Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tildrakizumab

Proprietary Product Name: Ilumya

Sponsor: Sun Pharma ANZ Pty Ltd

September 2019

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
~	approximately
ADA	Anti-drug antibodies
AE	Adverse event
AI	Autoinjector
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ASaT	All Subjects as Treated
AST	Aspartate transaminase
AUC	Area under the plasma concentration time curve
BSA	Body surface area
CI	Confidence Interval
CL	Clearance
cLDA	Constrained longitudinal data analysis
C_{max}	Maximum plasma concentration
CRP	C-reactive protein
CT	Computed Tomography
CV%	Coefficient of variability express as a percentage
DAE	Discontinuation due to adverse event
DILI	Drug-Induced Liver Injury
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of Clinical Interest
E_{max}	Maximum effect
EQ-5D	European Quality of Life 5 Dimensions

Abbreviation	Meaning
EU	European Union
F	Bioavailability
FAS	Full analysis set
FDA	Food and Drug Administration
GGT	Gamma glutamyl transferase
GMR	Geometric mean ratio
HAQ	Health assessment questionnaire
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IL	Interleukin
IL-23R	Interleukn-23 receptor
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
K_D	Dissociation constant
MACE	Major adverse cardiovascular events
NA	Not applicable
NR	Non-responders
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PFS	Pre-filled syringe
PGA	Physician's Global Assessment
PGAP	Patient Global Assessment of Pain
PK	Pharmacokinetics

Abbreviation	Meaning
PKPD	Pharmacokinetic pharmacodynamic
QTcF	heart rate-corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SC	Subcutaneously
SD	Standard deviation
SF-36	Short Form (36) Health Survey
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
TNF	Tumour necrosis factor
ULN	Upper limit of normal
US	United States
V	Volume of distribution
VAS	Visual analogue scale

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	5 September 2018
Date of entry onto ARTG	10 September 2018
ARTG number:	290683

Active ingredient:	Tildrakizumab
Product name:	Ilumya
Sponsor's name and address:	Sun Pharma ANZ Pty Ltd Suite 2 02 Level 2 12 Waterloo Road Macquarie Park 2113
Dose form:	Solution for injection
Strength:	100 mg/1 mL
Container:	Prefilled syringe
Pack size(s):	1 mL
Approved therapeutic use:	*Ilumya is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.*
Route(s) of administration:	Subcutaneous injection
Dosage:	The recommended dose of Ilumya is 100 mg by subcutaneous injection at Weeks 0, 4 and every 12 weeks thereafter. If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regularly scheduled interval.

Product background

This AusPAR describes the application by the sponsor to register Ilumya tildrakizumab, a new biological entity, for the following indication:

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

Psoriasis is a common chronic skin condition with a prevalence of 1.3% to 2.2% in the United Kingdom (UK).[1] It is an inflammatory condition with a relapsing and remitting course. Onset is usually in young adults, but can be at any age. It is associated with chronic arthritis in around 10% of patients. Nail changes occur in half of affected patients. Plaque psoriasis is the most common form (90% of patients) and is characterised by well-delineated red, scaly plaques. The extent of involvement can vary from a few patches to generalised involvement.

Psoriasis decreases quality of life in a number of ways: chronic itch, bleeding, scaling, nail involvement. This can result in loss of employment opportunities and social interactions. Patients with psoriasis have increased risks of comorbidity: cardiovascular disease, lymphoma and non-melanoma skin cancer.

Treatment options

Current treatment options can be divided into

- first line, topical therapies;
- second line therapies including phototherapy and systemic non-biological therapies, and
- third line, biological therapies including:
  - Tumour necrosis factor alpha (TNFα) inhibitors:
    - Ustekinumab (authorised in Australia for: Plaque Psoriasis, Stelara is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
  - T helper (Th)17 lymphocyte depletion:
    - Secukinumab (authorised in Australia for: Plaque psoriasis, Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy).
  - IL-17 inhibition
    - Ixekizumab (authorised in Australia for: Taltz is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy).

Regulatory status

This is the first application to the Therapeutic Goods Administration (TGA) with regard to Ilumya (tildrakizumab) 100 mg/1 mL solution for injection in pre-filled syringe.

[1] Clinical guideline (CG153) Psoriasis: assessment and management. National Institute of Clinical Excellence (NICE) (2012). https://www.nice.org.uk/guidance/cg153/chapter/Appendix-Information-to-facilitate-discussion-of-risks-and-benefits-of-treatments-for-people-with-psoriasis

An application has been submitted to the European Union (EU), using the Centralised Procedure (Rapporteur: Germany; Co-rapporteur: Ireland) on 6 March 2017, and is pending. The proposed indication in the EU is:

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

An application has been submitted in the United States (US) on 23 March 2017 and is pending. The proposed indication in the US is:

> *[Tildrakizumab] is a humanized antibody to the p19 subunit of interleukin-23 indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*

The sponsor intends to submit an application in Canada in 2017 and states 'the application has not been deferred, withdrawn or rejected in any other countries'.

The dossiers differ in information, which is country specific. In addition, the dosing proposed in the US is different to that proposed in Australia and the EU:

> *[Tildrakizumab] is administered by subcutaneous injection. The recommended dose is 100 mg at Weeks 0, 4, and every twelve weeks thereafter. Patients weighing >90 kg may benefit from a dose of 200 mg (two 100 mg injections).*

The clinical information differs in the US and global dossier have the final Integrated Summary of Safety (ISS) and Efficacy (ISE), whereas the EU dossier has a draft version of the ISS and ISE.

Product Information

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

II. Registration time line

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

Table 1: Registration timeline for Submission PM-2017-02274-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2017
First round evaluation completed	22 December 2017
Sponsor provides responses on questions raised in first round evaluation	8 March 2018
Second round evaluation completed	16 April 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	22 June 2018
Sponsor's pre-Advisory Committee response	31 August 2018

Description	Date
Advisory Committee meeting	2 August 2018
Registration decision (Outcome)	5 September 2018
Completion of administrative activities and registration on ARTG	12 September 2018
Number of working days from submission dossier acceptance to registration decision*	227

*Target timeframe for standard applications is 220 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Drug substance (active ingredient)

- Australian Biological Name (ABN): tildrakizumab
- Chemical name: Anti-(human interleukin 23) immunoglobulin G1 (human-Mus musculus monoclonal heavy chain) disulfide with human- Mus musculus monoclonal light chain, dimer
- CAS Registry Number: 1326244-10-3.

Structure

Tildrakizumab is a monoclonal antibody that binds to human interleukin-23 (IL-23). It is composed of two identical heavy chains of 446 amino acids each and two identical light chains of 214 amino acids each linked by interchain disulphide bonds with an overall molecular weight of 147 kDa.

Table 2: General properties of drug substance

Parameter	Value	Method
Physical Form and Appearance	100 mg of the active ingredient per mL in 10 mM histidine buffer, pH 6.0, 70 mg per mL sucrose, and 0.5 mg per mL polysorbate 80. Stored in frozen condition.	The liquid drug substance appearance at room temperature is clear to slightly opalescent to slightly yellow.
Solution pH	5.8-6.1 with target pH 6.0	Potentiometry
Extinction Coefficient	1.44 $L.g^{-1}.cm^{-1}$ at 280 nm	Determined empirically by amino acid compositional analysis using ultraviolet (UV) spectrophotometry on solutions of the product having known protein contents.
Protein pI	8.75	Determined by cIEF
Biological Properties	The mechanism of action for tildrakizumab involves inhibition of multiple inflammatory pathways via binding of the soluble ligand, Interleukin-23 (IL-23), and preventing its interaction with the IL-23 receptor (IL-23R).	

Drug product

Description and composition of the drug product

Tildrakizumab solution for injection is a sterile, preservative-free, clear to slightly opalescent and colourless to slightly yellow solution, for subcutaneous use, provided as 100 mg of tildrakizumab in a 1 mL single-dose prefilled syringe with a combination safety device.

Tildrakizumab solution in a prefilled syringe is referred to as the drug product (DP). Tildrakizumab solution in a prefilled syringe assembled with a combination safety device is referred to as the combination product.

Below is a table to show the composition of tildrakizumab solution for injection

Table 3: Composition of tildrakizumab solution for injection

Ingredient	Compendial Grade	Target amount per Unit[a]	Target Concentration (mg/mL)	Function
Tildrakizumab	Not applicable	100.0 mg	100.0	Active pharmaceutical ingredient
L-Histidine[b]	Ph. Eur./USP	0.495 mg	0.495	Buffer
L-Histidine hydrochloride monohydrate[b]	Ph. Eur.	1.42 mg	1.42	Buffer
Polysorbate 80	Ph. Eur./USP	0.5 mg	0.5	Surfactant/stabiliser
Sucrose	Ph. Eur./USP	70.0 mg	70.0	Stabiliser/tonicity modifier
Water for Injection	Ph. Eur./USP	qs to 1.0 mL	NA	Solvent

a) Target amount is based on extractable volume of 1.0 mL per syringe. Excess volume (target of 0.08 mL) of tildrakizumab above 1.0 mL is included during syringe filling to ensure recovery of the label claim of 100 mg tildrakizumab per syringe; b) L-histidine and L-histidine hydrochloride monohydrate are combined during drug substance manufacturing to a targeted buffer strength of 10 mM and target pH 6.0. Ph. Eur = European Pharmacopoeia; USP = United States Pharmacopoeia-National Formulary.

Quality summary and conclusions

Summary of quality data evaluation report

There are no objections on quality grounds to the approval of Ilumya tildrakizumab solution for injection 100 mg/1 mL pre-filled syringe.

Proposed conditions of registration:

- It is a condition of registration that all batches of Ilumya tildrakizumab solution for injection 100 mg/1 mL pre-filled syringe imported into Australia must comply with

the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

- It is a condition of registration that each batch of Ilumya tildrakizumab solution for injection 100 mg/1 mL pre-filled syringe imported into 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.

Summary of microbiological data evaluation report

There are no further objections from a microbiological perspective to approval for the application to register Ilumya tildrakizumab 100 mg/mL solution for injection.

IV. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was good and in general accord with the International Conference on Harmonisation (ICH) Guideline on nonclinical evaluation of biotechnology-derived pharmaceuticals (ICH S6).[2] All pivotal toxicity studies were conducted according to Good Laboratory Practice (GLP) standards. Tildrakizumab is a humanised antibody against human interleukin 23 (IL-23) and has no affinity for rodent IL-23; thus most studies investigating the kinetics and toxicity of tildrakizumab were conducted in cynomolgus monkeys, as tildrakizumab does interact with IL-23 in this species. The sponsor did not conduct any genotoxicity or carcinogenicity studies, which is acceptable for this biological product (ICH S6).[2]

Pharmacology

Primary pharmacology

Binding studies confirmed a high affinity of tildrakizumab for human and cynomolgus monkey IL-23p19 (dissociation constant (K_D) 297 and 47 pico moles (pM), respectively), which share 98% amino acid sequence homology. No binding of tildrakizumab was observed to rat or mouse IL-23 and tildrakizumab did not bind to human IL-12. Amino acid sequence homology between humans and rodents was 72 to 77%.

