriasis placebo-controlled integrated analysis set* and *Maintenance dosing period, psoriasis maintenance integrated analysis set* including details of

- Infection-related TEAEs (AESIs)
- Injection site reactions (AESI)
- Allergic reactions/hypersensitivities (AESI)
- Cytopenias (AESI)
- Cerebro-cardiovascular events (AESI)
- Malignancies (AESI)
- Hepatic events (AESI)
- Depression and suicide/self-injury (AESI)
- Autoimmune disorders (AESI)
- PCP and ILD (AESI)

Details of Immunogenicity are also described in Attachment 2.

First round assessment of benefit-risk balance

The first round benefit-risk balance is favourable for ixekizumab at the proposed dosage regimen for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or chemotherapy.

First round recommendation regarding authorisation

It is recommended that ixekizumab be approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Comment: The wording of the recommended indication differs from that being proposed by the sponsor as it includes reference to treatment of candidates for systemic therapy or phototherapy. These were inclusion criteria for each of the pivotal Phase III studies.

Clinical questions

The clinical evaluator had the following questions for the sponsor:

Efficacy

1. The sponsor is requested to indicate whether it intends to submit studies to the TGA for evaluation investigating the efficacy and safety of ixekizumab for the treatment of children and adolescents with moderate to severe plaque psoriasis.
2. In the primary psoriasis placebo-controlled integrated analysis set (Studies RHAZ, RHBA and RHBC), the baseline mean body mass index (BMI) (SD) was 30.5 (7.15) kg/m^2, which indicates that, on average, patients in the pivotal studies were obese (BMI criterion for obese ≥ 30 and < 40 kg/m^2). Furthermore, based on BMI criteria 33.7% of the patient population was overweight, 34.9% were obese and 10.2% were

extremely obese with only 19.7% of the patient being of normal weight. Please comment on whether the BMI values for the study population patient are representative of the general population of patients with moderate to severe plaque psoriasis likely to be treated with ixekizumab.

Safety

3. The submitted data indicates that the 5 (0.1%) patients in the all psoriasis ixekizumab-exposure analysis set reported the suicide/self-injury related TEAE of suicide attempt, and that suicide attempt was reported in a further 4 patients in this analysis set after the database lock. Please update all data on suicide/self-injury related TEAEs, including suicide attempts, and compare these events in patients in the placebo, etanercept and ixekizumab treatment groups.
4. The submitted data indicate that treatment emergent high creatine kinase levels in the all psoriasis ixekizumab-exposure integrated analysis set were reported in 10.5% of patients, and that in order to further evaluate the effect of ixekizumab on CK and potentially related clinical outcomes, TEAEs (for example, renal insufficiency and rhabdomyolysis) were evaluated. Please provide the results of the TEAE evaluation.
5. In the pooled data, there was a significantly higher proportion of patients in the psoriasis maintenance integrated analysis set with treatment emergent high systolic blood pressure in the total ixekizumab group compared to placebo (16.9% (n = 113) versus 11.8% (n = 39)). This finding is inconsistent with the results in the primary psoriasis placebo-controlled integrated analysis set, where the proportion of patients with treatment emergent high systolic pressure was similar in the total ixekizumab and placebo groups (5.4% (n = 88) versus 7.1% (n = 38), respectively). Please comment on this observation.
6. The sponsor's Summary of Clinical Safety included a discussion of the mean changes from last observation at baseline to the last post-baseline observation laboratory cytopaenic events in the psoriasis maintenance integrated analysis set. However, the data in this section could not be verified, as the reference to the source Table was incorrect. Please provide the table with the relevant data.
7. The sponsor's attention is drawn to what appears to be an incorrect heading in the table summarising potential drug induced liver injury in the primary psoriasis placebo controlled integrated analysis set. The heading refers to the psoriasis placebo-controlled and active controlled integrated analysis set (Studies RHBA and RHBC) but the data in the table appears to refer to the primary psoriasis placebo-controlled integrated analysis set (Studies RHAZ, RHBA and RHBC).
8. The sponsor's attention is drawn to what appears to be an incorrect heading in the table summarising the hepatotoxicity data for the all psoriasis ixekizumab exposures integrated analysis set. The data appear to relate to the maintenance dosing period (psoriasis maintenance integrated analysis set). Please provide a table with the data for the all psoriasis ixekizumab exposures integrated analysis set.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ixekizumab for the proposed usage are unchanged from those identified in the First round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of ixekizumab for the proposed usage are unchanged from those identified in the First round assessment of risks.

Second round assessment of benefits-risk balance

The benefit-risk balance of ixekizumab, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

It is recommended that Taltz be approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or chemotherapy. The inclusion criteria for each of the 3 pivotal studies required that patients be candidates for phototherapy and/or systemic therapy. Therefore, it is considered that for completeness this condition should be added to the indication.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), ixekizumab EU-RMP version 1 dated 13 September 2015 with the Australian Specific Annex (ASA) version 1 dated 22 July 2015 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 12 below.

Table 12. Summary of ongoing safety concerns

Safety Concerns	
Important Identified Risks	None
Important Potential Risks	Serious infections Serious hypersensitivity Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
Missing Information	Long-term safety (such as malignancies and other events with a low frequency and/or long latency)

Safety Concerns	
	Use in pregnancy Use in very elderly (≥ 75 years)

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance to monitor all the safety concerns. Additional pharmacovigilance comprises an observational post-authorisation safety registry (CORRONA) in the US to monitor all the safety concerns except 'Use in pregnancy' and an observational pregnancy study in the US using electronic medical records to monitor 'Use in pregnancy'.

Risk minimisation activities

The sponsor proposes routine risk minimisation to mitigate all the safety concerns. No additional risk minimisation is considered necessary by the sponsor.

Reconciliation of issues outlined in the RMP report

Table 13 (below) summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the TGA's evaluation of the sponsor's responses.

Table 13. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the non-clinical and clinical evaluators through requests for information and/or the evaluation reports. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*Lilly acknowledges this recommendation and aims to provide all relevant and necessary information on safety issues and their pertinence to the RMP.*	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
2. The draft PI provides reports of neutropaenia in clinical trials. It is noted that the frequency and severity of reported cases in ixekizumab group was lower than in etanaercept group. The EU-RMP includes discussion on neutropenia as a potential mechanism of 'serious infection', which acknowledges that the two are related, but different issues. It is also noted that neutropaenia is an important identified risk for another IL-17A inhibitor (secukinumab). Given the potential impact of this risk on patient safety and its difference from infection, the sponsor should add this risk to the ASA as an important identified risk.	*The sponsor agrees with the evaluator in that neutropenia has been identified as an Undesirable Effect to be included in the ixekizumab PI. However, any associated risk for this effect should be driven primarily by the clinical consequences of the observed event, that is, infection or even serious infections should the neutrophil count fall to a clinically concerning level. The sponsor maintains that the consequences of neutropaenia do not warrant that it be classified as an 'important identified risk' in the RMP. Our position is based on a number of different considerations, not the least that the concept of risk per se is determined by the outcome of the adverse reaction. The overall lack of serious outcomes related to neutropaenia observed in the clinical development programme for ixekizumab to date, as discussed below, does not warrant that neutropenia should be classified as an 'important identified risk.'* *These considerations are as follows: Differentiation between an Adverse Drug Reaction (ADR) and Risk. The terms 'adverse reaction' and 'risk' are not synonymous in that:* *1. ADR denotes the degree of causal association between an AE and a medicinal product* *2. Risk denotes the probability of an adverse outcome or the potential of a medicinal product to cause harm to patients.* *The EMA Guideline on Good Pharmacovigilance Practices (GVP) Annex 1, Definitions document does not provide a definition of 'risk' per se, but does provide a definition of ADR, which is consistent with that of other regulatory agencies, including the US FDA. We have also provided the most recent consensus agreement on the definition of risk per Council for International Organizations of Medical Sciences Working Group IX (CIOMS IX).* *Concept of an Important Risk: The concept of an important risk, originally agreed by international consensus in ICH E2E guidelines finalised in 2004 and incorporated into EU guidelines since that time, was that an important identified risk is one that is likely to produce a substantial and demonstrably adverse impact on patients/public health and benefit risk balance of the product, that is, poses a hazard. Consistent with this view, according to EMA GVP Annex I, Definitions (Rev 3; EMA) a risk should be considered important if it '…could have an impact on the benefit-risk balance of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness*	The evaluator has noted the sponsor's response. Please refer to 'Recommendation 2, 4, 5, 6' in the following subsection 'Summary of recommendations'

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
	of the risk and the impact on public health.' *This position is also consistent with the most recent international consensus from the ICH E2C(R2) Implementation Working Group Question and Answer (Number 13.2: Points to Consider – 31 March 2014): 'In characterising the risk, … the MAH should consider whether or not the risk is important.* *A risk may not be important if it is infrequent, non-serious, reversible, and readily managed with no significant impact on the individual patient or public health.* *Even a common ADR may not constitute an important risk if it is not linked to clinically significant adverse sequelae' (ICH E2C(R2)).* *Outcomes (Risks) for Ixekizumab: The clinical data for ixekizumab demonstrate that in the majority of cases, it was apparent that patients with low neutrophil counts do not have such counts persistently and only have transient excursions below the lower limit of normal. Furthermore, most observed laboratory cases of neutropenia were findings of low grade only, with no adverse sequelae and which did not require discontinuation of treatment. In particular, incidences in which Grade 3 neutropenia were reported at some time post-baseline were uncommon (0.2%) and similar to placebo and no clear associations with infections reported as an AE were noted.* *In patients treated with ixekizumab, 12 cases of higher grade neutropaenia (10 CTCAE Grade 3 and 2 CTCAE Grade 4) were reported in the updated All Psoriasis Ixekizumab Exposure Integrated Analysis Set (data cut-off date 09 Apr 2015). The only ixekizumab-treated patient with Grade ≥ 3 neutropaenia at more than 1 visit had laboratory data entry errors as the source of this laboratory finding (Study RHBC). Only 4 patients, discussed below, with laboratory reports of Grade ≥ 3 neutropenia (0.1% of the overall population), experienced a potentially related event of infection based on the timing of the laboratory report of neutropaenia relative to that of the infection; none of these infections were reported as SAE:* *Study RHAZ, patient treated with ixekizumab 80 mg every 4 weeks (Q4W), reported an event of severe diverticulitis on Day 266, and Grade 3 neutropenia preceded the event on Day 249 with a value of 0.64 x 10^9 cells/L. On Day 259 (prior to reported event), total neutrophil count was 3.03 x 10^9 cells/L, and the patient was reported as recovered from the event on Day 275.* *Study RHBA, patient treated with ixekizumab 80 mg*	

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
	every 12 weeks (Q12W) during the Maintenance Dosing Period, reported an event of viral gastroenteritis on Day 162. The patient's previous total neutrophil count was 1.92 x 10^9 cells/L on Day 134, and Grade 3 neutropenia was recorded after the infection, with a total neutrophil count of 0.9 x 10^9 cells/L on Day 197. The patient recovered from the infection on Day 163. Neutrophil count was 1.58 x 10^9 cells/L at the next measurement on Day 246. *Study RHBA, patient treated with ixekizumab 80 mg Q2W in the Induction Dosing Period followed by ixekizumab 80 mg Q12W, experienced otitis externa on 21 Jan 2015; the patient's neutrophil count was 0.86 x 10^9cells/L on 29 Jan 2015. The patient was treated with a topical antibiotic. On 09 Feb 2015, the patient's neutrophil count was 1.84 X 10^9 cells/L.* *Study RHBC, patient treated with ixekizumab 80 mg Q4W, reported an event of nasopharyngitis on Day 277 and was reported to have a total neutrophil count of 0.55 x 10^9 cells/L on Day 284. This patient clearly had laboratory error or laboratory artefact as the cause of this finding, perhaps due to sample handling/transport/stability issues resulting in falsely, markedly low values for all haematology parameters at only 1 visit (narrative provided in Appendix 1). Repeat haematology testing 3 days later, with no treatment or transfusions, demonstrated all haematology parameters consistent with the patient's previous values. No treatment was reported for the nasopharyngitis, which was resolved on Day 285.* *No infections were reported for the only other patient with a laboratory report of Grade 4 neutropaenia. Of all patients experiencing CTCAE Grade 3 or 4 neutropaenia, none were reported to require pharmacological treatment of neutropaenia (such as filgastrim/granulocyte-colony stimulating factor) and none were reported to have serious sequelae. Only 2 patients in the ixekizumab psoriasis development programme discontinued study treatment prematurely due to an AE of neutropaenia; both had nadir neutrophil counts of > 1.0 x 10^9 cells/L.* *Although reference to neutropaenia and infrequent Grade ≥3 neutropenia have been noted in the PI, the adverse effect itself does not warrant classification as an 'important identified risk' as the concept of risk is driven by the outcomes of the effect; in this case, infections, serious infections, or even sepsis as a direct result of the low white cell count. To qualify as an important risk, clinically concerning sequelae indicating harm to patients and sufficient to impact on public health or benefit-risk would have been expected but the data do not support this for neutropenia. The*	