Tildrakizumab neutralised IL-23 under in vitro conditions. In three different bioassays, tildrakizumab inhibited IL-23 mediated proliferation of Ba/F3 cells transfected with human IL-23R;[3] and IL-12Rβ1, inhibited the IL-23 mediated phosphorylation of STAT3 in KIT225 leukemic T cells and inhibited the IL-23 mediated production of interferon-gamma (IFNγ) in primary human splenocytes. In these three bioassays, the inhibition of IL-23-induced biological activity had an IC50 range of 59 to 189 pM in human IL-23 and 118 pM for monkey IL-23 (in the KIT225 assay).

The anatomical distribution of IL-23 and its 2 receptor subunits was performed in panel of human, monkey and mouse tissues, with mRNA expression similar across all species. The expression of IL-23 and IL-12p40 and the IL-23 receptor subunits (IL-23R and IL-12Rβ1) was low in all tissues. The highest expression of IL-23 and IL-12p40 was found in the immune tissues (thymus, lymph nodes, bone marrow, appendix and tonsils) of all species.

[2] ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals
[3] IL-23R = Interleukn-23 receptor

The highest expression of IL-23R was found in the lymphoid tissues (lymph nodes, spleen, tonsils and appendix) with detectable levels also found in the lung and heart. IL-12Rβ1 was widely distributed, most notably in the immune organs and the gastrointestinal tract.

In skin biopsies from psoriasis patients and colonic biopsies from patients with Crohn's disease, IL-23p19 mRNA levels were increased in the diseased tissue samples compared to normal tissue samples from diseased and healthy patients.

As tildrakizumab does not bind to rodent IL-23, a mouse anti-mouse IL-23 surrogate antibody (SCH900598) was developed. This antibody binds to mouse IL-23 with a KD of 3.5 to 6.7 pM. This antibody was mainly used in secondary pharmacology studies as described below.

Secondary pharmacodynamics and safety pharmacology

In vivo studies assessed IL-23 neutralisation on host immune defence in monkeys, mice and in mouse models of *Salmonella, Listeria monocytogenes* or *Mycobacterium bovis* infection. Tumour risk in rodents treated with mouse anti-mouse IL-23 was also assessed, as well as the biological activity of tildrakizumab in an anti-CD40 mouse model of intestinal disease and a humanised mouse model of psoriasis. Immunohistochemical cross-reactivity studies were also conducted to evaluate binding of tildrakizumab to human and monkey tissues.

Pre-treatment of colitis anti-CD40 mice with mouse anti-mouse IL-23p19 mAb (5 to 240 mg/kg) resulted in a dose-dependent decrease in the severity of colon pathology compared to control mice as demonstrated by less crypt disruption, goblet cell loss and necrosis in the lamina propria and a downregulation of the expression of genes associated with neutrophil infiltration and myeloid activation.

Treatment with a single dose of tildrakizumab in monkeys, or mouse anti-mouse IL-23p19 in mice, had no effect on circulating neutrophils, monocytes or lymphocytes levels.

In mouse models of *Mycobacterium bovi* BCG infection, IL-23 neutralisation with mouse anti-mouse IL-23p19 did not increase the mycobacterial burden in the spleen, liver or lung compared to isotype control mice and did not delay host defence responses during the 6 week post infection period. In contrast, neutralisation of IL-12/23p40 or TNFα resulted in increased disease burdens in these organs. Similarly, in a mouse model of *Salmonella* infection or Listeria infection, IL-23 neutralisation did not increase the bacterial burden in the organs analysed (small intestines, mesenteric lymph nodes, liver and spleen), except for an increase in the liver burden in the *Listeria* model, and animal survival rates were comparable to isotype control animals. In all three disease models, neutralisation of IL-23 had no effect on serum cytokine levels. Collectively these results suggest that IL-23 neutralisation in animal models does not increase infection liability. In mice transfected with a PDV squamous carcinoma cell line, reduced tumour growth and resistance to tumour induction was observed following treatment with mouse anti-mouse IL-23p19 prior to or after implantation of tumour cells, suggesting that IL-23 neutralisation may reduce the carcinogenic potential in animals.

Studies on tissue cross-reactivity in samples from humans and cynomolgus monkeys were conducted using tildrakizumab. There was general comparability in tissue staining between the normal human and cynomolgus monkey tissue panels. Tildrakizumab staining of cardiac myocytes was observed in the human tissue panel examined, but not in the cynomolgus monkey tissue panel. Staining observed only in the cynomolgus monkey tissue panel and not in the human tissue panel included cortical epithelium in adrenal, ductal epithelium in pancreas and prostate, sweat gland epithelium in skin, and proteinaceous material in prostate. IL-23 expression and/or synthesis has been described

for mononuclear cells, as well as low levels in serum and extracellular fluid (Ma et al.; 2004).[4] Expression of IL-23 has also not been reported for the remaining tissue elements stained with tildrakizumab in this study. The observed staining in these tissues might represent either previously unrecognised sites of IL-23p19 expression or true tissue cross-reactivity. The staining observed in this study was cytoplasmic in nature, and it is unlikely that cytoplasm and cytoplasmic structures would be accessible to the test article *in vivo*, which suggests minimal toxicological relevance.

Specialised safety pharmacology studies on tildrakizumab were not conducted; however, safety pharmacology parameters were integrated into the protocols of Good Laboratory Practice (GLP) repeat dose toxicity studies (3 and 9 months) in cynomolgus monkeys. No notable changes to CNS (neurological, behaviour and body temperature), electrocardiographic (heart rate, QT interval duration and corrected QT interval duration) or respiratory parameters were reported. Overall, no effect on functions of CNS, cardiovascular and respiratory systems is predicted with fortnightly dosing of tildrakizumab.

Pharmacokinetics

Pharmacokinetic and toxicokinetic characteristics of tildrakizumab were assessed in Cynomolgus monkeys and in mice. Single dose assessments in monkeys were conducted following doses of 0.4, 4 or 40 mg/kg administered subcutaneously (SC) or a dose of 40 mg/kg administered intravenously (IV). In mice, a single dose of tildrakizumab was administered by the SC or IV route at a dose of 4 mg/kg and IV at a dose of 25 mg/kg. Repeat dose toxicokinetic data were determined in monkeys receiving fortnightly doses of tildrakizumab at 10, 30, 40, 100 or 140 mg/kg administered SC or 140 mg/kg IV. It should be noted that tildrakizumab does not bind to mouse IL-23 and therefore toxicokinetic parameters obtained in mouse studies do not reflect any effects of tildrakizumab binding to IL-23 in this species.

Tildrakizumab showed slow systemic distribution following SC administration, reaching maximum serum levels at around 3 days post-dose. Bioavailability of tildrakizumab was high in monkeys (40 to 91.5%). Volume of distribution was 62.2 mL/kg (in contrast, human V_d = 10.8 L, ~ 180 mL/kg for a 60 kg adult) and clearance (CL) was slow (CL = 2.66 mL/day/kg) following bolus IV administration. Elimination from the systemic circulation was slow after SC administration, with a half-life of 10-21 days (compared to around 23 days in humans). Repeat dosing did not uncover differences in exposures of tildrakizumab (as area under the plasma concentration time curve (AUC)) between male and female animals, which were dose proportional.

Distribution was assessed in mice following IV administration of 5.8 mg/kg of fluorescently labelled tildrakizumab. Mean tissue to blood ratios were < 0.5 at all time-points examined indicating no organ uptake or accumulation. Distribution of tildrakizumab to the fetus during gestation was demonstrated in cynomolgus monkeys, with a fetal/maternal serum ratio of 0.8 at a dose of 300 mg/kg SC on GD140. Similarly, the infant/maternal serum ratio was 0.96 to 1.36 on post-partum day 7 and 28 and up to 4.9 on post-partum day 178 to 182. Tildrakizumab was also detected in the breast milk of lactating monkeys.

No specific studies on metabolism or excretion were conducted. This is acceptable given the protein nature of the drug in accordance with the guideline ICH S6 (R1).[2]

[4] Ma XT, et al. (2004) Expression and regulation of interleukin-23 subunits in human peripheral blood mononuclear cells and hematopoietic cell lines in response to various inducers. *Cell Biol. Int.,* 2004; 28:689-697.

Blood samples were collected in the repeat dose studies to monitor the development of anti-tildrakizumab antibodies (ADAs), with a low incidence of ADAs noted (1/72 animals) across the 3 and 9 month repeat dose toxicity studies. ADAs were noted in several maternal animals in the embryofetal and pre- and postnatal development studies, both during gestation and after parturition.

Overall, the pharmacokinetic (PK) studies showed that the cynomolgus monkey is an appropriate animal model for toxicity testing.

Pharmacokinetic drug interactions

Treatment with IL-23 had no effect on C-reactive protein expression or the activity of CYP450 enzymes in *in vitro* studies conducted in human hepatocytes. Furthermore, results reported in the literature indicate that IL-23 does not alter the expression or activity of CYP2B6, CYP2C9, CYP2C19 and CYP3A4 in human hepatocytes. In clinical studies conducted in subjects with moderate to severe psoriasis, CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4-mediated metabolism was not affected by treatment with tildrakizumab following administration of a probe cocktail consisting of caffeine, warfarin, omeprazole, dextromethorphan and midazolam.

These results are consistent with the nature of tildrakizumab. As a fully human monoclonal antibody, tildrakizumab is expected to be metabolically degraded through peptide hydrolysis and is therefore unlikely to interact with other drugs via cytochrome P450 enzymes or transporters.

Toxicity

Acute toxicity

Acute toxicity from a single dose of tildrakizumab via the clinical route (SC) and the IV route was examined in Cynomolgus monkey in a non-GLP compliant study. Tildrakizumab was well tolerated, with no treatment-related effects observed for bodyweight or clinical pathology. Redness at the SC injection site following treatment with tildrakizumab at all dose levels was observed. Tildrakizumab treatment did not affect the expression of the IL-23 receptor (IL-23R) by T cells, B cells, NK cells, or myeloid cells or the production of IL-17 and IL-22 ex-vivo, or the plasma concentrations of biomarkers including IL-17, INFγ, IL-6, INFα or IgE. The maximum non-lethal dose in this study was 40 mg/kg (the highest dose tested). Tildrakizumab is therefore considered to have low acute toxicity.

Repeat-dose toxicity

The repeat dose toxicity of tildrakizumab was evaluated in two GLP-compliant studies of 3 and 9 months duration in cynomolgus monkeys. The choice of species is acceptable on the basis of the high amino acid sequence homology of 98% between monkey and human IL-23, and pharmacokinetic considerations. The duration of the pivotal studies was consistent with the possible long-term clinical use of tildrakizumab and was in accordance with ICH guidelines.[5] Doses were administered via the SC route, the clinical route of administration, and via the IV route (3 month study only), and were administered once per fortnight.

[5] ICH S4 Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)

Relative exposure

Exposure ratios have been calculated based on animal:human plasma $AUC_{0–14d}$ values. The clinical AUC values predicted by 1-compartment population PK modelling are used for exposure comparison. The AUC data used for animals is the mean of male and female values on the last sampling occasion.

Relative exposures based on AUC were high (> 20 fold) to very high (> 50 fold).

Table 4: Relative exposure in repeat-dose toxicity studies in cynomolgus monkeys

Study details	Dose (mg/kg/fortnight)	AUC0–14d (µg·day/mL)	Exposure ratio#
Study No. 07184 (3 months) Fortnightly dosing (dose 7)	40; SC	14500	142
	140; SC	40700	399
	140; IV	47550	466
Study No. 6377-625 (9 months) Fortnightly dosing (dose 13)	10; SC	3290	32
	30; SC	9255	91
	100; SC	27950	269
Human: Population PK analysis (1-compartment model)	200 mg	612	-

= 6 x animal:human plasma $AUC_{0–14d}$ (monkeys received 6 doses within the 12 week dose interval used in humans)

Major toxicities

Tildrakizumab was well tolerated in repeat-dose toxicity studies following SC doses up to 140 mg/kg/fortnight for 3 months and up to 100 mg/kg/fortnight for 9 months. No tildrakizumab-related mortality or morbidity was observed. There were no tildrakizumab-related clinical signs.

No remarkable adverse effects on body weight, food consumption, body temperature or clinical pathology parameters were observed following tildrakizumab administration. There were also no tildrakizumab-related findings in ophthalmoscopic and physical examinations. Post-mortem examinations revealed no tildrakizumab-related macroscopic observations or adverse effects on organ weights. Histopathological changes consisted of minimal perivascular mononuclear infiltrates at the SC injection site in all treated animals in the 9 month study and mononuclear cell infiltration at the SC injection site in treated animals in the 3 month study. These findings are considered to be a nonspecific response to the injection of a foreign protein and not a direct effect of tildrakizumab.

Genotoxicity

The genotoxic potential of tildrakizumab was not examined in dedicated nonclinical studies, which is acceptable for a biotechnology-derived pharmaceutical as per ICH guideline.[2]

Carcinogenicity

The carcinogenic potential of tildrakizumab was not examined in dedicated nonclinical studies, which is acceptable under the guideline.[2] Conventional carcinogenicity bioassays in rodents are not appropriate since rodents are not responsive to tildrakizumab and are

also likely to develop antibodies to tildrakizumab over time. Life-time carcinogenicity studies in primates are not ethically feasible.

Reproductive toxicity

Reproductive toxicity was evaluated in embryofetal development and pre-/postnatal development studies in cynomolgus monkeys. Animals received fortnightly SC doses of tildrakizumab of up to 300 mg/kg/fortnight. Dosing in the embryofetal development study covered the period of organogenesis (gestation day 20 to 118), while dosing in the pre-/postnatal development study ceased at parturition (started from gestation day 50). The embryofetal and pre-/postnatal development studies also included measurement of tildrakizumab in serum (maternal, fetal/infant) and milk, toxicokinetic parameters were determined. The study designs were generally acceptable in view of the limitations associated with relying on primate animal models. Timing and duration of dosing was also acceptable and appropriate for primate models.

Relative exposure

Table 5: Relative exposure in reproductive toxicity studies

Species	Study (Study no.)	Dose (mg/kg/fortnight); SC	AUC_{0-14d} (µg·day/mL)	Exposure ratio#
Monkey (Cynomolgus)	Embryofetal (Study SNBL 120.06) Sampling: GD 118	10	1720	17
		100	16300	160
		300	48500	475
	Pre/postnatal development (Study TT#12-9004) Sampling: GD 120	10	1979^	19
		100	18083^	177
Human: Population PK analysis (1-compartment model)		200 mg	612	–

= animal: human plasma AUC0–14d; ^AUC (µg.hr/mL) divided by 24 hours to convert to AUC (µg.day/mL)

The relative exposure achieved in the reproductive toxicity studies was moderate at the lower doses (10 mg/kg/fortnight) and very high at the doses of 100 to 300 mg/kg/fortnight.

Placental transfer was demonstrated in cynomolgus monkeys, with tildrakizumab detected in fetal serum. Fetal to maternal serum ratios were in the order of 82%, 61% and 77% for 10, 100 and 300 mg/kg dose groups, respectively, suggesting that rate of transfer is high, in addition, given the slow elimination half-life, the likelihood of tildrakizumab levels persisting in the fetal circulation is high. This may also explain the relatively high exposure of infant to tildrakizumab, which showed time-dependent increases in infant to maternal tildrakizumab serum ratios (1.15 to 2.63) even though the tildrakizumab concentration in milk was low (< 0.2% of maternal serum level). These results suggest that the placental transfer of tildrakizumab and its long elimination half-life explain the high infant serum levels of tildrakizumab.

The embryofetal development study tested three doses of tildrakizumab (10, 100 and 300 mg/kg), administered once per fortnight via the SC route during the period of organogenesis, with caesarean section conducted on GD 140. There were no maternal treatment-related changes or mortalities. Fetal effects seen in the treated groups were overall comparable to the vehicle group, with no evidence of embryofetal toxicity or malformations. An increase in relative fetal heart weight was observed in the high dose treatment group (13%), however this was not considered to be treatment-related as there were no corresponding changes in the absolute weight. There was a higher incidences of lumbar rib in the mid and high dose treatment groups relative to controls (2/11 cf. 1/10) but as a skeletal variation the difference was small and considered incidental. Very few animals were positive for anti-tildrakizumab ADAs in both control and treatment groups. Nevertheless, there were no treatment-related effects on embryofetal development in Cynomolgus monkeys. The NOAEL was ≥ 300 mg/kg/fortnight.

For the pre-/postnatal development study pregnant females received fortnightly tildrakizumab injections (two treatment groups of 10 and 100 mg/kg) via the SC route from the period of organogenesis to parturition. Infants were observed for a further 6 months after birth. One maternal animal in the mid dose group was found dead on GD 155, likely due to complications during delivery with signs of transmural haemorrhage of the uterus observed. No other deaths or adverse effects on maternal health were reported and rates of fetal loss were comparable between the treated and vehicle control groups. Overall, the length of gestation was not affected by treatment and the total number of infants delivered was similar between groups. External assessments found no overall difference in morphometric measurements of infants from treatment groups cf. vehicle group. There were no treatment-related effects on neurobehavioural parameters, heart and respiration rates, haematology or clinical chemistry evaluations. Infant immune functions were also not affected by tildrakizumab exposure, as shown by no changes to lymphocyte subsets between treatment groups, and no effects on primary or secondary humoral responses to KLH antigen.

A notable finding was that a total of seven infants across control and treated groups died or were euthanised within 15 days of birth. Of these, 4 of the 7 infants died or were euthanised due to signs of maternal neglect and subsequent failure of the infants to thrive (1 in control, 2 each at 10 mg/kg and 100 mg/kg). Maternal neglect is considered a background finding in primigravid cynomolgus monkeys and is not treatment-related. The overall number of combined fetal and infant losses was within the testing facility historical control range (0 to 20%), however the death of two neonates at 100 mg/kg was considered by the sponsor not to be related to maternal neglect and to be of uncertain relationship to tildrakizumab.

Of the 2 infants that were found dead in the 100 mg/kg group (Day 12 or Day 15), external assessments of infants did not reveal any developmental changes that were due to tildrakizumab exposure. Post-mortem analyses found signs of jaundice (generalised yellowing of the skin, mucous membranes and sclera) and histopathology of the thymus (lymphoid depletion) consistent with stress, and in the liver and kidney (moderate diffuse degeneration/necrosis of hepatocytes with collapse of the liver parenchyma and minimal diffuse mixed inflammatory cell infiltrate, scattered eosinophilic intranuclear inclusion bodies in the renal cortical tubular epithelial cells) consistent with a viral infection. It is noted that the background incidence of viral infections in infant cynomolgus monkeys is unknown, and therefore the role of tildrakizumab at 100 mg/kg in the death of 2 infants unrelated to maternal neglect is uncertain. The NOAEL for infant development is considered to be 10 mg/kg/fortnight.

Pregnancy classification

The sponsor proposed Pregnancy Category B1;[6] for tildrakizumab. A B1 category is considered appropriate for this product in the absence of any maternal or foetal effects in adequately conducted embryo/fetal and pre- and postnatal development studies in female monkeys. This is consistent with the pregnancy category for ustekinumab.

Local tolerance

The local tolerance of tildrakizumab was examined in a Good Laboratory Practice (GLP)-compliant study in rabbits following IV, intra-arterial, intramuscular and paravenous administration. Neither oedema nor erythema were observed following treatment and there were no treatment-related macroscopic or microscopic changes. Tildrakizumab was well tolerated in repeat-dose toxicity studies in cynomolgus monkey following SC administration, with histopathology at the injection site consisting of mononuclear cell infiltration observed in the dermis in all treated animals. In addition, in a 9-month study, minimal perivascular mononuclear infiltrates were observed at the injection site in treated monkeys following SC administration. These changes are considered to be reactions to the injection of foreign protein and not adverse.

Phototoxicity

Phototoxicity studies were not conducted using tildrakizumab. This is acceptable in accordance with ICH guidelineS10.[7]

Paediatric use

Tildrakizumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- Tildrakizumab has high affinity for human IL-23 (K_D 297 pM). Affinity for monkey IL-23 was high (KD 47 pM) but absent for rodent IL-23. Tildrakizumab neutralised IL-23 under in vitro conditions, with an IC_{50} range of 59-189 pM for human IL-23 and 118 pM for monkey IL-23. Expression of IL-23 and its receptor subtypes (IL-23R and IL-12Rβ1) was low in a panel of human, monkey and mouse tissues. The highest levels of IL-23 expression were found in the immune tissues (thymus, lymph nodes, bone marrow, appendix and tonsils) in all species. Expression of IL-23p19 was increased in skin biopsies from psoriasis patients and colonic biopsies from patients with Crohn's disease.
- Tildrakizumab staining was generally comparably between the tested panel of human and monkey tissues and was cytoplasmic.
- Safety pharmacology parameters were assessed in the GLP repeat dose toxicity studies and were found to be unremarkable. No notable changes to CNS (neurological, behaviour and body temperature), electrocardiographic (heart rate, QT interval duration and corrected QT interval duration) or respiratory parameters were reported.
- In monkeys tildrakizumab showed slow systemic distribution (T_{max} 3 days), a long elimination half-life (t½ 10 to 21 days) and high bioavailability when administered by the clinical route (SC). Serum levels were dose proportional. Human pharmacokinetic

[6] 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.
[7] ICH guideline S10: Photosafety evaluation of pharmaceuticals

parameters were similar to those noted in cynomolgus monkeys (T_{max} ~ 6.2 days; $t_{½}$ ~ 23 days), showing first order absorption and slow clearance with steady state attained by week 16 of dosing under the clinical regimen (week 0 and 4 and Q12w thereafter). The PK studies showed that the monkey is an appropriate animal model for toxicity testing.