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
	sponsor has acknowledged that there is the possibility for important clinical outcomes of neutropenia, namely serious infection, and that has already been included as an 'important potential risk' in the RMP.	
3. The evaluator has also noted the advice on immunogenicity in the draft PI. The development of neutralising antibodies is a separate issue from hypersensitivity as the clinical consequences are different. The sponsor should add immunogenicity to the ASA as an important identified risk.	*Regarding advice on immunogenicity in the PI, the evaluator has commented specifically regarding NAbs and associated response to treatment, as well as efficacy outcomes as related to treatment-emergent anti-drug antibodies (TE-ADA)-positive versus TE-ADA-negative status. These comments are addressed with respect to the PI in our response to TGA Recommendation 2. The sponsor agrees that the development of NAbs is a separate concern from hypersensitivity because the clinical consequences are different.* *As related to the RMP, the sponsor acknowledges that NAbs may lead to loss of efficacy and in theory can have a negative impact on benefit-risk balance of a pharmacologic agent due to reduction in benefit. The sponsor's position is that classification of immunogenicity as an important identified risk as related to development of NAbs and potential loss of efficacy is not justified by the clinical data. This position is based on a number of different considerations, particularly as presented above in response to TGA Recommendation 2, the concept of risk per se is determined by the probability of detrimental clinical outcomes of the AE, in this case, the likelihood of adverse outcomes due to loss of efficacy.* *The proposed PI provides the following information on immunogenicity of ixekizumab, which the sponsor considers appropriate for patients with moderate-to-severe psoriasis:* *'Immunogenicity: Approximately 9 to 17% of patients treated with Taltz at the recommended dosing regimen developed anti-drug antibodies, the majority of which were low titres and not associated with reduced clinical response up to 60 weeks of treatment. However, approximately 1% of patients treated with Taltz had confirmed neutralizing antibodies associated with low drug concentrations and reduced clinical response. An association between immunogenicity and treatment emergent adverse events has not been established.'* *With respect to the development of NAbs and potential loss of efficacy, the available data would indicate that:* *1. The proportion of ixekizumab patients with NAb positive samples was low (approximately 1% of patients treated with the recommended dose of Taltz*	The sponsor's has demonstrated with available evidence that the development of neutralising antibodies is 'nonserious, non-life-threatening, and does not pose an immediate danger to the patient'. In addition, it is 'clinically apparent to the patient and practitioner, allowing for prompt consultation and alteration in management'. This is acceptable. Therefore, the sponsor's response is acceptable.

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
	had confirmed NAbs associated with low drug concentrations and reduced clinical response). *2. Loss of efficacy, if it occurs, is:* *a) Non-serious, non-life-threatening, and does not pose an immediate danger to the patient* *b) Clinically apparent to the patient and practitioner, allowing for prompt consultation and alteration in management, if necessary, as would be consistent with usual clinical practice. This situation contrasts with medicinal products used to treat conditions that are not visible or not associated with signs and symptoms until far advanced, for example, those used to treat hypertension or hypercholesterolemia, such that lack of efficacy would be associated with a potential safety concern.* *c) Management of individual patients is best undertaken through usual clinical practice, (that is, monitoring the patient's response), and continuing or discontinuing ixekizumab therapy should be based primarily on the clinical outcome of the patient.* *Conclusion: The sponsor concludes that the development of NAbs with potential loss of efficacy is not significantly impactful to the benefit-risk balance for individual patients or public health to warrant classification as an 'important identified risk.' Based on these factors, the sponsor considers that immunogenicity does not warrant addition to the RMP as an important identified risk.*	
4. 'Serious infections' and 'serious hypersensitivity' are risks well known for monoclonal antibody interleukin inhibitors with plausible mechanisms established. They should be re-categorised as 'important identified risks'.	*'Serious infections' conclusion: based on the considerations presented above, the sponsor concludes that the profile of infections observed with ixekizumab does not constitute an 'important identified risk' as the associated outcomes do not warrant such a classification at this stage of knowledge. The vast majority of the infections observed during treatment with ixekizumab are not associated with clinically concerning outcomes; hence, the sponsor considers that this position is consistent with the spirit and intent of prevailing definitions and standards, including ICH and CIOMS.* *The sponsor's rationale for classifying serious infections as an 'important potential risk' was based on the possibility that a different profile with more frequent and clinically impactful outcomes could occur with increased exposures in patients in routine clinical practice. However, experience to date indicates that infections with serious or clinically concerning outcomes occur too infrequently to impact benefit risk or public health to warrant classification as an 'important identified risk.' Based on these factors, the*	The evaluator has noted the sponsor's response. Please refer to 'Recommendation 2, 4, 5, 6' in the following subsection 'Summary of recommendations'

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
	sponsor requests that 'serious infections' be retained as an 'important potential risk' for ixekizumab in the RMP. *'Serious hypersensitivity' conclusion: based on the considerations presented above, the sponsor concludes that the profile of hypersensitivity reactions observed with ixekizumab does not constitute an 'important identified risk' as the associated outcomes do not warrant such a classification at this stage of knowledge. This position acknowledges that hypersensitivity reactions have been observed in patients treated with ixekizumab, but also takes into account that the associated risk is driven by the potential for serious outcomes and their likely impact on benefit risk and public health. As summarised above, the vast majority of the hypersensitivity events observed during treatment with ixekizumab are not associated with clinically concerning outcomes; hence, we consider that this position is consistent with the prevailing definitions and standards, including ICH and CIOMS. It also takes into account the profiles of serious hypersensitivity seen with similar products in this class.* *The sponsor's rationale for classifying serious hypersensitivity as an 'important potential risk' acknowledged that, whilst hypersensitivity events classified as serious occurred in a very small percentage of patients in a clinical trial setting, there is a possibility that a different profile with more frequent and clinically impactful outcomes could occur with increased exposures in patients in routine clinical practice. Based on these factors, the sponsor requests that 'serious hypersensitivity reactions' be retained as an 'important potential risk' for ixekizumab in the RMP.*	
5. The following missing information for secukinumab appears to apply to ixekizumab. The sponsor should add them to the ASA as missing information: use in patients with severe cardiac disease or uncontrolled hypertension; use in lactation; use in patients with severe hepatic impairment; use in patients with severe renal	*The concept of (important) missing information originated by international consensus with ICH E2E (Pharmacovigilance Planning) (ICH Tripartite Guideline) and has been subsequently adopted on an international basis. The basic premise is that, what is now referred as 'missing information' should comprise that which constitutes a critical gap in knowledge, usually at the time of authorisation. Examples of such situations include outstanding safety questions or insufficient information in subpopulations that are likely to be exposed in everyday practice or for whom lacking information is clinically relevant. It should not necessarily include every exclusion criterion used in the clinical development programme or every subpopulation under- represented if not relevant to use in clinical practice.*	The evaluator has noted the sponsor's response. Please refer to 'Recommendation 2, 4, 5, 6' in the following subsection 'Summary of recommendations'

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
impairment.	*Based on these fundamental and internationally accepted principles, the sponsor considers that the following populations should not be considered 'missing information' on the basis of lack of relevance to the target population and /or how it is anticipated to be used in clinical practice, for example, potential for off label use.*	
6. Major adverse cardiovascular events (MACE) is an important potential risk for secukinumab and has been related to IL-12/23 inhibitors. The sponsor should provide justification to why this risk is unrelated to ixekizumab, or add it to the ASA as an important potential risk.	*The question suggests that major adverse cerebro-cardiovascular events (MACE) should be regarded as a class effect of IL inhibitors in general, and hence a basis for its classification as an 'important potential risk' for ixekizumab. Whilst the IL-12/23 inhibitors for psoriasis (that is, ustekinumab and briakinumab, which was withdrawn from development) have had imbalances of MACE in the treatment groups compared to placebo, leading to concerns regarding cardiovascular safety of these drugs[20], these agents target 2 cytokines, and have a potentially wider spectrum of effects than either the IL-17A inhibitors secukinumab or ixekizumab. Additionally, longer-term clinical trial and post-marketing data for ustekinumab have not shown increased risk of MACE in patients with psoriasis[21], nor have safety data from clinical trials for other indications[22] shown such a risk. The basis for MACE events being considered as an*	The evaluator has noted the sponsor's response. Please refer to 'Recommendation 2, 4, 5, 6' in the following subsection 'Summary of recommendations'

[20] Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, Langley RG, de Lemos JA, Daoud Y, Blankenship D, Kazi S, Kaplan DH, Friedewald VE, Menter A. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. JAMA. 2011;306(8):864-871.
Tzellos T, Kyrgidis A, Trigoni A, Zouboulis CC. Association of ustekinumab and briakinumab with major adverse cardiovascular events: An appraisal of meta-analyses and industry sponsored pooled analyses to date. Dermatoendocrinol. 2012;4(3):320-323.
Dommasch ED, Troxel AB, Galfand JM. Major cardiovascular events associated with anti-IL 12/23 agents: A tale of two meta-analyses. J Am Acad Dermatol. 2013;68:863-865.
[21] Kimball AB, Papp KA, Wasfi Y, Chan D, Bissonnette R, Sofen H, Yeilding N, Li S, Szapary P, Gordon KB; PHOENIX 1 Investigators. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. J Eur Acad Dermatol Venereol. 2013;27(12):1535-1545.
Papp K, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, Fakharzadeh S, Chevrier M, Calabro S, Langholff W, Krueger G. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Drugs Dermatol. 2015;14(7):706-714.
[22] Gottlieb A, Menter A, Mendelsohn A, Shen Y-K, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009;373:633–640.
McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, Li S, Wang Y, Mendelsohn AM, Doyle MK. Ustekinumab in patients with active psoriatic arthritis: results of the phase 3, multicenter, double-blind, placebo-controlled PSUMMIT I Study. Ann Rheum Dis. 2012;71:107.
Sandborn WJ, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, Johanns J, Blank M, Rutgeerts P; Ustekinumab Crohn's Disease Study Group. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology. 2008;135:1130–1141.

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
	'important potential risk' for secukinumab is unclear, as clinical trial data[23]) did not show a safety signal for these events. *The sponsor notes that the overall exposure-adjusted incidence rate (EAIR) of adjudicated MACE in the All Psoriasis Ixekizumab Exposure Integrated Analysis Set at the time of database lock for the original submission was 0.72 per 100 patient-years (CI: 0.50 to 1.02). This included N = 4030 patients treated with ixekizumab and 4321.8 patient-years of exposure in all 5 adjudicated psoriasis clinical studies. The updated All Psoriasis Ixekizumab Exposure Integrated Analysis Set, with database lock of 09 Apr 2015 which included 4035 patients treated with ixekizumab amounting to an overall exposure of 6026.4 patient-years, showed an EAIR of MACE of 0.63 per 100 patient-years (CI: 0.46 to 0.87) across the adjudicated studies (0.1 for vascular death, 0.4 for nonfatal myocardial infarction, and 0.1 for nonfatal stroke per 100 patient-years, respectively).* *While the background rates for MACE in a population with moderate-to-severe plaque psoriasis is not well characterised, there is sufficient evidence that MACE and cardiovascular disease in general have a higher prevalence in a population with moderate-to-severe plaque psoriasis.[24] This risk appears to be independent of smoking, obesity, and hyperlipidaemia.[25] The EAIR of MACE observed in the ixekizumab clinical development programme is comparable to those reported from registries and medical records database studies. Taking into consideration differences in severity of disease (data include incidence in early/mild psoriasis in whom incidence of MACE is lower than that for the target population) and the fundamental differences between registries, medical records database studies, and randomised clinical trials.* *Therefore, the sponsor considers that the observed rate of MACE seen in the ixekizumab-treated population in the clinical development programme is more likely to be a reflection of disease morbidity in the target population and not a potential adverse*	

[23] [FDA] Food and Drug Administration. Secukinumab (AIN457) advisory committee briefing material: available for public release. 12 September 2014. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM419023.pdf. Accessed March 2016.