- Based on *in vitro* studies, IL-23 does not affect hepatic C-reactive protein expression or the expression and activity of P450 enzymes, therefore clinical drug-drug interactions through P450 pathways are unlikely.
- Tildrakizumab had a low order of acute oral toxicity in monkeys.
- Two repeat dose toxicity studies (tildrakizumab 10, 30, 40, 100 and 300 mg/kg/fortnight) by the clinical (SC, 3 and 9 months) route were conducted in monkeys. Treatment-related effects were minimal. Injection site reactions were the main effect, evident by microscopic evaluation only.
- No genotoxicity or carcinogenicity studies were conducted, which is acceptable for a biotechnology–derived pharmaceutical.
- A pre/postnatal development study reported no adverse effects on maternal health, no effect to length of gestation, infant morphometric measurements, neurobehavioural parameters, heart rate assessments, humoral responses to KLH antigen and lymphocyte subset populations. There was an increased incidence of infant loss in the high dose group (100 mg/kg), where four infants died or were euthanized within 15 days postnatal. Of these, two deaths were related to maternal neglect, with two deaths considered to be of an uncertain relationship to tildrakizumab treatment. Therefore, the NOAEL for infant development is 10 mg/kg/fortnight.
- Tildrakizumab was found to cross the placenta (fetal: maternal serum ratio 0.6 to 4.9) in monkeys. Milk transfer studies showed a low amount of tildrakizumab excreted in the milk (< 0.2%). Tildrakizumab had no effect on menstrual cycling, sperm parameters and showed no histological changes to reproductive tissues in monkeys. There were also no effects on embryofetal development (NOAEL ≥ 300 mg/kg/fortnight).

Nonclinical conclusions and recommendation

- The submitted data were in general accordance with the ICH guideline.[2] All pivotal repeat-dose toxicity and reproductive toxicity studies were GLP-compliant.
- Primary pharmacology studies provided sufficient evidence of tildrakizumab affinity and selectivity for human and monkey IL-23, as well as neutralisation of its actions.
- Treatment-related effects associated with fortnightly injections were minimal and limited to injection site reactions, which were evident by microscopic evaluation only.
- Pregnancy Category B1 is considered appropriate.[6]
- Overall, there are no nonclinical objections to the registration of tildrakizumab (Ilumya).

V. Clinical findings

Introduction

Clinical rationale

The following clinical rationale has been extracted from the Clinical Overview:

'Although traditional systemic therapies for the treatment of psoriasis are reasonably effective, their long-term use may be limited because of loss of efficacy and/or adverse effects. Many subjects who are treated with anti-TNF agents do not achieve an adequate response, measured by at least a 75% improvement in the Psoriasis Area and Severity Index (PASI) from Baseline (PASI 75), or the agents lose efficacy over time. Furthermore, the inhibition of TNFα leads to generalized immunosuppression and the possibility of serious side effects, such as infections, congestive heart failure, demyelinating disease, lymphoma, and infusion-related events (Enbrel SmPC).

Targeting specific molecules involved in the pathology of psoriasis rather than inducing generalised immunosuppression through TNFα inhibition has the potential for safer treatments for subjects with moderate to severe plaque psoriasis. Other biologic treatments for psoriasis, such as ustekinumab, ixekizumab, and secukinumab, target IL-12/IL- 23, and IL-17, which are known to be involved in the pathogenesis of psoriasis. There continues to be a need for treatment options with convenient dosing that maximise response and show a durable effect while demonstrating safety and tolerability. Thus, a significant unmet need remains for novel, safe, highly effective, and convenient treatments for subjects with moderate to severe plaque psoriasis.'[8,9]

Guidance

The following guidance applies to the present application:

- Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr).
- Note for guidance on population exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95).
- Committee for Medicinal Products for Human Use (CHMP) Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use. EMA/CHMP/BMWP/86289/2010 (24 May 2012).

Contents of the clinical dossier

Scope of the clinical dossier

The clinical dossier represented a clinical development program for a new biological entity. The dossier contained data from six Phase I studies, one Phase IIa study and two Phase II studies.

There were also integrated analyses for efficacy, safety and immunogenicity. There were two simulation studies informing dose selection. There was one population pharmacokinetic study. The data included patients who were treated for over 1 year, but

[8] Shear N H Fulfilling an unmet need in psoriasis. Do biologicals hold the key to improved tolerability? Drug Safety 2006; 29: 49-63
[9] Schon MP and Boehncke WH Psoriasis *NEJM* 2005 352: 1899-1912

not for longer durations such as 18 months or 2 years. There were no reports from long-term follow-on studies.

Paediatric data

There were no paediatric data. A clinical trial in psoriasis patients aged 6 to 18 years has been deferred as part of the Paediatric Investigation Plan (PIP), to allow for the demonstration of efficacy and safety in adults prior to paediatric investigation.

With regard to the Pediatric Plan, agreed with the Food and Drug Administration (FDA, USA), a partial waiver has been granted for children younger than 6 years of age with moderate to severe chronic plaque psoriasis on the grounds that necessary studies are impossible or highly impractical due to the extremely low prevalence of moderate to severe psoriasis in this population.

A deferral has been granted to initiate the study in paediatric patients from 6 to < 18 years with moderate to severe chronic plaque psoriasis after completing the adult phase III program. The sponsor proposes an open label PK/safety study followed by a single multicentre randomized, placebo- and active comparator- controlled clinical trial to study the efficacy, long term safety and pharmacokinetics (PK) of tildrakizumab in paediatric patients from 6 to < 18 years of age.

The completion of the paediatric study is anticipated for April 2024, with a target date for submission of the results by December 2024.

Good clinical practice

The clinical studies were stated to have been, and appeared to have been, conducted in accordance with Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 6: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK- Single dose	Study P05661/P004
		Study P05776/P005
PK in special populations	Target population § - Multi dose	Study P05382/P001
		Study P05495/P003
	Crohn's disease	Study P05839/P006
	Other special population	Study P06306/P007

PK topic	Subtopic	Study ID
PK interactions	CYP substrate cocktail	Study P08630/P009
Population PK analyses	Healthy subjects and target population §	Study mk-3222- ppk

§ Subjects who would be eligible to receive the drug if approved for the proposed indication

Evaluator's conclusions on pharmacokinetics

The PK of tildrakizumab have been adequately characterised. Tildrakizumab has the typical PK characteristics of an antibody based drug. The absorption characteristics after a SC dose are suitable for the proposed indication: T_{max} of 6 days and absolute bioavailability of 73% at the 200 mg dose level. Volume of distribution (V) reflects intravascular plasma, indicating tildrakizumab is predominantly intravascular and not distributed to the tissues. The t½ is 25 to 30 days. There is little inter-individual and intra-individual variability in PK. There are no significant interactions with CYP enzymes. The PK section of the PI is supported by the PK data submitted by the sponsor.

Pharmacokinetics in healthy subjects

Absorption

Sites and mechanism of absorption

- In Study P05776/P005 T_{max} with the SC administration was 6 days.

Bioavailability

Absolute bioavailability

- In Study P05776/P005 mean (90% confidence interval (CI)) bioavailability for subcutaneous (SC) administration, compared to IV, was 80 (62 to 103) % for the 50 mg dose and 73 (46 to 115) % for the 200 mg dose. CL/F[10] was 197 to 282 mL/day. Mean (90% CI) bioavailability in volunteers who were ADA positive was similar: 85.8 (67.6 to 109) % for the 50 mg dose and 64.7 (35.7 to 117) % for the 200 mg dose.

Bioequivalence of clinical trial and market formulations

The Phase IIa and III clinical trial formulation is the same as that proposed for marketing.

Bioequivalence of different dosage forms and strengths

- In Study P08630/P009 there was no significant difference in exposure to tildrakizumab by pre-filled syringe (PFS) compared to PFS with autoinjector (AI). The geometric mean ratio GMR (90% CI) for $AUC_{0-\infty}$ PFS + AI/PFS was 1.17 (0.81 to 1.70) and for maximum plasma concentration (C_{max}) was 1.08 (0.79 to 1.47).

Dose proportionality

- In Study P05661/P004, the PK of tildrakizumab were dose-proportional (linear) in the dose range 0.1 to 10 mg/kg.
- In Study P05776/P005 with SC dosing there was dose proportionality for AUC and C_{max}.

[10] F = bioavailability

- In Study P06306/P007 tildrakizumab was dose-proportional for C_{max} and AUC when administered SC in the dose range 50 mg to 400 mg.
- In Study P05495/P003, in the dose range 5 mg to 200 mg, exposure to tildrakizumab was dose proportional.

Distribution

Volume of distribution

- In Study P05661/P004, the plasma concentration versus time profile was consistent with a two-compartment model with rapid redistribution and Vd was 75.6 to 106 mL/kg.
- In Study P05776/P005 mean (CV%[11]) Vd/F was 6600 (17) mL for the 50 mg SC dose and 10400 (105) mL for the 200 mg SC dose.

Metabolism

Tildrakizumab is an antibody and is eliminated through catabolism.

Excretion

Routes and mechanisms of excretion

- In Study P05661/P004, in the dose range 0.1 to 10 mg/kg by IV administration the CL of tildrakizumab was in the range 2.04 to 2.52 mL/day/kg and t½ was 24.6 to 29.7 days. CL was not increased in the volunteers who were ADA positive: 1.96 to 2.52 mL/day/kg.
- In Study P05776/P005 CL/F was 197 to 282 mL/day for the 50 mg and 200 mg SC doses respectively.

Intra and inter individual variability of pharmacokinetics

- In Study P05661/P004 intra-individual variability was low: CV% for CL was in the range 5 to 23%, for Vd was 10 to 37%, for C_{max} was 4 to 9% and for $t_{½}$ was 12 to 44%.
- In Study P05776/P005 variability expressed as CV% was 26 to 38 % for C_{max}, 12 to 22% for $t_{½}$, 20 to 46% for AUC, 27 to 119% for CL/F and 19 to 107% for Vd/F for the 50 mg and 200 mg SC doses respectively.

Pharmacokinetics in the target population

- In Study P05382/P001, in the dose range 0.05 to 10 mg/kg by IV administration mean t½ ranged from 20.2 to 26.9 days, CL from 1.57 to 2.50 mL/kg/day, and Vd from 58.3 to 91.6 mL/kg in the dose range 0.05 to 10 mg/kg. Accumulation ratios after the third dose ranged from 0.959 to 1.08 for AUC and 1.04 to 1.06 for C_{max}. These parameters were all similar to those in healthy volunteers.
- In Study P05839/006, in patients with Crohn's disease, in the dose range 0.5 to 10 mg/kg IV, mean CL ranged from 2.55 to 3.27 mL/kg/day, $t_{½}$ from 20.6 to 25.0 days, and Vd from 77.5 to 103 mL/kg.

Pharmacokinetics in special populations

Pharmacokinetics according to age

- In the population pharmacokinetic analysis age had statistically significant effects on CL and V, but these effects were not clinically significant.

[11] CV% = Coefficient of variability express as a percentage

Pharmacokinetics in other special population / with other population characteristic

- In Study P06306/P007there was no significant difference between the PK parameters in Japanese, Chinese and Caucasian volunteers. The PK parameters for IV tildrakizumab in Japanese volunteers were similar to those in other populations.

Population pharmacokinetics

The sponsor provided one population pharmacokinetic (PopPK) analysis (PopPK analysis MK-3222-PPK). The structural model was one compartment with first order absorption and elimination. The typical values for CL and V were 0.297 L/day and 10.7 L respectively. Variability, expressed as CV%, for CL and V were 29% and 21% respectively. The final covariate model included effects on CL for age, weight, albumin, gender, race and ethnicity, effects on bioavailability for healthy volunteer status and formulation; and effects on V for age, weight and gender. The only clinically significant effect on exposure was for weight.

The GMR (90% CI) for paraxanthine/caffeine $AUC_{0-\infty}$ caffeine +tildrakizumab/caffeine was 1.05 (0.85 to 1.30) and for C_{max} was 1.12 (0.98 to 1.27).

The GMR (90% CI) for 5-OH-omeprazole/omeprazole $AUC_{0-\infty}$ omeprazole plus tildrakizumab/omeprazole was 0.96 (0.77 to 1.19) and for C_{max} was 0.99 (0.85 to 1.15).

Pharmacodynamics

Studies providing pharmacodynamic data

Studies that provided pharmacodynamics data are listed in the table below.

Table 7: Submitted pharmacodynamics (PD) studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on PASI §	Study P05382/P001
	Effect on PASI §	Study P05495/P003
Secondary Pharmacology	Effect on Crohn's disease	Study P05839/P006

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacodynamics

The pharmacodynamics of tildrakizumab have been adequately characterised. There is a plateau of effect from the 50g dose level, and the majority of effect is reached by Week 12. However, there is measurable improvement in effect up to the 200 mg dose level and up to Week 28. There were no suitable biomarkers for effect, but the clinical measures of effect were suitable for measuring response. Hence, biomarkers did not contribute to the monitoring of tildrakizumab. The pharmacodynamic information in the Product Information is supported by the data submitted in the dossier.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

The Phase I studies indicated good tolerability for tildrakizumab up to 10 mg/kg.

Phase II dose finding studies

Based on the findings of Study P05495/P003 the sponsor performed a model-based analysis of dose response. This analysis indicated a plateauing of response from 50 mg, and little effect of body weight > 100 kg.

Phase III pivotal studies investigating more than one dose regimen

The sponsor performed further exposure response analyses using the data from the Phase IIa and III studies. The data were modelled using a maximum effect (E_{max}), using the plasma concentration data and the efficacy outcome data from the studies.

Using the simulations of the concentration effect relationship data, the sponsor performed a risk-benefit analysis that indicates no significant difference between the 100 mg dose level and the 200 mg dose level. Based on these analyses the sponsor is recommending the 200 mg dose level because of a slightly greater benefit in responders, and a greater benefit in partial responders, over time.

Evaluator's conclusions on dose finding for the pivotal studies

The sponsor has provided sufficient justification for the dosage regimens selected for the pivotal studies.

Efficacy

Studies providing efficacy data

The sponsor provided two Phase III studies in support of efficacy:

- Study 010: a placebo controlled study, with two dose levels for tildrakizumab.
- Study 011: a placebo and comparator (etanercept) controlled study, with two dose levels for tildrakizumab.

Evaluator's conclusions on efficacy

The two Phase III efficacy and safety studies were designed and conducted in accordance with the guideline.[12] The study populations were similar to the intended target population in Australia. The outcome measures were appropriate. The comparators were appropriate, and were used at effective doses.

Both Study 010 and Study 011 were designed to answer a number of questions and as a consequence were complicated, and difficult to interpret. However, because of the study designs the results also answer a number of clinically relevant questions.

Tildrakizumab has superior efficacy to placebo in the treatment of moderate to severe chronic plaque psoriasis over a 12 week period. Efficacy was demonstrated for PASI-75

[12] Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr)

response, Physician's Global Assessment (PGA), PASI-90 response and PASI-100 response. There was clinically and statistically significant benefit demonstrated for tildrakizumab for both clinical measures (PASI and PGA) and patient reported outcomes (Dermatology Life Quality Index (DLQI)).

Tildrakizumab was superior to etanercept over a 28 week period. This was demonstrated for PASI-75 for both tildrakizumab doses, but only for the 200 mg dose level for PGA response.

The treatment benefit was maintained for up to 64 weeks of continuous treatment with no loss of response rates.

There was no apparent difference in efficacy between the 100 mg dose and the 200 mg dose in establishing response. There may be some benefit of the 200 mg dose over the 100 mg dose in maintaining response, but this was not demonstrated to be significant in Study 010. There appeared to be some additional benefit in PASI-100 with the 200 mg dose level up to Week 28.

There was significant benefit demonstrated for dermatology specific patient reported outcomes (DLQI), and an indication of benefit for general patient reported outcome (SF-36, EQ-5D[13]).

In patients who cease tildrakizumab and relapse, response is regained with both the 100 mg and 200 mg dose levels, with no apparent effects on response rates.

There was no indication of rebound effects when treatment was ceased.

There were no subgroup effects on efficacy. Efficacy has been demonstrated in Caucasian and Asian patients in Study 010 but there were few Black patients, and efficacy has not been demonstrated in this population.

In patients who are partial responders, there appears to be benefit in continuing treatment because in this group response rates increased up to Week 64.

Patients who did not respond to etanercept showed response when switched to tildrakizumab.

There was no significant improvement in response when the dose was increased from 100 mg to 200 mg in patients previously treated with 100 mg.

Efficacy was not demonstrated for psoriatic arthritis, but the analysis was underpowered because it was only applied to a subset of patients.

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies with safety as the sole primary outcome.

Pivotal and/or main efficacy studies

There were two pivotal studies, Study 010 and Study 011 that collected data for adverse events (AE), vital signs, laboratory tests and electrocardiograms (ECG).

[13]SF-36= Short Form (36) Health Survey; EQ-5D = European Quality of Life 5 Dimensions

Other studies

Other efficacy studies

There were no other efficacy studies.

Studies with evaluable safety data: dose finding and pharmacology

There were seven clinical pharmacology studies that collected data for AEs, vital signs, laboratory tests and ECGs. Three of these studies exposed patients to tildrakizumab, and four exposed volunteers. The safety data for the volunteer studies are discussed briefly with each study (not included in this AusPAR). There were no clinically relevant safety issues identified in the volunteer studies.

Studies evaluable for safety only

There were no studies evaluable for safety only.

Patient exposure

A total of 1994 volunteers and patients have been exposed to tildrakizumab, with 1391 exposed for ≥ 52 weeks. There were 1041 patients exposed to the proposed 200 mg dose level. There were no patients aged < 18 years, 155 aged ≥ 65 to < 75 years and 20 aged ≥ 75 years. There were 1433 (71.9%) males and 561 (28.1%) females. There were 1615 (81.0%) White patients and 277 (14.0%) Asian. There were 90 (4.5%) patients with a history of hepatic impairment. There were 609 (30.5%) patients with mild renal impairment, 56 (2.8%) with moderate renal impairment and one with severe renal impairment. There were 463 (23.2%) patients with cardiac impairment. There were 1986 patients with moderate and/or severe psoriasis exposed to tildrakizumab.

- In Study P05382/P001, in the dose range 0.05 to 10 mg/kg by IV administration, there were 57 patients exposed to three doses of tildrakizumab and 20 to placebo.
- In Study P08630/P009 there were 20 patients with moderate to severe psoriasis exposed to two doses of tildrakizumab 28 days apart.
- In Study P05495/P003, conducted in patients with moderate-to-severe psoriasis, in Part 1 where subjects were treated with 2 doses (Week 0 and Week 4) and followed up for 16 weeks, there were 42 patients exposed to 5 mg, 92 to 25 mg, 89 to 100 mg, 86 to 200 mg and 46 to placebo (355 in total). In Part 2, where patients were treated every 12 weeks for up to 4 doses, there were 13 patients exposed to 5 mg, 94 to 25 mg, 153 to 100 mg and 79 to 200 mg (339 in total).
- In Study 010 there were 383 patients exposed to tildrakizumab 100 mg, with 197 exposed for > 56 weeks, and 401 to 200 mg, with 213 exposed for > 56 weeks.
- In Study 011 there were 489 patients exposed to tildrakizumab 100 mg, with 218 exposed for > 52 weeks and 527 exposed to 200 mg with 151 exposed for > 52 weeks.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Integrated safety analyses

In the Integrated Analysis of Safety there was one patient in the tildrakizumab 200 mg group and one in the etanercept that met predetermined criteria for abnormalities in hepatic function.

Pivotal and/or main efficacy studies

- In Study 010 one patient in the placebo group discontinued because of abnormal liver function tests. There were no trends in mean values.

- In Study 011 there were no clinically significant abnormalities in hepatic function reported.

Studies with evaluable safety data: dose finding and pharmacology

- In Study P08630/P009 increased alanine transaminase (ALT) was reported in three (15%) patients.
- In Study P05495/P003, one subject discontinued because of elevated ALT and gamma glutamyl transferase (GGT).

Renal function and renal toxicity

Integrated safety analyses

Impairment in renal function was not identified as a safety issue.

Pivotal and/or main efficacy studies

- In Study 010 and Study 011 there were no clinically significant abnormalities in renal function reported.

Studies with evaluable safety data: dose finding and pharmacology

- In Study P05495/P003, there were no clinically significant abnormalities in renal function reported.
- In Study P08630/P009 hyperglycaemia was reported in six (30%) patients.

Haematology and haematological toxicity

Integrated safety analyses

There were no clinically significant abnormalities in haematology reported.