[24] Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol. 2008;159(4):895-902.
Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. Arch Dermatol. 2009;145(6):700-703.

[25] Gaeta M, Castelvecchio S, Ricci C, Pigatto P, Pellissero G, Cappato R. Role of psoriasis as independent predictor of cardiovascular disease: a meta-regression analysis. Int J Cardiol. 2013;168(3):2282–2288.

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
	effect of the drug. Thus, MACE would not warrant classification as an 'important potential risk' in the RMP. *The role of the cytokine IL-17 in atherosclerosis is still unclear and IL-17 has been found to be both pro- and anti-atherogenic in the animal model.[26] Inconclusive findings from clinical studies have been suggestive of a pro-atherogenic role of IL-17 in atherosclerosis, whereas another study found atheroprotective effects of IL-17 by maintaining plaque stability through the induction of proliferation of smooth muscle cells and collagen in atherosclerotic plaques.[26]* *In summary and based on available data, the sponsor considers that the EAIR of MACE (0.63 per 100 patient-years) seen in the ixekizumab-treated population in the clinical development programme is more likely to be a reflection of disease morbidity in the target population and not a potential adverse effect of the drug. Thus, MACE would not warrant classification as an 'important potential risk' in the RMP.*	
7. Both post-authorisation registries are to be conducted in the US with protocols expected to be submitted in late 2016. The sponsor should provide justification to how findings from these studies are applicable to the Australian context or propose other measures to monitor the safety concerns. Protocols for the studies should be submitted to the TGA for review once they are available.	*Sponsor's response: The sponsor would like to clarify with TGA that the company is proposing a single registry, namely, the Consortium of Rheumatology Researchers of North America (Corrona) Psoriasis Registry. This registry is a prospective, multicentre, US-based observational, disease registry for patients with psoriasis and will include patients identified in a routine clinical setting who have started on or switched to a systemic agent for psoriasis within the previous 12 months. The registry plans to enrol up to 4000 ixekizumab-treated patients and 4000 reference patients, followed for 8 years. This study will assess inflammatory bowel disease, serious infections, serious hypersensitivity, and other safety outcomes. The registry will also collect maternal and infant outcomes. Furthermore, the sponsor is proposing an additional observational study to evaluate the use of ixekizumab during pregnancy. The Corrona registry is anticipated to be the largest source of routinely and consistently collected observational data on post-market exposure to ixekizumab.* *The ability to generalise findings from the US registry to Australian patients is based on differences between these 2 populations. The following points are to be considered: the mechanism by which immunosuppression is anticipated to lead to adverse outcomes, the distribution of risk factors for the adverse outcomes, and treatment patterns.*	The evaluator has noted the sponsor's clarification. The sponsor's response on the applicability of US studies is acceptable.

[26] Gong F, Liu Z, Liu J, Zhou P, Liu Y, Lu X. The paradoxical role of IL-17 in atherosclerosis. Cell Immunol. 2015;297(1):33-39.

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
	Firstly, there is no reason to believe that US and Australian patients with psoriasis would respond differently to the effects of immunosuppression. Since the mechanism by which immunosuppression may lead to adverse outcomes is the same, the results from the US registry are expected to be applicable to the Australian population. *Secondly, a comparison of data from the Australian Psoriasis Registry (APR) and large US insurer show a similar distribution of age, sex, and other important risk factors for serious infections, inflammatory bowel disease, and malignancy[27] Differences in the categorisation of obesity and lack of smoking data preclude a direct comparison of these risk factors; however, in the general US and Australian populations, the prevalence of smoking and obesity is comparable[28]. Therefore, the distribution of risk factors for adverse outcomes is similar between US and Australian population.* *Finally, practice patterns for the use of biologic medications to treat psoriasis differ between the US and Australia. In Australia, a higher disease severity and more treatment failures are required before a biologic therapy can be initiated.[29] Although practice patterns are different, the Corrona registry is expected to capture a heterogenous group of patients with psoriasis, including patients with highest level of disease severity, ensuring applicability of these results to Australian patients with psoriasis.*	
8. The proposed observational pregnancy study in the EU-RMP is not referred to by the ASA. The sponsor	*No response provided.*	The sponsor has not provided a direct response to this recommendatio

[27]Abuabara K, Lee H, Kimball AB. The effect of systemic psoriasis therapies on the incidence of myocardial infarction: a cohort study. Br J Dermatol. 2011;165(5):1066-1073.
[APR] Australasian Psoriasis Registry. Update on Australian Psoriasis Registry. May 2015 Newsletter; Data held by the Skin & Cancer Foundation Victoria.
Wu JJ, Nguyen TU, Poon KY, Herrinton LJ. The association of psoriasis with autoimmune diseases. J Am Adad Dermatol. 2012;67(5):924-930.
[28] [WHO] World Health Organisation. Prevalence of tobacco use among adults and adolescents. Available at: http://gamapserver.who.int/gho/interactive_charts/tobacco/use/atlas.html. Accessed February 2016a.
[WHO] World Health Organisation. Global Health Observatory Map Gallery. Available at: http://gamapserver.who.int/mapLibrary. Accessed February 2016b.
[29]Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Leonardi CL, Lim HW, Van Voorhees AS, Beutner KR, Ryan C, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011;65(1):137-74.
Baker C, Mack A, Cooper A, Fischer G, Shumack S, Sidhu S, Soyer HP, Wu J, Chan J, Nash P, Rawlin M, Radulski B, Foley P. Treatment goals for moderate to severe psoriasis: an Australian consensus. Australas J Dermatol. 2013;54(2):148-54.

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
should provide clarification to this or propose other measures to monitor 'use in pregnancy' in Australia.		n. Even though the study may use records from Corrona Registry, it has different objectives and different milestones. The EU-RMP also refers to this study as a separate study from Corrona Registry. The sponsor should include this study and the 3 year clinical follow-up of all recipients of ixekizumab in the ongoing extensions of studies RHAZ, RHBA, and RHBC in the updated ASA to be submitted to the TGA..
9. The sponsor should provide plans to alternative additional pharmacovigilance measures in the event of rejection, deferral, or withdrawn of submission in the US.	*Ixekizumab received a Positive Opinion from the EU CHMP on 26 Feb 2016, leading the Applicant to believe it is very likely that ixekizumab will be approved in the US. In the event the US ixekizumab Biologics License Application (BLA) is rejected, deferred, or withdrawn, there are options to conduct post-marketing safety surveillance in European registries. Lilly has conducted a Feasibility Study of European registries in 2015 and identified 3 (in Denmark, Germany, and Italy) that, due to their quality of data, willingness to collaborate, and add outcomes to routine data collection, would make them satisfactory alternatives in the event that ixekizumab is not approved in the US (and therefore, the Corrona study cannot provide ixekizumab safety data). An additional 3 were identified (in UK, Switzerland, and Sweden) which may be suitable, albeit they have some limitations.*	The sponsor's response is acceptable.
10. In regard to the proposed routine risk minimisation activities, it is recommended to the	*The sponsor appreciates the TGA recommendation to 'consider more detailed guidance on the actual period during which live vaccination should be avoided based on available evidence, eg. 'Vaccination with live vaccine is not recommended during treatment and up*	The sponsor's response to the recommendation on live vaccines is

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
Delegate that the draft product information document be revised as follows: Patient groups not studied in clinical trials: the approved PI for secukinumab contains advice on key exclusion criteria, which include 'patients with HIV, hepatitis B, hepatitis C, history of malignancy, uncontrolled hypertension and congestive heart failure, patients with blood cell count < 2500/microL, neutrophils < 1500/microL', etc. This provides important information for clinicians to consider the difference between the clinical trial subjects and psoriasis patient population. Further, these patient populations are also at a higher risk of experiencing adverse events. It is recommended that the same approach be taken for ixekizumab.	*to [period] after discontinuation.''* *The sponsor's proposal in the draft PI that 'Taltz should not be used with live vaccines' was based on current recommendations for patients with rheumatic diseases treated with immune-modulating medicines[30] and the lack of available data on the response to live vaccines in patients treated with Taltz. Controlled clinical studies of co-administration of ixekizumab or broader group of immune-modulating medicines with live vaccines have not been performed. Recommendations on actual periods during which live vaccinations should be avoided in immunosuppressed patients including patients receiving biologics, vary widely and are not consistent across different geographies. The European League Against Rheumatism (EULAR) in its guidelines on vaccination in adult patients recommends 'avoiding the use of live attenuated vaccines in immunosuppressed patients with autoimmune inflammatory rheumatic diseases whenever possible' but was silent on intervals between administration of a biologic and when patients can be given live vaccines.[31] The American College of Rheumatology (ACR) in its 'Recommendations for the Use of Disease-Modifying Anti-Rheumatic Drugs and Biologics in the Treatment of Rheumatoid Arthritis (RA)' states that all appropriate vaccines including live attenuated (Herpes Zoster) vaccinations should be undertaken before starting a DMARD or a biologic, but remained silent on the interval between discontinuation of a biologic and administration of a live vaccine.[32] In its 2011 recommendations for special populations, the Centers for Disease Control and Prevention (CDC) stated that immunosuppression (that is, high-dose steroids, biological response modifiers, chemotherapy, AIDS) is a contraindication for Herpes Zoster vaccine (HZV). They included in their recommendations that age appropriate patients who are anticipating immunodeficiency due to initiation of*	acceptable. The sponsor has not provided a direct response to the other recommendations. The recommendations on patient groups not studied in clinical trials and on infection remain for the Delegate's determination.

[30] Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Kone-Paut I, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis. 2011;70(10):1704–12.
Kroger AT, Sumaya CV, Pickering LK, Atkinson WL. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(2):1-64.
Van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70(3):414-22.
[31] Van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70(3):414-22.
[32] Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL Jr, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res. 2012; 64:625–639.

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
Advice on pathology tests should use units that are commonly used in Australia. Infection: the sponsor has advised in the EU-RMP that 'due to the mechanism of action/immunosuppressive potential of medicines of the anti-TNF or anti-IL classes, patients with evidence of untreated latent TB or certain viral infections such as Hepatitis B may be at greater risk of reactivation or exacerbation of their underlying disease'. In comparison, relevant advice provided in the draft PI under 'Precautions - infections' is rather general. It is recommended that the Delegate considers adding the above advice provided to the PI. Live vaccines: the draft PI states that 'Taltz should not be used with live vaccines' in the draft PI. It is recommended that the Delegate considers more detailed guidance on the actual period during which live	*treatments or progression of illness should be offered HZV.*[33] *The current recommendation is that all patients anticipating therapy with biologics such as ixekizumab should receive all age appropriate vaccinations prior to initiation of therapy, while live vaccines should not be administered concurrently with such therapies. The time period of risk following use of a biologic and administration of a live vaccine is not expected to be uniformly predictable among various vaccines and patient populations, and likely depends on multiple factors including an individual patient's overall immune status (for example, as impacted by age, comorbidities, other concomitant immunomodulatory medications) and any expected residual immunity from prior vaccination or natural exposure to the target pathogen. The sponsor has identified a publication describing the lack of development of varicella or herpes zoster in 551 adult patients with autoimmune diseases given live, attenuated HZV for prevention of herpes zoster during treatment with anti-TNF biologic agents).*[34] *There is also a report of 17 adult patients with rheumatoid arthritis who were receiving infliximab and who were re-vaccinated, more than 10 years after their most recent yellow fever vaccination, with live, attenuated yellow fever vaccine. There was no clinical development of illness suggestive of yellow fever.*[35] *Another publication describes 15 children re-vaccinated with live, attenuated measles, mumps, and rubella vaccine during treatment with etanercept and low-dose methotrexate for juvenile idiopathic arthritis, without the occurrence of vaccine-associated disease.*[36] *These reports highlight the fact that the time period of risk for administration of a live vaccine following a biologic is not well documented, at least among these live vaccines and patient populations, making it unhelpful to prescribe a single time period for all relevant situations.* *The sponsor considers that the likelihood of concurrent use of a live vaccine and biologic is low, as it is effectively off label use, given experience with*	

[33] Kroger AT, Sumaya CV, Pickering LK, Atkinson WL. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(2):1-64.
[34] Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, Saag KG, Baddley JW, Curtis JR. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA. 2012;308(1):43-49.
[35] Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC, Lima RA. Yellow fever revaccination during infliximab therapy. Arthritis Care & Research. 2010;62(6):896-898
[36] Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology. 2009;48:144-148.