Pivotal and/or main efficacy studies

- In Study 010 there were no trends in mean haematology values or clinically significant abnormalities.
- In Study 011 there were no clinically significant abnormalities in haematology parameters reported.

Studies with evaluable safety data: dose finding and pharmacology

In Study P05495/P003, there were no clinically significant abnormalities in haematology parameters reported.

Electrocardiograph findings and cardiovascular safety

Integrated safety analyses

The sponsor performed an integrated analysis of all the QT-interval corrected for heart rate (QTc) data from the clinical studies. None of the 192 subjects included in this analysis exceeded the critical values of heart rate-corrected QT interval using Fridericia's formula (QTcF) > 500 ms or a change from baseline in QTcF interval (ΔQTcF) > 60 ms.

Pivotal and/or main efficacy studies

- In Study 010 there were no trends in mean ECG values or clinically significant abnormalities.
- In Study 011 there were no clinically significant abnormalities in ECG parameters reported.

Studies with evaluable safety data: dose finding and pharmacology

- In Study P05495/P003, there were no clinically significant changes in ECG parameters reported.

Vital signs and clinical examination findings

Integrated safety analyses

No clinically significant trends in vital signs were identified.

Pivotal and/or main efficacy studies

- In Study 010 there were no trends in mean vital signs or clinically significant abnormalities.
- In Study 011 there were no clinically significant abnormalities in vital signs reported.

Studies with evaluable safety data: dose finding and pharmacology

No clinically significant trends in vital signs were identified.

Immunogenicity and immunological events

Integrated safety analyses

The immunogenicity report states an overall rate of treatment emergent ANA of 7.6% and of neutralising antibodies of 3.4% in the Phase IIa and III studies. In patients with treatment emergent neutralising antibodies, there was a decrease in mean tildrakizumab concentrations.

CL of tildrakizumab was increased in the presence of treatment emergent neutralising antibodies, but not by the presence of ANA alone. Efficacy was reduced in patients who were treatment emergent neutralising antibody positive, but not to the extent where it would restrict the use of tildrakizumab in this group. There did not appear to be any effect of ADA or neutralising antibodies on immunological AEs or AEs overall.

Pivotal and/or main efficacy studies

- In Study 010 treatment emergent ADA were detected in 26 (7.2%) patients with 100 mg, 35 (9.3%) patients with 200 mg and six (31.6%) patients who had their dose increased from 100 mg to 200 mg. Neutralising antibodies were detected in 18 (5.0%) patients with 100 mg, 18 (4.8%) patients with 200 mg and four (21.1%) patients who had their dose increased from 100 mg to 200 mg.
- In Study 011 drug hypersensitivity reactions were reported in four patients (0.9 /100 patient years) in the tildrakizumab 100 mg group, one (0.2 /100 patient years) in the 200 mg and none in the etanercept and one (2.9 /100 patient years) in the placebo. Treatment emergent ANA were reported in 50 (5.8%) patients treated with tildrakizumab. Neutralising antibodies were reported in 16 (1.8%) patients. Neither ANA nor neutralising antibody status appeared to affect efficacy.

Studies with evaluable safety data: dose finding and pharmacology

- In Study P05382/P001, in the dose range 0.05 to 10 mg/kg by IV administration, there were 9 (17.6%) patients who developed ADA, with two (3.9%) developing neutralising antibodies.
- In Study P06306/P007 four (8%) volunteers developed ADA, two (4%) developed neutralising antibodies. There was no effect of antibodies on PK.
- In Study P05495/P003, in the dose range 5 mg to 200 mg, ADA were developed in 25 (8%) of the pre-treatment ADA negative population, and 10 (3%) developed neutralising antibodies. AEs and efficacy did not appear to be affected by ADA.

Serious skin reactions

Serious skin reactions were not identified as a safety issue in the dossier.

Malignancy

Integrated safety analyses

In the Integrated Analysis of Safety, the sponsor reported malignancy in two (0.3%) patients with tildrakizumab 100 mg, one (0.1%) with 200 mg, three (0.2%) with 100/200 mg, none with placebo and one (0.3%) with etanercept. There was no statistically significant difference between any of the tildrakizumab groups and placebo.

Pivotal and/or main efficacy studies

- In Study 010 malignancies were reported in five patients (1.3 /100 patient years) during tildrakizumab 100 mg, six patients (1.4 /100 patient years) with 200 mg and two patients (1.2 /100 patient years) with placebo.
- In Study 011 malignancies were reported in eight patients (1.8 /100 patient years) in the tildrakizumab 100 mg group, four (1.0 /100 patient years) in the 200 mg and four (2.6 /100 patient years) in the etanercept and none in the placebo.

Studies with evaluable safety data: dose finding and pharmacology

- In Study P05495/P003, there were three malignancies reported as serious adverse events (SAEs): malignant melanoma in the 25 mg group; malignant melanoma in situ and rectal cancer in the 100 mg group.

Serious infections

Integrated safety analyses

In the Integrated Analysis of Safety, the sponsor reported severe infection in one (0.1%) patients with tildrakizumab 100 mg, two (0.3%) with 200 mg, three (0.2%) with 100/200 mg, and none with etanercept. There were no statistically significant differences between any of the tildrakizumab groups and placebo.

Pivotal and/or main efficacy studies

- In Study 010 serious infections were reported in four patients (1.0 /100 patient years) during tildrakizumab 100 mg, six patients (1.4 /100 patient years) with 200 mg and one patient (0.6 /100 patient years) with placebo. Although the number of affected patients is small this does suggest a dose effect.
- In Study 011 severe infections were reported in five patients (1.1 /100 patient years) in the tildrakizumab 100 mg group, eight (1.9 /100 patient years) in the 200 mg and three (2.0 /100 patient years) in the etanercept and one (2.9 /100 patient years) in the placebo.

Studies with evaluable safety data: dose finding and pharmacology

In Study P05495/P003, in Part 1, there was one serious infection reported as a SAE: bacterial arthritis in a patient in the 25 mg group.

Post marketing data

No post marketing data were included in the submission.

Evaluator's conclusions on safety

Tildrakizumab (Ilumya) appears to have a favourable safety profile. There is no apparent difference in the safety profile of the 200 mg dose level compared to the 100 mg.

The overall rate of treatment emergent adverse events (TEAEs) is similar with either tildrakizumab 100 mg or 200 mg compared to either placebo or etanercept. In the placebo controlled safety pool (to Week 12) TEAEs were reported in 48.2% patients with

tildrakizumab 100 mg, 47.9% with 200 mg, 54.0% with etanercept and 53.8%. with placebo.

There were few deaths in the development program, and when adjusted for duration of exposure to treatment there does not appear to be an excess in the tildrakizumab groups. The following deaths were reported:

- In Study 010 there was one death in the tildrakizumab 200 mg group (aneurysm; femoral and aortic).
- In Study 011 there were four deaths (0.9 /100 patient years) in the tildrakizumab 100 mg group (steatohepatitis/alcoholic cardiomyopathy, acute myeloid leukaemia, respiratory arrest, myocardial infarction) and one (0.2 /100 patient years) in the 200 mg after being randomised from etanercept (sepsis).
- In Study P05495/P003, there was one death in the 100 mg group (unknown cause).

SAEs were reported at similar rates for tildrakizumab, placebo and etanercept. In the placebo controlled safety pool (to Week 12) SAEs were reported in ten (1.4%) patients with tildrakizumab 100 mg, 16 (2.3%) with 200 mg, seven (1.1%) with etanercept and six (1.7%) with placebo. In Study 010, SAEs were reported in 20 patients (5.1 /100 patient years) during tildrakizumab 100 mg, 35 patients (8.4 /100 patient years) with 200 mg and nine (5.3 /100 patient years) with placebo. In Study 011, SAEs were reported in 30 patients (6.6 /100 patient years) in the tildrakizumab 100 mg group, 26 (6.2 /100 patient years) in the 200 mg, four (11.5/100 patient years) in the placebo and 20 (13.0 /100 patient years) in the etanercept.

Discontinuation due to AE occurred at a similar rate with tildrakizumab, placebo and etanercept. In the placebo controlled safety pool (to Week 12) discontinuation due to adverse event (DAE) were reported for four (0.6%) patients with tildrakizumab 100 mg, nine (1.3%) with 200 mg, six (1.9%) with etanercept and four (1.1%) with placebo.

There were no safety issues identified with regard to drug-induced liver injury (DILI) or renal injury. There were no safety issues identified with regards to haematology.

The rates of minor and/or serious infections were not increased with tildrakizumab relative to placebo.

The dossier complies with the Note for guidance on population exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95). A total of 1994 volunteers and patients have been exposed to tildrakizumab, with 1391 exposed for ≥ 52 weeks. There were 1041 patients exposed to the proposed 200 mg dose level.

The dossier complies with the guideline.[14] The immunogenicity report states an overall rate of treatment emergent ANA of 7.6% and of neutralising antibodies of 3.4% in the Phase IIa and III studies. In patients with treatment emergent neutralising antibodies, there was a decrease in mean tildrakizumab concentrations. CL of tildrakizumab was increased in the presence of treatment emergent neutralising antibodies, but not by the presence of ANA alone. Efficacy was reduced in patients who were treatment emergent neutralising antibody positive, but not to the extent where it would restrict the use of tildrakizumab in this group. There did not appear to be any effect of ADA or neutralising antibodies on immunological AEs or AEs overall.

However, there does appear to be an excess of malignancies reported with tildrakizumab. In the Integrated Analysis of Safety, the sponsor reported malignancy in two (0.3%) patients with tildrakizumab 100 mg, one (0.1%) with 200 mg, three (0.2%) with

[14] Committee for Medicinal Products for Human Use (CHMP) Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use. EMA/CHMP/BMWP/86289/2010 (24 May 2012)

100/200 mg, none with placebo and one (0.3%) with etanercept. The following malignancies were reported in the individual studies:

- In Study 010malignancies were reported in five patients (1.3 /100 patient years) during tildrakizumab 100 mg, six patients (1.4 /100 patient years) with 200 mg and two patients (1.2 /100 patient years) with placebo.
- In Study 01 malignancies were reported in eight patients (1.8 /100 patient years) in the tildrakizumab 100 mg group, four (1.0 /100 patient years) in the 200 mg and four (2.6 /100 patient years) in the etanercept and none in the placebo.
- In Study P05495/P003, there were three malignancies reported as SAEs: malignant melanoma in the 25 mg group; malignant melanoma in situ and rectal cancer in the 100 mg group.

In the opinion of the evaluator, there are insufficient data to conclude that tildrakizumab is associated with malignancy because of the much longer duration of treatment exposure relative to placebo in the clinical trials. The sponsor has included malignancy in the safety specification as an Important Potential Risk.

First round benefit-risk assessment

First round assessment of benefits

Below is a table comparing benefits versus risks in accordance to the proposed indication.

Table 8: Benefits and risks in accordance to the indication

Indication	
Benefits	Strengths and Uncertainties
Tildrakizumab has superior efficacy to placebo in the treatment of moderate to severe chronic plaque psoriasis over a 12 week period. Efficacy was demonstrated for PASI-75 response, PGA, PASI-90 response and PASI-100 response. There was clinically and statistically significant benefit demonstrated for tildrakizumab for both clinical measures (PASI and PGA) and patient reported outcomes (DLQI). Tildrakizumab was superior to etanercept over a 28 week period. This was demonstrated for PASI-75 for both tildrakizumab doses, but only for the 200 mg dose level for PGA response. The treatment benefit was maintained for up to 64 weeks of continuous treatment with no loss of response rates. There was no apparent difference in efficacy between the 100 mg dose and the 200 mg dose in establishing response. There may be some benefit of the 200 mg dose over the	The two Phase III efficacy and safety studies were designed and conducted in accordance with the Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr). The study populations were similar to the intended target population in Australia. The outcome measures were appropriate. The comparators were appropriate, and were used at effective doses. Both Study 010 and Study 011 were designed to answer a number of questions and as a consequence were complicated, and difficult to interpret. However, because of the study designs the results also answer a number of clinically relevant questions.

Indication	
100 mg dose in maintaining response, but this was not demonstrated to be significant in Study 010. There appeared to be some additional benefit in PASI-100 with the 200 mg dose level up to Week 28. There was significant benefit demonstrated for dermatology specific patient reported outcomes (DLQI), and an indication of benefit for general patient reported outcome (SF-36, EQ-5D). In patients who cease tildrakizumab and relapse, response is regained with both the 100 mg and 200 mg dose levels, with no apparent effects on response rates. There was no indication of rebound effects when treatment was ceased. There were no subgroup effects on efficacy. Efficacy has been demonstrated in Caucasian and Asian patients in Study 010 and Study 011 but there were few Black patients, and efficacy has not been demonstrated in this population. In patients who are partial responders, there appears to be benefit in continuing treatment because in this group response rates increased up to Week 64. Patients who did not respond to etanercept showed response when switched to tildrakizumab. There was no significant improvement in response when the dose was increased from 100 mg to 200 mg in patients previously treated with 100 mg.	

First round assessment of risks

Below is a table comparing risks vs strengths and uncertainties.

Table 9: Risks versus strengths and uncertainties

Risks	Strengths and Uncertainties
The overall rate of TEAEs is similar with either tildrakizumab 100 mg or 200 mg compared to either placebo or etanercept. The safety profiles of tildrakizumab 100 mg and 200 mg were similar. There were few deaths in the development program, and when adjusted for duration of exposure to treatment there does not appear to be an excess in the tildrakizumab groups. SAEs were reported at similar rates for tildrakizumab, placebo and etanercept. Discontinuation due to AE occurred at a similar rate with tildrakizumab, placebo and etanercept. The rates of minor and/or serious infections were not increased with tildrakizumab relative to placebo. There appears to be an excess of malignancies reported with tildrakizumab. The overall rate of treatment emergent ANA was 7.6% and of neutralising antibodies was 3.4%. Neither limited the use of tildrakizumab	A total of 1994 volunteers and patients have been exposed to tildrakizumab, with 1391 exposed for ≥ 52 weeks. There were 1041 patients exposed to the proposed 200 mg dose level. There were no data for treatment duration > 64 weeks. There were no safety data for special populations such as children, pregnancy or lactation.

First round assessment of benefit-risk balance

The benefit-risk balance for Ilumya (tildrakizumab) in the proposed usage is favourable. The benefit-risk balance for the 200 mg dose level is more favourable than that for the 100 mg dose level because of a slightly greater benefit and no difference in risk. The potential for increased malignancy with tildrakizumab will require prospective monitoring.

First round recommendation regarding authorisation

The clinical evaluator has no objection to the authorisation of Ilumya (tildrakizumab) for the indication of:

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

The decision to authorise Ilumya (tildrakizumab) should take into consideration the measures the sponsor proposes to monitor the long-term risk of malignancy with Ilumya (tildrakizumab).

Clinical questions and second round evaluation of sponsor's responses

Safety

Question 1

Does the sponsor have any safety data in patients who have a positive human immunodeficiency virus (HIV) test result, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) test result?

Sponsor's response

The sponsor does not have safety data in patients who have a positive human immunodeficiency virus (HIV) test result, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) test result.

Evaluator's comments

There are no safety data for patients with HIV, hepatitis B or hepatitis C. The risk with hepatitis B or hepatitis C would be reactivation, and with HIV increased susceptibility to opportunistic infections. Hence, in the absence of safety data these conditions should be listed as precautions. This would alert prescribers to the need for additional monitoring, and would enable patients to make a more informed choice.

Question 2

What specific measures does the sponsor propose to address the Important Potential Risk of malignancy?

Sponsor's response

The sponsor is conducting two ongoing Phase III studies (Studies PN10 and PN11) which are in the long-term extension phase and will provide data from patients up to 5 years of treatment; and, in addition, a prospective observational study using the CORRONA psoriasis registry, which will collect data for up to 8 years.

Evaluator's comments

The sponsor's response is satisfactory. In the opinion of the evaluator, the proposed ongoing studies will be of sufficient duration, and sufficient sample size, to capture a clinically significant increase in malignancy risk.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Ilumya (tildrakizumab) in the proposed usage are unchanged from those in the first round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Ilumya (tildrakizumab) in the proposed usage are unchanged from those in the first round evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance for Ilumya (tildrakizumab) in the proposed usage is favourable. The benefit-risk balance for the 200 mg dose level is more favourable than that for the 100 mg dose level because of a slightly greater benefit and no difference in risk. The potential for increased malignancy with tildrakizumab will require prospective monitoring.

Second round recommendation regarding authorisation

The clinical evaluator has no objection to the authorisation of Ilumya (tildrakizumab) for the indication of:

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

The decision to authorise Ilumya (tildrakizumab) should take into consideration the measures the sponsor proposes to monitor the long-term risk of malignancy with Ilumya (tildrakizumab).

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[15]

The sponsor has submitted EU-RMP version 0.1 (28 February 2017; data lock point (DLP) 16 April 2016) and Australian Specific Annex (ASA) version 0.1 (21 June 2017) in support of this application. These are the first versions of the EU-RMP and ASA and will consider any changes as a result of ongoing EMA Pharmacovigilance Risk Assessment Committee (PRAC) review and TGA assessment, respectively, prior to finalisation and implementation of the RMP. In their response, the sponsor submitted ASA version 0.2 (dated 5 February 2018).

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

[15] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 10: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None				
Important potential risks	Hypersensitivity	ü	–	ü	–
	Immunogenicity	ü	–	ü	–
	Serious infections	ü	ü	ü	–
	Malignancies	ü	ü	ü	–
	Major adverse cardiac events (MACE)	ü	ü	–	–
Missing information	Safety in children and adolescents	ü	ü	ü	–
	Safety in pregnant and lactating women	ü	–	ü	–
	Safety in patients with severe hepatic impairment	ü	–	ü	–
	Safety in patients with severe renal impairment	ü	–	ü	–
	Long term safety	ü	ü	–	–
	Use in patients with active infections (e.g. HIV, HBsAg, HCV etc.)*	ü	–	ü	–

* This safety concern was added in the sponsor's response to the Round 1 RMP evaluation.

- Additional pharmacovigilance activities in the ASA are in line with the EU-RMP. Australian patients are included in one of the ongoing studies. A patient registry is proposed to be conducted in the USA. The data from this registry study and from the ongoing clinical trials is considered to be applicable to Australia. There are no additional Australian-specific pharmacovigilance activities proposed.
- No additional risk minimisation activities are proposed, which is considered acceptable.

New and outstanding recommendations from second round evaluation

The recommendations made in the first round evaluation, along with consideration of the sponsor response were adequately addressed.

- The sponsor should amend the Black Triangle Scheme symbols that have been added to the PI and CMI to have side lengths of at least 5 mm. Further information on these requirements may be found on the TGA website.

Proposed wording for conditions of registration

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

The suggested wording is:

> The Ilumya EU-Risk Management Plan (RMP) (version 0.1, dated 28 February 2017, data lock point 16 April 2017), with Australian Specific Annex (version 0.2, dated 5 February 2018), included with submission PM-2017-02274-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

VII. Overall conclusion and risk/benefit assessment

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

Introduction

Regarding information on the condition being treated, it is stated in the clinical evaluation report (CER) that psoriasis is a common chronic skin condition with a prevalence of 1.3% to 2.2% in the UK (NICE Guideline 2012)[16]. It is an inflammatory condition with a relapsing and remitting course. Onset is usually in young adults, but can be at any age. It is associated with chronic arthritis in around 10% of patients. Nail changes occur in half of affected patients. Plaque psoriasis is the most common form (90% of patients) and is characterised by well-delineated red, scaly plaques. The extent of involvement can vary from a few patches to generalised involvement.

Psoriasis decreases quality of life in a number of ways: chronic itch, bleeding, scaling, nail involvement. This can result in loss of employment opportunities and social interactions. Patients with psoriasis have increased risks of comorbidity: cardiovascular disease, lymphoma and non-melanoma skin cancer.

As outlined in the CER, the current treatment options are discussed below.

Current treatment options

First-line therapies (topical therapies):

- Corticosteroids
- Vitamin D and vitamin D analogues
- Dithranol
- Tar preparations

Second-line therapies:

- Phototherapies:

[16] https://www.nice.org.uk/guidance/cg153

  - Broad- or narrow-band ultraviolet B light
  - Psoralen plus UVA light (PUVA)
- Systemic non-biological therapies:
  - Ciclosporin
  - Methotrexate
  - Acitretin

Third line therapies:

- TNFα inhibitors:
  - Adalimumab
  - Etanercept
  - Infliximab
- IL12 / IL23 inhibitors:
  - Ustekinumab (authorised in Australia for: plaque psoriasis):

    Stelara is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- Th17 lymphocyte depletion:
  - Secukinumab (authorised in Australia for: Plaque psoriasis):

    Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy).
- IL-17 inhibition
  - Ixekizumab
    - § Taltz is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy).

Therapy would usually commence with topical treatment: a potent corticosteroid with vitamin D or a vitamin D analogue (Nice Guideline 2012). Phototherapy would be offered to patients with plaque or guttate pattern psoriasis that cannot be controlled with topical treatments alone. Systemic non-biological therapy would be offered to patients if:

- psoriasis cannot be controlled with topical therapy; and
- it has a significant impact on physical, psychological or social wellbeing; and,
- One or more of the following apply:
  - psoriasis is extensive (for example, more than 10% of body surface area affected or a Psoriasis Area and Severity Index (PASI) score of more than 10); or
  - psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high impact sites); or
  - phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of Baseline disease severity within 3 months).