Recommendation in RMP evaluation report and sponsor's response	Sponsor's response	RMP evaluator's comment
vaccination should be avoided based on available evidence, eg. 'Vaccination with live vaccine is not recommended during treatment and up to [period] after discontinuation.'	*other biologics which all warn against concomitant use, as well as specifically for ixekizumab, which will have the warning/precaution stated above. No data have been identified that demonstrate that biologics and live vaccines administered concurrently result in clinical complications that would impact public health or the benefit-risk for patients.* *In conclusion, the sponsor considers that based on the current limited evidence and available recommendations from professional and government authorities, decisions on the actual period to avoid live vaccines after discontinuation of therapy will best be made by health care providers in consideration of the expected benefit and risk for the individual patient. The sponsor proposes retention of the current statement in the BLA application, 'TALTZ should not be used with live vaccines.'*	

Summary of recommendations

The RMP evaluator has noted that ixekizumab gained market authorisation in the EU in April 2016. In its assessment report, the CHMP endorsed version 4 of the EU-RMP.[37]

The sponsor should submit the updated EU-RMP (version 4) and also submit an updated ASA to the TGA prior to the date on which the TGA Delegate is due to make a decision on the submission. Differences between the EU-RMP and the ASA in terms of the safety concerns, pharmacovigilance and risk minimisation activities should be compared with justification provided for any differences.

In addition, the following recommendations made in the Round 1 report have not been adequately addressed by the sponsor. Details on the following outstanding issues are presented in Table 13 above.

Recommendations 2, 4, 5 and 6: These recommendations relate to the list of safety concerns. The sponsor has rejected all the recommended changes in its response to TGA requests for information and provided justifications. However, in version 4 of the EU-RMP all the safety concerns recommended by the RMP evaluator have been included in the Summary of Safety Concerns.[37] The only exception is 'use in patients with severe cardiac disease or uncontrolled hypertension'. The sponsor has provided acceptable justification to not add 'use in patient with severe cardiac disease or uncontrolled hypertension' as 'missing information'. Therefore, the sponsor's response is acceptable on this issue. However, the sponsor's response to other recommendations is not acceptable as it is inconsistent with its updated EU-RMP and should be addressed by the sponsor.

Recommendation 8: The sponsor has not responded directly to this recommendation. Even though the study may use records from Corrona Registry, it has different objectives and different milestones. The EU-RMP also refers to this study as a separate study from Corrona Registry. The sponsor should include this study and the 3 year clinical follow-up

37. European Public Assessment Report (EPAR) for Taltz, ixekizumab. 23 February 2016; EMA/CHMP/190631/2016

of all recipients of ixekizumab in the ongoing extensions of Studies RHAZ, RHBA, and RHBC in the updated ASA to be submitted to the TGA.

Recommendation 10: The sponsor's response to the recommendation on live vaccines is acceptable. However, the sponsor has not provided a direct response to the other recommendations. The recommendations on patient groups not studied in clinical trials and on infection remain for the Delegate's determination.

Recommendation on Pregnancy category: the non-clinical evaluator has made recommendation to change the Pregnancy category from B1 to C.[16,17] The RMP evaluator agrees with the non-clinical evaluator's recommendation. The RMP documents, including relevant part of the PI should be updated to reflect the correct Pregnancy category approved by the TGA.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

No suggested wording could be provided at this stage as the sponsor is required to submit the updated EU-RMP with the ASA. The updated EU-RMP, accepted by the EMA, has incorporated most of the recommendations on the list of safety concerns made by the RMP evaluator.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There are no objections on quality grounds to the approval of Taltz ixekizumab 80 mg/mL solution for injection prefilled syringe and Taltz ixekizumab 80 mg/mL solution for injection prefilled pen other than outstanding GMP clearances. The sponsor advised in an email dated on 23 May 2016 that GMP applications for four manufacturing sites were submitted between 16 and 20 May 2016 and that approvals are pending.

The biological evaluator has proposed conditions of registration.[38]

Nonclinical

Primary pharmacology studies provided sufficient evidence of ixekizumab affinity and selectivity for human and monkey IL-17A, as well as neutralisation of its actions.

Treatment-related effects associated with weekly injections were minimal and limited to injection site reactions which resolved by the next dosing interval.

Ixekizumab was found to cross the placenta (fetal:maternal serum ratio approximately 0.2) in monkeys. Milk transfer studies showed a low amount of ixekizumab excreted in the milk (< 0.2%). Ixekizumab had no effect on menstrual cycling, sperm parameters or

[38] *Details of the proposed conditions for approval are given in Section II, Quality findings: Quality Summary and Conclusions of this document.*

caused histological changes to reproductive tissues in monkeys, and is not anticipated to affect fertility. There were also no effects on embryofetal development (NOAEL ≥ 50 mg/kg/week).

Although there were no treatment-related changes to immune responses or lymphocyte populations in neonates, there is a theoretical risk of compromised neonatal immunity and the pregnancy category C is considered appropriate based on the pharmacological action of ixekizumab.

A pre/post-natal development study reported no adverse effects on maternal health, no effect to length of gestation, infant morphometric measurements, neurobehavioural parameters, ophthalmology assessments, heart rate assessments, NK-mediated cytolytic activity, humoral responses to KLH antigen and lymphocyte subset populations. A number of infants from ixekizumab-treated groups died or were euthanised within 6 days of birth (2 from mid-dose group; 5 from the high dose group out of a total of 18 infants). The predominant cause was maternal neglect, and an association to ixekizumab could not be excluded. Pregnancy Category C was considered appropriate.

Clinical

Pharmacology

Pharmacokinetics

The average bioavailability of ixekizumab following across SC injection sites of thigh, arm and abdomen was estimated to be in the range of 54% to 90% (54% with 35% inter individual variability in Study RHAG alone; 60% to 90% in the Primary PopPK, analysis estimated resulted based on the starting doses of 160 mg, followed by 80 mg Q2W or Q4W up to Week 12). Bioavailability was highest when ixekizumab was administered via the thigh compared to administration via the abdomen or arm. Population typical values for SC bioavailability of 75% were observed for thigh administration and 60% for other sites of administration. The data are consistent with published SC bioavailability estimates for other IgG human monoclonal antibodies.

Pharmacokinetics were broadly linear over the dose range 5 mg to 160 mg SC. Absorption following SC injection was slow, with a median T_{max} (estimated from the final PK model) of 5 days. On SC dosing of ixekizumab mean (SD) C_{max} and $AUC_{(0\text{-}14d)}$ estimates in the 160 mg starting dose group (80 mg Q2W regimen) were 19.9 (8.15) µg/mL and 154 (58.1) µg day/mL, respectively. The time to reach steady state was estimated to be 8 weeks for both dosing regimens. Once steady state had been reached, mean (SD) $C_{max,ss}$ and $C_{trough,ss}$ estimates were 21.5 (9.16) µg/mL and 5.23 (3.19) µg/mL, respectively, for the Q2W dosing regimen, and 14.6 (6.04) µg/mL and 1.87 (1.30) µg/mL, respectively, for the Q4W dosing regimen.

Total volume of distribution at steady state was estimated at 7.11 L, suggesting ixekizumab has limited distribution into extravascular tissues. Vd is comparable with reported values for other IgG monoclonal antibodies. The Primary PopPK Analysis identified body weight as significant predictor of volume of distribution, with the volume of distribution increasing as body weight increased.

There were no clinical studies investigating the metabolism of ixekizumab. However, ixekizumab is a large monoclonal antibody with a molecular weight of 149,049 Dalton and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. Geometric mean (geometric CV%) serum clearance for ixekizumab was 0.0161 L/h (37%), and appeared to be independent of dose over the range 5 mg to 160 mg. The geometric mean (geometric CV%) of the $t_{½}$ calculated from the individual post hoc estimates was approximately 13 days (40%).

Body weight was a significant covariate on the clearance of ixekizumab. The effect of bodyweight was shown in a sub-study of Study RHBL and is described in the clinical evaluation. That sub-study examined the PK of ixekizumab in patients in three weight categories: < 80 kg; 80 to 100 kg; and > 100 kg. The clinical evaluation report shows the extent of effect of increasing weight in reducing the AUC of ixekizumab. The ratio GM $AUC_{0\text{-t last}}$ for bodyweight > 100 kg/bodyweight < 80 kg was 0.632. There was considerable overlap in exposure and no dose adjustment according to body weight is considered to be warranted.

No studies were performed in patients with hepatic or renal impairment. Given the product is a monoclonal antibody this is acceptable.

Pharmacodynamics

The PD of ixekizumab was explored through exposure-response (PK/PD) relationships relating to efficacy, safety and immunogenicity. These analyses examined the relationship between predicted serum levels of ixekizumab at the end of the induction period at Week 12, and at the end of the maintenance dosing period at Week 60, in Phase III studies.

The primary efficacy measures for exposure-response modelling were Static Physician Global Assessment (sPGA) and Psoriasis Area and Severity Index (PASI) response. This model indicated that patients with palmoplantar psoriasis had a 13% lower E_{max} (maximum effect) compared to patients with no palmoplantar involvement, resulting in a reduced probability of achieving an sPGA(score of 0 or 1) score at Week 12. Using the median Week 12 serum trough ixekizumab concentration of 5.71 µg/mL, the probability of achieving an sPGA(score of 0 or 1) was 0.79 for a patient with palmoplantar involvement compared to 0.88 for a patient without palmoplantar involvement. Heavier patients also had a lower maximum effect estimate (E_{max}) and thus a lower probability of achieving an sPGA(score of 0 or 1) score compared to lighter patients. This effect of weight was in addition to the effect of weight previously identified in the PK model where an increase in weight was associated with a decrease in exposure.

Data from 270 patients were available for the Week 60 exposure-response estimates. For the sPGA(0) response, there was a larger response at Week 60 compared to Week 12 for the same estimated drug exposure suggesting that time may play a role in obtaining complete skin clearance.

The PASI exposure-response analyses also suggested that patients with palmoplantar involvement will be somewhat less likely to respond well to ixekizumab compared with patients with psoriasis affecting other areas. Previous treatment with a biologic agent was associated with a reduced probability of achieving PASI 90 given the same extent of predicted exposure to ixekizumab.

There appeared to be a positive relationship between ixekizumab concentration and injection site reactions, with a higher incidence at higher ixekizumab concentrations. Additionally, while there was no apparent ixekizumab concentration relationship for the other AEs of special interest assessed (infections, hypersensitivity reactions, *Candida* infections and staphylococcal infections) during the maintenance period there was a weak association during the induction period for Candida infections and new or worsening neutropenia Grade 2 or higher.

Immunogenicity and treatment outcomes: Treatment emergent anti-drug antibodies (TE-ADA) were present in 4.5% (104/2293) patients prior to induction treatment and were present at any time during the 12-week induction period in 11.2% (256/2293) patients given ixekizumab, with a slightly higher incidence in those given the monthly dosing (13.4%) compared with the fortnightly dosing (9.0%).

During the induction period neutralising antibodies (NAb) were present in 1.0% 24/2293 patients, (0.4% of ixekizumab 80 mg Q2W patients, 1.7% of ixekizumab 80 mg Q4W

patients, and 1.0% overall). Across all groups, for patients identified as treatment emergent (TE) ADA positive, 83.2% of the NAb analyses were inconclusive due to serum concentrations of ixekizumab exceeding the drug tolerance threshold of the NAb assay in the samples tested.

In the Maintenance Dosing Period, the incidence of TE-ADA positive patients was 21.4% (141 of 659) and confirmed NAb positive patients was 0.8% (5 of 659) among the efficacy evaluable patients who were ixekizumab treated sPGA (score of 0 or 1) responders during the Induction Dosing Period and who remained on ixekizumab up to Week 60. There was a weak positive association between efficacy and absence of TE-ADA in the induction period. In patients treated with ixekizumab (80 mg Q2W or 80 mg Q4W), a PASI 75 at Week 12 was observed in 72.7% (186/256) of TE-ADA positive patients and 87.9% (1791/2037) of TE-ADA negative patients. In the placebo group, 25% (1/4) of ADA-positive patients achieved a PASI 75 at Week 12 compared to 4.4% (34/777) of ADA-negative patients.

The proportion of patients achieving a sPGA (score of 0 or 1) response at Week 12 was lower in TE-ADA positive patients compared to TE-negative patients (65.6% [168/256] versus 81.1% (1652/2037)). The clinical evaluator considered this difference clinically meaningful and suggested that consideration should be given to testing ixekizumab ADA status in patients not responding to the drug during the induction dosing period.

During the maintenance period in patients exposed to ixekizumab a PASI 75 at Week 60 was achieved by 61.7% (87/141) of TE-ADA positive patients and 63.5% (329/518) of TE-ADA negative of patients, respectively. In general, patients who were NAb positive had reduced ixekizumab concentrations and responded poorly or not at all to treatment with ixekizumab.

The All Psoriasis Ixekizumab Exposures dataset comprised 4107 patients enrolled in 6 studies. Treatment Emergent Adverse Events (TEAEs) were reported more frequently in ADA-negative patients than in ADA-positive patients (persistent or transient) (78.4% versus 47.2%, respectively). The incidence of patients in the two treatment groups (ADA-positive (persistent or transient) versus ADA-negative) for the following TEAEs were: death (0% versus 0.1%); SAEs (8.0% versus 6.9%); discontinuation of the study drug (2.3% versus 4.4%); injection site reactions (7.4% versus 14.3%); anaphylaxis (0.2% versus 0.5%); and non-anaphylaxis allergic reactions/ hypersensitivities (3.5% versus 8.6%).

QTc assessment was not performed. This is acceptable for a monoclonal antibody.

Dose selection for the Phase III studies was based on the exposure-response analysis data from the combined Phase I and II studies. Additionally, Study RHAJ, a Phase II dose-ranging and efficacy study described in Section 4 of the CER showed that a 150 mg dose of ixekizumab was associated with higher responses by Week 12 compared to the lower doses studied (10 mg, 25 mg, and 75 mg). These analyses lead to the selection of a 160 mg starting dose (two 80 mg injections) for evaluation in the Phase III studies. Dose finding continued in the Phase III studies with the efficacy and safety of ixekizumab 80 mg given Q2W or Q4W during the induction phase and Q4W or Q12W in the maintenance phase of those studies.

Efficacy

There were 3 Phase III studies regarded as pivotal (Studies RHAZ, RHBA and RHBC). These are described in section 7 of the CER.

These studies were multi-centre, randomised, double-blind and placebo-controlled. Each study assessed two doses of ixekizumab in the induction period. Both ixekizumab dose regimens commenced with 160 mg SC in the first week followed by either 80 mg Q2W or Q4W.

- Study RHAZ had a 12 week induction period followed by a re-randomised blinded maintenance dosing period to Week 60 and a planned long-term extension period in which patients are to receive study treatment to Week 264. The two induction dose regimens of ixekizumab were compared with placebo in the induction period and ixekizumab doses of 80 mg Q4W and Q12W were compared with placebo in the maintenance period using a randomised withdrawal design. A total of 1296 patients were randomised.
- Study RHBA had a12 week induction period and a maintenance period which is ongoing. In addition to the two ixekizumab dose regimens an active control (etanercept 50 mg twice weekly) and placebo control were included in the induction period. In the maintenance period ixekizumab 80 mg Q4W or Q12W was to be compared with placebo, using a randomised withdrawal design. A total of 1224 patients were randomised.
- Study RHBC had a 12 week induction period and only that data were included in the submission. Long-term safety and efficacy of 80 mg ixekizumab every 4 weeks are to be evaluated for up to a total of 5 years. This study compared the two induction dose regimens of ixekizumab with placebo and etanercept 50 mg twice weekly. A total of 1225 patients were randomised.

In all three pivotal studies efficacy was assessed primarily using the sPGA and PASI. The sPGA is the physician's determination of the patient's psoriasis severity at a given time point on a 6 point scale (0 = cleared, 1 = minimal, 2 = mild, 3 = moderate; 4 = marked, 5 = severe). Overall lesions are categorised by descriptions for induration, erythema, and scaling. The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 (for no psoriasis) to 72 (for the most severe disease). The PASI scores were categorised as at least 50%, 75%, 90% or 100% improvement in PASI score from baseline.

These studies enrolled adult patients with a confirmed diagnosis of chronic plaque psoriasis for at least 6 months and who were candidates for phototherapy and/ or systemic therapy. Study subjects were also required to have ≥ 10% Body Surface Area involvement, a sPGA score of ≥ 3, and PASI score ≥ 12 at screening and at baseline. Subjects were permitted to have taken prior systemic psoriasis therapy (biologic and non-biologic, excluding IL-17A antagonists or alpha-4-integrin agents), topical therapies, phototherapy, and vaccines. Each allowed prior therapy must have been discontinued prior to baseline for a protocol-specified time-period. During the study, limited use of topical therapies was allowed, as was the use of non-live seasonal vaccinations and/or emergency vaccinations.

These studies had the following co-primary efficacy endpoints which were assessed at Week 12:

- proportion of patients with sPGA (score of 0 or 1) with at least a 2-point improvement from baseline; and
- proportion of patients achieving at least a 75% improvement from baseline (PASI 75) from baseline

The placebo multiple imputation (pMI) method was used for the analysis of co-primary efficacy endpoints and for the analysis of the percentage improvement in PASI scores at Week 12 (Visit 7). The pMI method assumes that the statistical behaviour of drug-treated and placebo-treated patients after discontinuing study medication becomes that of placebo-treated patients. Multiple imputations were used to replace missing outcomes (sPGA score and PASI score) for drug-treated and placebo-treated patients who

discontinued using multiple draws from the posterior predictive distribution estimated from the placebo arm. The binary outcomes, sPGA (score of 0 or 1) and PASI 75, were then derived from the imputed data.

In addition to the comparison of each dose of ixekizumab with placebo, Studies RHBA and RHBC assessed non-inferiority of each dose of ixekizumab with etanercept at Week 12. These comparisons of the proportion of subjects with a sPGA (0 or 1) at Week 12, were to be conducted only if the ixekizumab dose and the etanercept results were significantly better than placebo. Treatment comparisons between etanercept and placebo in the proportion of patients achieving an sPGA (score of 0 or 1) response at Week 12 (Visit 7) was also analysed using the Cochran Mantel Haenszel (CMH) test stratified by pooled centre. Missing data were imputed using the non-responder imputation (NRI) method. The PASI 75 at Week 12 non-inferiority assessment was conducted only if both the ixekizumab dose and the etanercept results were was significantly better than placebo. Treatment comparisons were analysed using the CMH test stratified by pooled centre. Missing data were imputed using the NRI.

For the ixekizumab/etanercept comparisons the non-inferiority margin was -12.0% for both sPGA (score of 0 or 1) and PASI 75 in each of the studies in which these comparisons were made. This difference was considered clinically unimportant and represents a ≥ 70% preservation of the etanercept treatment effect (based upon the difference between etanercept and placebo) observed in historical Phase III studies for etanercept 50 mg twice weekly compared with placebo.[39],[40]

Major secondary endpoints included the proportion of subjects with a sPGA score of 0 (clear), a reduction of at least 90% in PASI (PASI 90) and a reduction of at least 100% in PASI (PASI 100).

In Studies RHAZ and RHBA there was a Maintenance Dosing Period (Period 3). This was a double-blind treatment period from Week 12 to Week 60 to evaluate the optimum dosing interval, the maintenance of response and/or remission, the occurrence of relapse or rebound following treatment withdrawal, and the response to re-treatment with ixekizumab following relapse in a re-randomised patient population.

At Week 12, patients entering the maintenance period were classified as either responders (sPGA score of 0 or 1) or non-responders (sPGA score > 1). Ixekizumab-treated patients who were classified as responders were re-randomised to treatment in the Maintenance Dosing Period at a 1:1:1 ratio to 1 of 3 treatment groups (ixekizumab 80 mg Q4W, ixekizumab 80 mg Q12W, or placebo) and considered the Maintenance Dosing Period Primary Population. Placebo- or etanercept-treated patients (Study RHBA only) who were classified as responders were assigned to placebo treatment. Patients who were classified as non-responders were given ixekizumab 80 mg Q4W in the Maintenance Dosing Period. Patients assigned to placebo were treated with ixekizumab 80 mg Q4W if they relapsed. No patients were given etanercept during maintenance periods.

Results for these studies were presented individually and as pooled results in Section 7 of the CER Attachment 2. In the induction dosing period, the primary psoriasis placebo-controlled integrated analysis set (Studies RHAZ, RHBA and RHBC) included 3126 patients in the ITT population with 1169 given ixekizumab 80 mg Q2W, 1165 given ixekizumab 80 mg Q4W, 792 given placebo, and 740 given etanercept.

[39] Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB; Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003;349(21):2014-2022.
[40] Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, Zitnik R, van de Kerkhof PC, Melvin L; Etanercept Psoriasis Study Group. A global Phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005;152(6):1304-1312.

The mean age of the total population was 45.5 years (range: 17 to 88 years), 67.7% were male, 92.6% were White and mean (SD) BMI was 30.5 (7.2) kg/m^2. Of the total population, 64.9% had used previous systemic therapy for psoriasis, 18.4% had used both non-biologic and biologic treatments. The mean sPGA score at baseline was 3.6 with 50.2% of patients having a baseline sPGA score of 3 (moderate disease severity) and 43.8% of patients having a baseline sPGA score of 4 (marked disease severity). The mean (SD) baseline PASI was 20.3 (7.9). The mean (SD) baseline % of BSA involvement was 27.5% (17.1%). The baseline demographic and disease characteristics were well balanced across the 4 treatment groups.

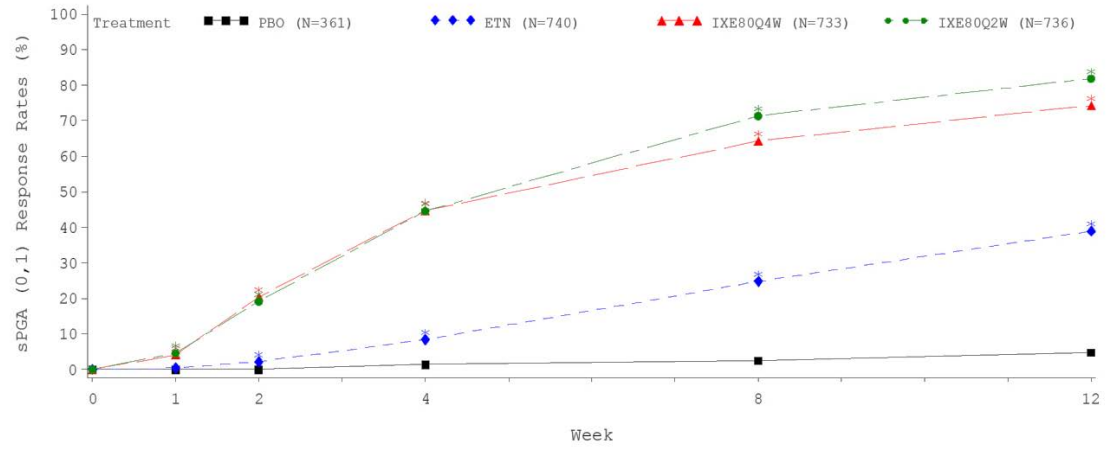
In each of these studies the comparisons for both the ixekizumab Q2W and Q4W were superior to placebo in the induction period. Results for the individual studies are presented in the CER. For the combined analysis results are shown below in Table 14.

Table 14. Response rates (NRI) at Week 12 for sPGA (score of 0 or 1) and PAS 75 in the induction dosing period; primary psoriasis placebo-controlled integrated analysis set, ITT population; IEA (Studies RHAZ, RHBA and RHBC)

	PBO (N = 792)	IXE 80 mg Q4W (N = 1165)	IXE 80 mg Q2W (N = 1169)
sPGA (score of 0 or 1) (Week 12)	31 (3.9%)	874 (75.0%)	956 (81.8%)
versus PBO; p-value		< 0.001	< 0.001
versus IXE80Q4W; p-value			< 0.001
PASI 75 (Week 12)	35 (4.4%)	951 (81.6%)	1037 (88.7%)
versus PBO; p-value		< 0.001	< 0.001
versus IXE80Q4W; p-value			< 0.001

For the combined analysis comparing etanercept with placebo and with either dose of ixekizumab, etanercept was superior to placebo. The proportion of patients achieving sPGA (score of 0 or 1) at Week 12 was 4.7%, 38.9%, 74.2% and 81.8% in the placebo, etanercept, ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups, respectively. The pairwise comparisons significantly favoured both ixekizumab treatment regimens over etanercept ($p < 0.001$, each comparison) and ixekizumab Q2W regimen over ixekizumab Q4W regimen. The sPGA (score of 0 or 1) response rates at each visit in the induction dosing period for the 4 treatment regimens are summarised below in Figure 2.

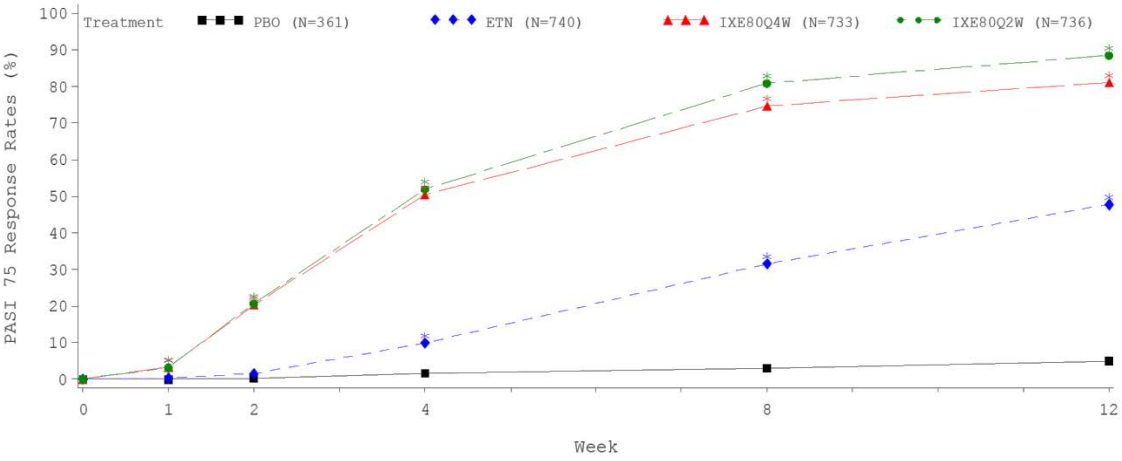
Figure 2. IEA (Study RHBA, RHBC) sPGA (score of 0 or 1) response rates, induction dosing period in the psoriasis placebo and active-controlled integrated analysis set; ITT population



Notes: PBO = Placebo; ETN= Etanercept; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q4W = Ixekizumab 80 mg Q4W; N = number of patients in the analysis population; NRI = non-responder imputation; sPGA = static physician global assessment.
* p-value <= 0.05 versus placebo.

The proportion of patients achieving PASI 75 at Week 12 was 5.0%, 47.7%, 81.0% and 88.5% in the placebo, etanercept, ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W groups, respectively. The pairwise comparisons significantly favoured both ixekizumab treatment regimens over etanercept ($p < 0.001$, each comparison) and the ixekizumab Q2W over the Q4W dose regimen. The PASI 75 response rates at each visit in the induction dosing period for the 4 treatment regimens are summarised below in Figure 3.

Figure 3. IEA (Study RHBA, RHBC) PASI 75 response rates induction dosing period in the psoriasis placebo- and active-controlled integrated analysis set; ITT population

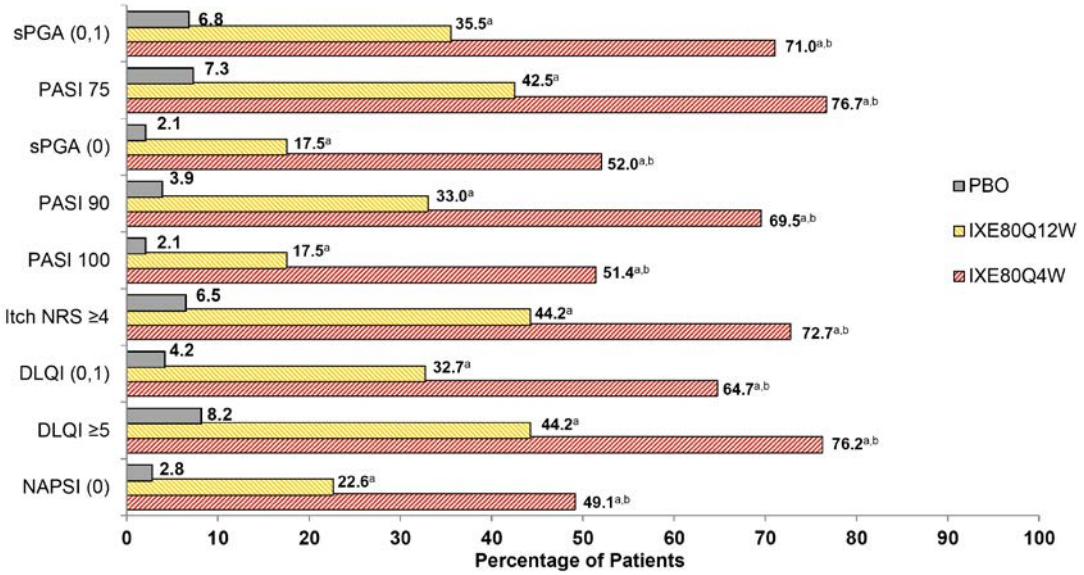


Notes: PBO = Placebo; ETN= Etanercept; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q4W = Ixekizumab 80 mg Q4W; N = number of patients in the analysis population; NRI = non-responder imputation; PASI = psoriasis area and severity index.
* p-value <= 0.05 versus placebo.

Secondary efficacy endpoints were also supportive of the ixekizumab Q2W dose regimen in the induction period.

In the maintenance integrated analysis set (Studies RHAZ and RHBA), statistically significant superiority ($p < 0.001$, all comparisons) for both ixekizumab regimens (80 mg Q12W and 80 mg Q4W) compared to placebo at Week 60 was demonstrated across a range of efficacy and health outcome endpoints.

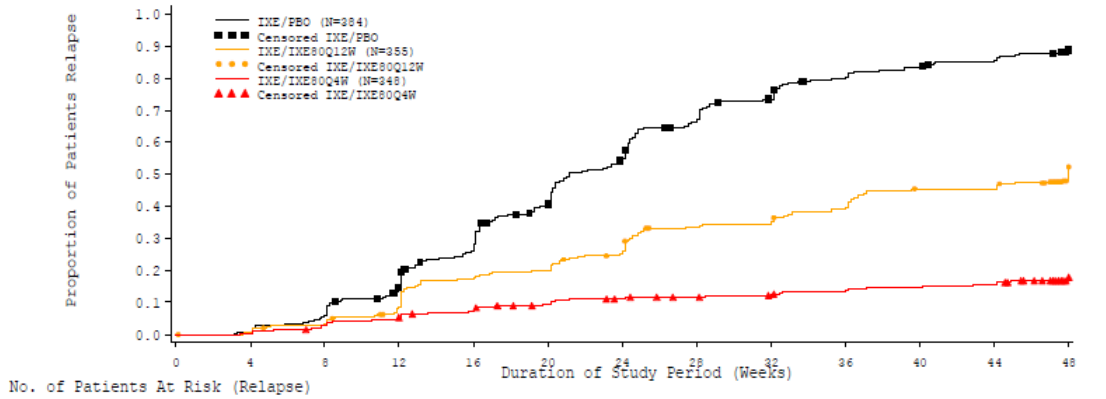
Figure 4. IEA (Study RHAZ, RHBA) Maintenance dosing period sPGA, PASI, Itch NRS, DLQI, NAPSI (%) responders Week 60 maintenance dosing period evaluable set



[a] p<.001 versus placebo
[b] p<.001 versus ixekizumab 80 mg Q12W

Relapse during the maintenance dosing period was defined as a sPGA ≥ 3. Of the patients who responded to ixekizumab at Week 12, the relapse rates in the maintenance dosing period were 84.4% (324/384) for patients re-randomised to placebo, 50.4% (179/355) for patients re-randomised to ixekizumab 80 mg Q12W and 17.2% (60/348) for patients re-randomised to ixekizumab 80 mg Q4W (Psoriasis Maintenance Integrated Analysis Set Efficacy Evaluable Patients (Studies RHAZ and RHBA)). The Kaplan-Meier plot to time to relapse for the maintenance group in the integrated efficacy analysis is reproduced in below in Figure 5.

Figure 5. Kaplan-Meier plot of time to relapse (sPGA ≥ 3) Maintenance Dosing Period, primary population-efficacy evaluable patients, Integrated Analysis Set



No. of Patients At Risk (Relapse)

IXE/PBO	384(2)	382(18)	364(32)	329(48)	277(51)	222(53)	167(43)	120(26)	92(22)	68(12)	56(6)	48(9)	33(2)
IXE/IXE80Q12W	355(2)	352(8)	343(18)	322(33)	289(9)	260(19)	259(26)	227(3)	224(16)	207(22)	184(0)	184(8)	154(13)
IXE/IXE80Q4W	348(1)	347(8)	338(8)	330(8)	320(7)	309(6)	301(2)	295(2)	291(4)	286(4)	282(3)	279(4)	226(3)

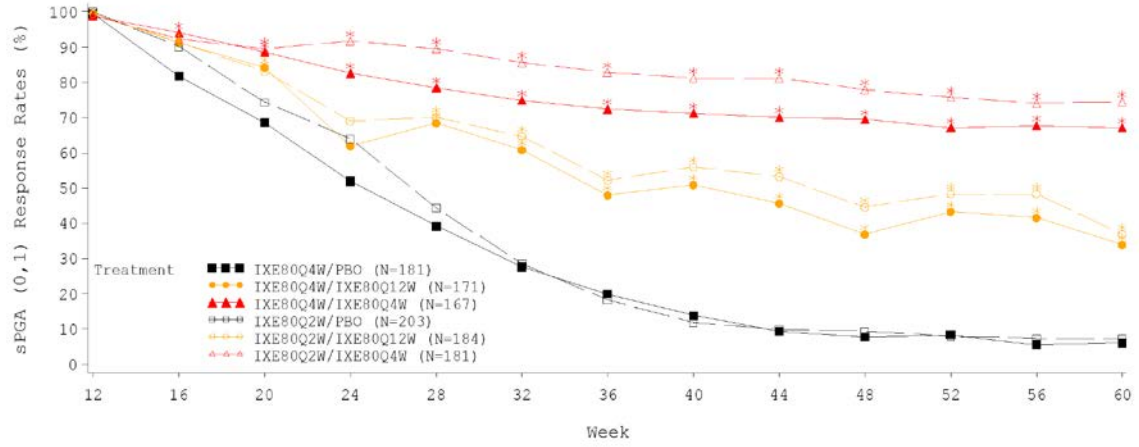
Notes: PBO = Placebo; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q12W = Ixekizumab 80 mg Q12W; N = number of patients in the analysis population;sPGA = static physician global assessment.

Rebound after ceasing treatment was reported in 3 (0.8%) of patients re-randomised to placebo in the maintenance period.

The sPGA (score of 0 or 1) and PASI 75 response rates at each visit from Week 12 to Week 60 are provided in below in Figure 6 and 7, respectively. Patients treated with placebo experienced a significant loss of sPGA response from Week 16 compared to patients

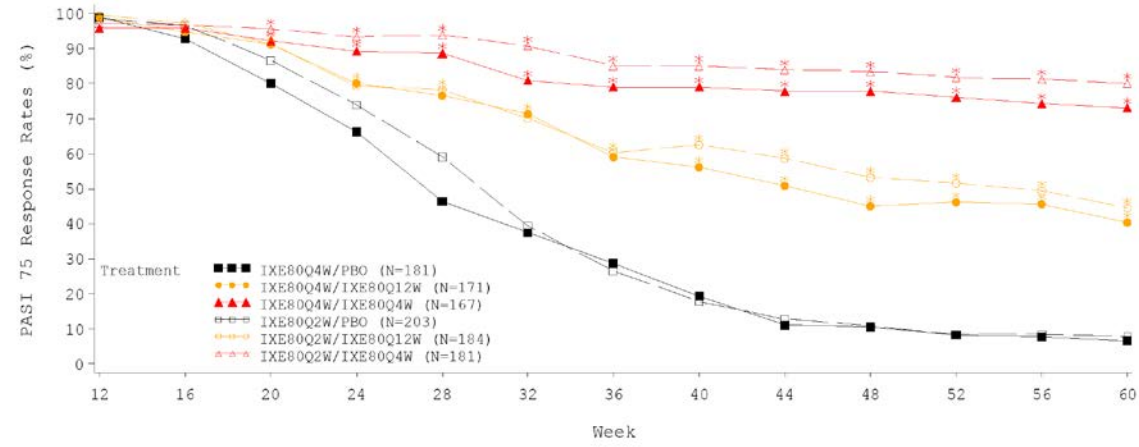
treated with 80 mg Q4W, and from Week 20 compared to patients treated with 80 mg Q12W. For PASI 75, patients treated with placebo experienced a significant loss of PASI 75 response from Week 20 compared to patients treated with 80 mg Q4W, and from Week 24 compared to patients treated with 80 mg Q12W.

Figure 6. IEA (Study RHAZ, RHBC) sPGA response rates, maintenance dosing period in the psoriasis maintenance integrated analysis set



Notes: PBO = Placebo; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q12W = Ixekizumab 80 mg Q12W; N = number of patients in the analysis population; NRI = non-responder imputation; sPGA = static physician global assessment.
* p-value <= 0.05 versus placebo.

Figure 7. IEA (Study RHAZ, RHBC) PASI 75 response rates, maintenance dosing period in the psoriasis maintenance integrated analysis set



Notes: PBO = Placebo; IXE80Q2W = Ixekizumab 80 mg Q2W; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q12W = Ixekizumab 80 mg Q12W; N = number of patients in the analysis population; NRI = non-responder imputation; PASI = psoriasis area and severity index.
* p-value <= 0.05 versus placebo.

In Study RHAZ patients who did not respond to ixekizumab 80 mg Q2W at Week 12, the response rate to treatment with 80 mg Q4W during the maintenance dosing period was 25.8% (16/62) for sPGA (score of 0 or 1) and 51.6% (32/62) for PASI 75 response at Week 60 (NRI) (see Section 7 of the CER (Attachment 2)). In Study RHBA for patients identified as non-responders to placebo or to etanercept at Week 12, 81.3% and 73.0% of patients, respectively, were able to achieve sPGA (score of 0 or 1) after 12 weeks of being treated with ixekizumab 80 mg Q4W in the Maintenance Dosing Period as shown in Table 15 below.

Table 15. Response rates during the maintenance period for non-responders to ixekizumab or etanercept in the induction period; Study RHBA

Parameter: sPGA (0,1)

By Individual Dose	IXE80Q4W/ PBO (N=72) n (%)	IXE80Q4W/ IXE80Q12W (N=61) n (%)	IXE80Q4W/ IXE80Q4W (N=57) n (%)	IXE80Q2W/ PBO (N=86) n (%)	IXE80Q2W/ IXE80Q12W (N=67) n (%)	IXE80Q2W/ IXE80Q4W (N=62) n (%)
Week 20(Visit 9) (Observed)						
Nx	68	58	54	83	63	59
Response [2]	42 (61.8%)	48 (82.8%)	48 (88.9%)	67 (80.7%)	55 (87.3%)	55 (93.2%
Week 20(Visit 9) (NRI)						
Response	42 (58.3%)	48 (78.7%)	48 (84.2%)	67 (77.9%)	55 (82.1%)	55 (88.7%
p-value [1] vs. PBO		0.016	0.002		0.550	0.125
Week 24(Visit 10) (Observed)						
Nx	61	53	52	77	61	59
Response [2]	30 (49.2%)	36 (67.9%)	46 (88.5%)	57 (74.0%)	46 (75.4%)	56 (94.9%
Week 24(Visit 10) (NRI)						
Response	30 (41.7%)	36 (59.0%)	46 (80.7%)	57 (66.3%)	46 (68.7%)	56 (90.3%
p-value [1] vs. PBO		0.056	<0.001		0.862	<0.001

Notes: PBO = Placebo; IXE80Q12W = Ixekizumab 80 mg Q12W; IXE80Q4W = Ixekizumab 80 mg Q4W; IXE80Q2W = Ixekizumab 80 m
Ixekizumab; NRI = non-responder imputation; N = number of patients in the analysis population; n = number of
specified category; Nx = number of patients with non-missing data in each category.
[1] p-value from Fisher's exact test.
[2] Percentage of response is calculated by n/Nx*100%.

Safety

In the all psoriasis ixekizumab exposures integrated analysis set, 4204 patients were exposed to ixekizumab at various doses and for various dosing periods, representing 4729.7 patients-years of exposure, with 2190 patients treated for ≥ 365 days and 1070 patients treated for ≥ 548 days and 378 patients treated for ≥ 378 days. Ixekizumab is also being developed for the treatment of rheumatoid arthritis with safety information from 4 studies with 532 patients exposed to ixekizumab. There were 4 data sets examined for safety and these are described in Section 8 of the CER (Attachment 2).

For patients given ixekizumab for psoriasis, Treatment-emergent Adverse Events (TEAE) considered by the investigator to be possibly related to the study drug were reported in 34.6% (1436/4204) of patients. TEAEs reported in ≥ 1.0% of patients, in descending order of frequency, were, injection site reaction (9.2%), nasopharyngitis (5.2%), injection site erythema (3.1%), URTI (2.2%), injection site pain (1.6%), headache (1.3%), and bronchitis (1.1%).

Overall 9 deaths were reported in patients randomised to treatment in the clinical development program, 8 in patients given ixekizumab (5 in the psoriasis program and 3 in the rheumatoid arthritis program and 1 death in a patient given etanercept. No patients given placebo died. Narratives of the deaths are in Section 8 of the CER (Attachment 2). In the psoriasis patient group the deaths were predominantly cardiovascular causes. In the rheumatoid group there was one death due to infection (granulomatous meningitis) in a patient exposed to multiple immune suppressant agents and one death of unknown cause.

For patients with psoriasis serious adverse events (SAE) were reported in 7.2% (303/4204) of patients. SAEs occurring in ≥ 0.2% of patients (≥ 7 patients) were: cellulitis (0.3%, n = 14), falls (0.2%, n = 9), acute myocardial infarction (0.2%, n = 8), myocardial infarction (0.2%, n = 8), and chronic obstructive pulmonary disease (0.2%, n = 7). In the rheumatoid arthritis patient group serious AEs were reported in 10.0% (53/532) of patients. SAEs occurring in ≥ 2 patients were: acute pancreatitis (0.6%, n = 3), pneumonia (0.6%, n = 3), anaemia (0,4% n =2), appendicitis (0.4%, n = 2), atrial fibrillation (0.4%, n = 2), ischaemic stroke, and non-cardiac chest pain (0.4%, n = 2).

For all psoriasis patients exposed to ixekizumab, AEs (including death) leading to discontinuation of the study drug were reported in 4.5% (190/4204) of patients. AEs (including death) resulting in discontinuation of the study drug reported in ≥ 4 (0.1%) patients were, tuberculin test positive (n = 14, 0.3%), latent tuberculosis (n = 7, 0.2%), injection site reaction (n = 6, 0.1%), ulcerative colitis (n = 4, 0.1%), Crohn's disease (n = 4, 0.1%), drug hypersensitivity (n = 4, 0.1%), exposure during pregnancy (n = 4, 0.1%), mycobacterium tuberculosis positive (n = 4, 0.1%), and psoriasis (n = 4, 0.1%).

In the induction period infection-related TEAE rate in the total ixekizumab group was significantly higher than in the etanercept group (26.0% versus 21.5%; p = 0.018). However, the only TEAE reported significantly more frequently in the total ixekizumab treatment group than in the etanercept treatment group was tonsillitis (0.5% versus 0%; p = 0.044). Infection-related TEAEs reported in ≥ 1% of patients in the total ixekizumab group are summarised in Section 8 in the CER (Attachment 2). Infection-related SAEs were reported in 2 (0.3%) patients in the ixekizumab 80 mg Q2W group (1 x each oral abscess, appendicitis), 5 (0.7%) patients in the ixekizumab 80 mg Q4W group (2 x erysipelas, 1 x each of acute pyelonephritis, urinary tract infection, urosepsis), and 3 (0.4%) patients in the etanercept group (1 x each cellulitis, intestinal abscess, streptococcal cellulitis). In the maintenance period infection-related TEAE exposure-adjusted incidence rates in the total ixekizumab and the placebo groups were similar (72.1 versus 77.7 per 100 patient years, respectively), as were the rates in the ixekizumab 80 mg Q12W and 80 mg Q4W groups (73.1 versus 71.3 per 100 patient-years, respectively).

In the overall safety population Infection-related SAEs were reported in 1.6% (n = 469) of patients, with no events being reported in ≥ 0.5% of patients. The most commonly reported SAE was cellulitis (0.3%, n = 4), and other events reported in ≥ 2 patients were 4 (0.1%) patients for appendicitis, 3 (0.1%) patients each for bronchopneumonia, diverticulitis, erysipelas, pneumonia, urinary tract infections, and 2 (< 0.1%) patients each for clostridium difficile infection, cystitis, gastroenteritis, osteomyelitis, post-operative wound infection, pyelonephritis, staphylococcal bacteraemia, and staphylococcal infection.

Tuberculosis was reported in 9 (0.2%) of patients, including latent tuberculosis in 8 (0.2%) patients and tuberculosis in 1 (<0.1%) patient. There were no confirmed events of new active TB or of reactivation of TB. Candida infections were reported in 2.6% (n = 109) of patients, with infections being reported in ≥ 1.0% of patients being vulvovaginal candidiasis 1.6% (n = 422 women), and oral candidiasis 1.3% (n = 456). Staphylococcal infections were reported in 0.6% (n = 426) of patients. Herpes zoster was reported in 0.5% (n = 423) of patients, and herpes simplex was reported in 2.2% (n = 494) of patients. There were no reports of viral hepatitis.

In the all Psoriasis ixekizumab exposures integrated analysis set, 'depression and suicide/self-injury' SMQ (broad) event were reported in 1.4% (n = 57) of patients, with the most common events being depression (1.1%, n = 47). Suicide attempt was reported in 5 (0.1%) patients, with none of these completed, all had risk factors for suicide and none considered by investigators to be related to study drug. An additional 4 cases were reported after the database lock. No suicide attempts were reported in the rheumatoid patient group.

In the all Psoriasis ixekizumab exposures analysis set, 21 (0.5%) patients reported an autoimmune disorder-related TEAE, including 9 (0.2%) patients with ulcerative colitis, 4 (0.1%) patients with Crohn's disease, 2 (< 0.1%) patients each with alopecia areata and autoimmune thyroiditis, and 1 (< 0.1%) patient each with coeliac disease, atrophic gastritis, multiple sclerosis, and rheumatic disorder. There were 7 (0.2%) patients with autoimmune disorder-related TEAEs, including 5 (0.1%) patients with Crohn's disease (3 x Crohn's disease, 1 x anal fistula, 1 x rectal fistula) and 2 (< 0.1%) patients with ulcerative colitis. Autoimmune disorder-related TEAEs leading to discontinuation of the

study drug were reported in 4 (0.1%) patients with Crohn's disease and 4 (0.1%) patients with ulcerative colitis.

Overall, in both the induction and maintenance dosing periods, the observed differences in laboratory parameters (haematology, clinical chemistry, and urinalysis), vital signs, and ECG changes (including QTc interval prolongation) between the total ixekizumab group and the placebo group are unlikely to be clinically significant. In addition, observed differences between the total ixekizumab group and the placebo group based on age, sex, and weight are unlikely to be clinically significant.

Risk management plan

RMP issues are not fully resolved. The RMP evaluator noted that ixekizumab gained market authorisation in the EU in April 2016. In its assessment report, the CHMP endorsed version 4 of the EU-RMP.

The sponsor should submit the updated EU-RMP (version 4) and also submit an updated ASA to the TGA prior to the date on which the TGA Delegate is due to make a decision on the submission. Differences between the EU-RMP and the ASA in terms of the safety concerns, pharmacovigilance and risk minimisation activities should be compared with justification provided for any differences.

The RMP evaluator also noted that some of their recommendations regarding changes to the Summary of Safety Concerns, while not accepted in the sponsor's response, had been agreed to for the EU-RMP. The only exception was 'use in patients with severe cardiac disease or uncontrolled hypertension'. The sponsor has provided an acceptable justification to not include that item in the Summary of Safety Concerns as 'missing information'. The sponsor's response to other recommendations was not accepted. An updated EU-RMP has been requested.

No suggested wording for the condition of registration relating to the RMP could be provided at this stage as the sponsor is required to submit the updated EU-RMP with the ASA. The updated EU-RMP, accepted by the EMA, has incorporated most of the recommendations on the list of safety concerns made by the RMP evaluator.

Risk-benefit analysis

Delegate's considerations

The proposed induction and maintenance dose regimens for ixekizumab are well supported by the clinical data. For induction the Q2W regimen has superior efficacy to the Q4W regimen. Both regimens had considerably higher efficacy than etanercept in the induction period. In those patients who achieved a response to ixekizumab relapse occurred relatively quickly for the majority of patients and these patients generally responded to re-introduction of active treatment.

In Study RHAZ patients who did not respond to ixekizumab 80 mg Q2W at Week 12 continued to the maintenance phase and received ixekizumab 80 mg Q4W. For these patients at Week 60 the response rate was 25.8% (16/62) for sPGA (score of 0 or 1) and 51.6% (32/62) for PASI 75. This suggests that for some patients who don't have an initial large response there was probably a benefit in continuing treatment, though the extent can't be quantified due to the absence of a continuing placebo treatment group in that study.

Efficacy of ixekizumab can be compared with secukinumab, an anti-IL 17A MAb approved for treatment of plaque psoriasis. For these products patients in the pivotal clinical trials

had a similar severity of psoriasis at baseline and both clinical development programs used PASI 75 and an assessment of 'clear or almost clear skin' at Week 12 of treatment as co-primary efficacy endpoints. The comparison is limited by the re-randomisation for maintenance treatment with ixekizumab which lead to a separate assessment of ongoing treatment in initial responders to treatment rather than going treatment or treatment as needed as occurred in the studies for secukinumab. Treatment as needed has not been explored as a maintenance option for ixekizumab. Maintenance doses of 80 mg SC Q4W appear to be optimal with improvement occurring within weeks of commencing treatment and relapse within weeks of ceasing treatment.

The high rate of relapse in patients with an initial response during the induction phase when given placebo, that is 50.4% in the combined analysis of Studies RHAZ and RHBA indicates that continuing treatment beyond 12 weeks is likely to be needed to maintain the response observed at Week 12. Loss of response was statistically significant from Week 16. It is not known if more durable responses would be seen with longer durations of initial treatment.

During the induction period, adverse events of special interest reported notably more frequently in the total ixekizumab group than in the placebo group included, infection-related TEAEs (including Candida infections), allergic/hypersensitivity reactions, reductions in laboratory assessed leucocyte, neutrophil and platelet counts, injection-site reactions, and autoimmune disorder-related TEAEs.

There was an imbalance in patients reporting attempted suicide between patients in the total ixekizumab group compared to the placebo group (0.1% (n = 2) versus 0%). In the maintenance period adverse events of special interest reported with a higher exposure-adjusted incidence rate in the total ixekizumab group compared to the placebo group were (respectively), Candida infections (3.7 versus 2.2), non-anaphylaxis allergic/hypersensitivity related TEAEs (7.9 versus 6.5), injection site reaction related TEAEs (9.7 versus 4.3), malignant related TEAEs (0.8 versus 0.5), depression and suicide self-injury (broad) (1.2 versus 1.1), and suicide attempt (broad) (0.2 versus 0). Differences in laboratory parameters (haematology, clinical chemistry, and urinalysis), vital signs, and ECG changes (including QTc interval prolongation) between the total ixekizumab group and the placebo group are unlikely to be clinically significant.

Autoimmune disorders, particularly inflammatory bowel disease, were reported more frequently in patients given ixekizumab than in those given placebo. It is not clear whether the incidences of these events will increase with increasing exposure, or whether patients with pre-existent autoimmune disease and moderate to severe plaque psoriasis should be offered treatment with ixekizumab.

Proposed action

Summary of issues

The optimal maintenance regimen hasn't been established. While recurrence of severity of psoriasis generally occurs within weeks of ceasing treatment after an initial response to ixekizumab, it isn't known if recurrence would be as rapid or as frequent if patients had longer initial treatment periods.

The extent of development of neutralising antibodies over years of treatment and the thus the potential for reduction in efficacy over time is not known. This may limit the long term effectiveness of ixekizumab. It is also not known if treatment interruption is likely to affect the rate of development of neutralising antibody.

There is a small increase in the total number of infections during the initial 12 months of treatment however it is not known if the incidence of infection and/ or of serious infections will increase over time.

Request for ACPM advice

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

1. Does the committee consider that maintenance treatment with ixekizumab should be limited to those patients who meet the criteria of 'response' after the 12-week induction phase of treatment?
2. Does the committee consider that treatment interruption should occur in patients who have maintained a response to treatment for some time? If so what period of treatment is advised prior to ceasing treatment?
3. Does the committee consider that patients should be assessed for tuberculosis prior to commencing treatment?

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

Pre ACPM preliminary assessment

The Delegate had no reason to say, at this time, that the application for ixekizumab should not be approved for registration, subject to further negotiation of the Product Information.

Sponsor's response to delegate's summary and request for ACPM advice

The sponsor agrees with the recommendation of the Delegate and the clinical evaluator to revise the indication to read:

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

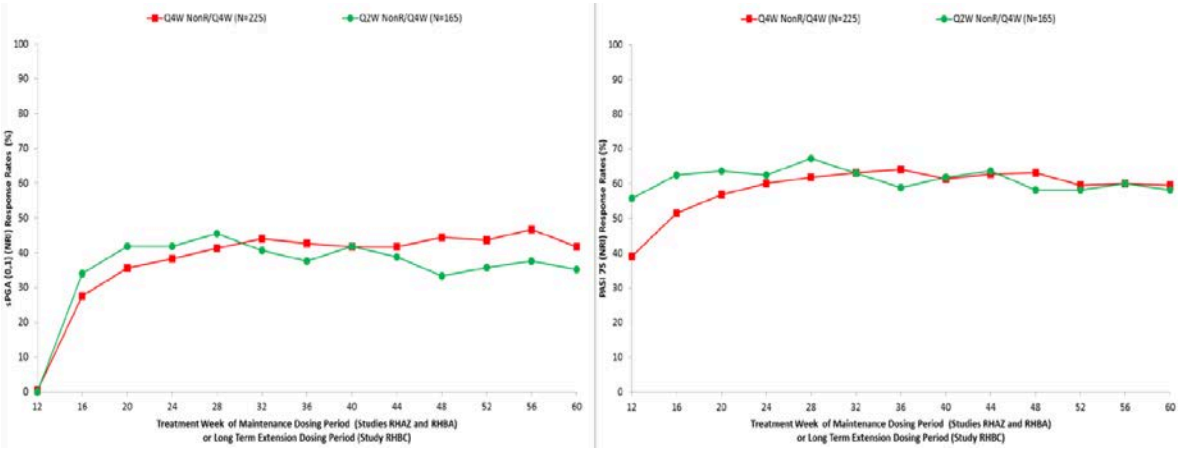
Sponsor's response to delegate's questions

1. *Does the committee consider that maintenance treatment with ixekizumab should be limited to those patients who meet the criteria of 'response' after the 12-week induction phase of treatment?*

Sponsor's response

As described by the Delegate and the clinical evaluator, a significant number of patients who had not achieved a sPGA score of 0 or 1 in response to ixekizumab 80 mg every 2 weeks (Q2W) at Week 12 subsequently achieved an sPGA score of 0 or 1 and/or at least a 75% improvement from baseline in PASI 75 by Week 60. These non-responder patients are presented in Figure 3 (below) which displays the time course of sPGA (score of 0 or 1) and PASI 75 response between Week 12 and Week 60. It can be seen that the proportion of these patients who achieve sPGA (score of 0 or 1) plateaus from Week 20. Therefore, the sponsor recommend that all patients should receive ixekizumab for at least 20 weeks following the treatment initiation. Treatment beyond this time should be left to the judgment of the physician.

Figure 8. sPGA (score of 0 or 1) and PASI 75 (NRI) response rates; sPGA (score of 0 or 1) non-responders at Week 12 to Week 60 of Maintenance Dosing Period or Long-Term Extension Dosing Period, secondary population, Study RHAZ



Abbreviations: NonR = non-responder; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = Static Physician Global Assessment.

2. *Does the committee consider that treatment interruption should occur in patients who have maintained a response to treatment for some time? If so what period of treatment is advised prior to ceasing treatment?*

Sponsor's response

Due to the high rate of relapse (sPGA ≥ 3) in patients who had responded to ixekizumab and then were re-randomised to placebo (84.4%), the sponsor agrees with the clinical evaluator that '*continued treatment after 12 weeks is necessary to maintain the treatment response observed at Week 12 with ixekizumab treatment*'. In addition, following relapse, 30.4% of these patients did not regain sPGA (score of 0 or 1) within 12 weeks of re-treatment. Given the high likelihood of relapse and the proportion of patients who will not regain response, the sponsor strongly recommends that treatment in responding patients should not be interrupted.

3. *Does the committee consider that patients should be assessed for tuberculosis prior to commencing treatment?*

Sponsor's response

The sponsor considers that the following statement from the PI suggests that TB assessment, active or latent, should be conducted prior to initiation to treatment:

> *'Taltz should not be given to patients with active tuberculosis. Consider anti-tuberculosis therapy prior to initiation of Taltz in patients with latent tuberculosis.'*

The requirement to assess TB is implicit in these two sentences.

Precautions: infections

The sponsor acknowledges the Delegate's recommendation to include a statement to monitor patient for signs and symptoms of active TB during and after treatment. However, based on the evidence presented in the clinical data, Taltz should be used with caution in patients with clinically important chronic or active infection.

The current wording in the PI states that patients should be instructed to '*seek medical advice if signs or symptoms suggestive of an infection occur*, and that *If a patient develops a serious infection or is not responding to standard therapy the patient should be closely monitored'* and '*Taltz should be discontinued until the infection resolves*'. This wording

sufficiently addresses the risk associated with TB infection or reactivation during treatment with Taltz.

The sponsor also responded to TGA's proposed amendments to the *Precautions: Effects on Fertility; Use in pregnancy* and *Use in lactation* statements in the draft PI document but these are beyond the scope of this AusPAR.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Taltz solution for injection prefilled pen and Taltz solution for injection prefilled syringe containing 80 mg/mL of ixekizumab to have an overall positive benefit-risk profile for the indication:

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

In making this recommendation the ACPM:

- noted that ixekizumab was superior to etanercept in the clinical studies.
- noted that ixekizumab was less effective in palmoplantar psoriasis.
- noted that there were no studies in hepatic and renally impaired patients.
- noted that there were more candida infections associated with the treatment, and there was an increase in the incidence of inflammatory bowel disease.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

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

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- There should be consistent wording in the PI/CMI about the risk associated with active tuberculosis and the need for TB screening and prophylactic anti-tuberculosis treatment if needed.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the committee consider that maintenance treatment with ixekizumab should be limited to those patients who meet the criteria of 'response' after the 12-week induction phase of treatment?*

Not necessarily if they are negative for ADA or have a low to moderate titre. Of patients in Study RHAZ who did not respond to ixekizumab 80 mg Q2W at Week 12 and who then received ixekizumab 80 mg Q4W during the maintenance period, 25.8% achieved an sPGA (score of 0 or 1) and 51.6% of patients achieved a PASI 75 response at Week 60 (NRI). Such response was evident by Week 20 of maintenance therapy. The ACPM recommends assessment of response after 20 weeks of initial treatment.

2. *Does the committee consider that treatment interruption should occur in patients who have maintained a response to treatment for some time? If so what period of treatment is advised prior to ceasing treatment?*

No. Treatment interruption after the 12 week induction was associated with a higher relapse rate, by Week 48 off treatment responses were maintained in only about 10% of patients.

3. *Does the committee consider that patients should be assessed for tuberculosis prior to commencing treatment?*

Yes. T_h17 cells and IL-17 are predominantly involved in resistance to extracellular pathogens while the INF-g pathway is critical to mycobacterial immunity. Mycobacterial infections were rare in the trials but data on exposure were not provided.

The ACPM 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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Taltz (ixekizumab) 80 mg/mL solution for injection prefilled syringe and solution for injection prefilled pen indicated for:

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

Specific conditions of registration applying to these goods

1. The implementation of the Taltz (ixekizumab) EU-RMP version 4 dated 24th February 2016 (data lock point 15 September 2014, 1 October 2014 for Study 11f-MC-RHBA) and the Australian Specific Annex version 0.2 to the EU-RMP version 4 dated 31st August 2016 and any future updates as agreed with the TGA.

Batch release testing & compliance with Certified Product Details (CPD)

2. It is a condition of registration that all batches of Taltz (ixekizumab) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
3. It is a condition of registration that each batch of Taltz (ixekizumab) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

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>.

Attachment 2. Extract from the Clinical Evaluation Report

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