The most commonly used non-biological systemic treatment is methotrexate.

Biological treatments would be used where non-biological drugs were contraindicated or ineffective. The usual first choice of biological systemic treatment would be a TNFα inhibitor. Patients would consider changing to an alternative biological drug in adults if:

- The psoriasis does not respond adequately to a first biological drug or;
- the psoriasis initially responds adequately but subsequently loses this response, (secondary failure) or;
- the first biological drug cannot be tolerated or becomes contraindicated.

The treatment algorithm supported by the Australian College of Dermatologists is presented below.

Figure 1: Psoriasis diagnosis and initial assessment algorithm

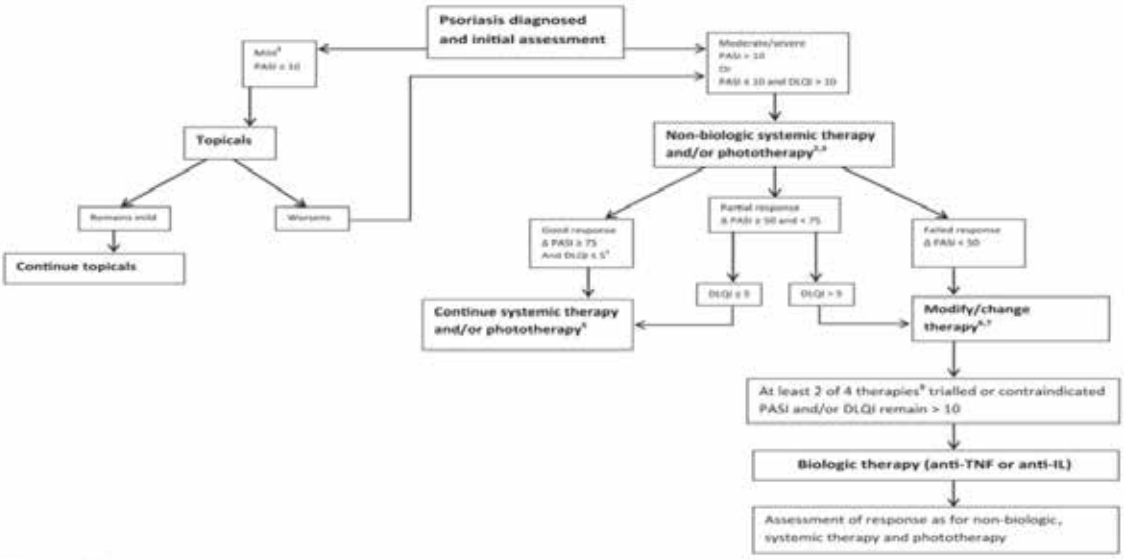


Figure 1 Treatment goals algorithm for patients with psoriasis in Australia.
Notes:
1. In absence of modifying features such as visible site, genital, palmoplantar, nails involvement, pruritus with excoriation (see text).
2. Appropriate time to review varies with each treatment and the range is 6–24 weeks.
3. Non-biologic therapies include methotrexate, cyclosporin and acitretin.
4. Psoriasis area severity index (Δ PASI) ≥75 but dermatological quality of life index (DLQI) ≥5 may occur if modifying features such as the visible site, genital, palmoplantar, nail involvement or pruritus are present or the response is discordant with patient's expectations. Physician assessment whether to continue, modify or change therapy.
5. Continuation/discontinuation is modulated by toxicity and contraindication.
6. Treatment change to take into account patient wishes.
7. In addition to change of treatment, modify may include adding topicals, adding other systemic treatment, increasing dose or frequency or hospital admission.
8. The Australian consensus group propose that two of four therapies as reasonable and best practice. The current requirement of the Australian reimbursement body, the Pharmaceutical Benefits Scheme, is three of four therapies.

Proposed drug class

Tildrakizumab (Ilumya) is a biological, immunomodulatory drug. It is a humanised IgG1/k monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. It is composed of two identical heavy chains of 446 amino acids each and two identical light chains of 214 amino acids each, linked by interchain disulfide bonds, with an approximate molecular weight of 147.0kDa. Tildrakizumab binds to the p19 protein subunit of the interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor.

Proposed therapeutic indication

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

Proposed dosage form and strength

100 mg/ 1 mL solution for injection in pre-filled syringe.

Proposed dosage and administration regimen

Adults

The recommended dose is 200 mg at Weeks 0, 4 and every 12 weeks thereafter.

Each 200 mg dose is given as two subcutaneous injections of 100 mg.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regularly scheduled interval.

Special populations

Elderly (≥ 65 years)

No dose adjustment is required (see Pharmacokinetics).

Renal or hepatic impairment

Ilumya has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

The safety and efficacy of Ilumya in children and adolescents under 18 years of age has not yet been evaluated.

Method of administration

Ilumya is administered by subcutaneous injection. Full instructions for use are provided in the CMI.

After proper training in subcutaneous injection technique, patients may self-inject Ilumya if a healthcare professional determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients.

Sites for injection include abdomen, thighs, or upper arm. Do not administer 5 cm around the navel or where the skin is tender, bruised, abnormally red, indurated or affected by psoriasis. Do not inject into scars, stretch marks, or blood vessels. Choose a different location for the second injection.

The pre-filled syringe should be visually inspected for particulate matter and discolouration prior to administration. Product exhibiting particulate matter or discolouration must not be used. Do not shake.

Inject the full amount (1 ml from each syringe) which provides a total of 200 mg of tildrakizumab (100 mg per syringe).

Ilumya does not contain any antimicrobial preservatives. Discard any unused product remaining in the pre-filled syringe. Ilumya pre-filled syringes are for single-use in one patient only.

Proposed changes to the product documentation

The clinical evaluator (CE) stated that no changes to the PI have been proposed.

Regulatory history

Concerning the Australian regulatory history, the CE stated that this is the first application to the TGA with regard to Ilumya (tildrakizumab) 100 mg/ 1 mL solution for injection in pre-filled syringe.

The orphan drug designation does not apply to the present application and there are no related submissions.

The overseas regulatory status is described above in Section I above.

The sponsor stated 'the application has not been deferred, withdrawn or rejected in any other countries'.

The clinical evaluator stated that the submitted dossiers differ in terms of being country specific. In addition, the dosing proposed in the US is different to that proposed in Australia and the EU:

> *'Trademark' is administered by subcutaneous injection. The recommended dose is 100 mg at Weeks 0, 4, and every twelve weeks thereafter. Patients weighing > 90 kg may benefit from a dose of 200 mg (two 100 mg injections).'*

Quality

The were no objections on quality grounds to the approval of Ilumya tildrakizumab solution for injection 100 mg/1 mL pre-filled syringe.

Proposed conditions of registration

The quality evaluator proposed the following conditions of registration

- It is a condition of registration that all batches of Ilumya tildrakizumab solution for injection 100 mg/1 mL pre-filled syringe imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- It is a condition of registration that each batch of Ilumya tildrakizumab solution for injection 100 mg/1 mL pre-filled syringe imported into 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.

Nonclinical

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines (ICH S6).[2] The overall quality of the nonclinical studies was generally high. All safety-related studies were GLP compliant.

- Tildrakizumab has high affinity for human IL-23 (KD 297 pM). Affinity for monkey IL-23 was high (KD 47 pM) but absent for rodent IL-23. Tildrakizumab neutralised IL-23 under in vitro conditions, with an IC_{50} range of 59 to 189 pM for human IL-23 and 118 pM for monkey IL-23. Expression of IL-23 and its receptor subtypes (IL-23R and IL-12Rβ1) was low in a panel of human, monkey and mouse tissues. The highest levels of IL-23 expression were found in the immune tissues (thymus, lymph nodes, bone marrow, appendix and tonsils) in all species. Expression of IL-23p19 was increased in skin biopsies from psoriasis patients and colonic biopsies from patients with Crohn's disease.
- Tildrakizumab staining was generally comparably between the tested panel of human and monkey tissues and was cytoplasmic.

- Safety pharmacology parameters were assessed in the GLP repeat dose toxicity studies and were found to be unremarkable. No notable changes to CNS (neurological, behaviour and body temperature), electrocardiographic (heart rate, QT interval duration and corrected QT interval duration) or respiratory parameters were reported.
- In monkeys tildrakizumab showed slow systemic distribution (T_{max}> 3 days), a long elimination half-life ((t½) 10 to 21 days) and high bioavailability when administered by the clinical route (SC). Serum levels were dose proportional. Human pharmacokinetic parameters were similar to those noted in cynomolgus monkeys (T_{max}> around 6.2 days; t½ around 23 days), showing first order absorption and slow clearance with steady state attained by week 16 of dosing under the clinical regimen (Week 0 and 4 and every 12 weeks thereafter). The PK studies showed that the monkey is an appropriate animal model for toxicity testing.
- Based on in vitro studies, IL-23 does not affect hepatic C-reactive protein expression or the expression and activity of P450 enzymes, therefore clinical drug-drug interactions through P450 pathways are unlikely.
- Tildrakizumab had a low order of acute oral toxicity in monkeys.
- Two repeat dose toxicity studies (tildrakizumab 10, 30, 40, 100 and 300 mg/kg/fortnight) by the clinical (SC, 3 and 9 months) route were conducted in monkeys. Treatment-related effects were minimal. Injection site reactions were the main effect, evident by microscopic evaluation only.
- No genotoxicity or carcinogenicity studies were conducted, which is acceptable for a biotechnology–derived pharmaceutical.
- A pre/postnatal development study reported no adverse effects on maternal health, no effect to length of gestation, infant morphometric measurements, neurobehavioural parameters, heart rate assessments, humoral responses to KLH antigen and lymphocyte subset populations. There was an increased incidence of infant loss in the high dose group (100 mg/kg), where four infants died or were euthanised within 15 postnataldays. Of these, two deaths were related to maternal neglect, with two deaths considered to be of an uncertain relationship to tildrakizumab treatment. Therefore, the no observed adverse effect level (NOAEL) for infant development is 10 mg/kg/fortnight.
- Tildrakizumab was found to cross the placenta (fetal: maternal serum ratio 0.6 to 4.9) in monkeys. Milk transfer studies showed a low amount of tildrakizumab excreted in the milk (< 0.2%). Tildrakizumab had no effect on menstrual cycling, sperm parameters and showed no histological changes to reproductive tissues in monkeys. There were also no effects on embryofetal development (NOAEL ≥ 300 mg/kg/fortnight).
- Primary pharmacology studies provided sufficient evidence of tildrakizumab affinity and selectivity for human and monkey IL-23, as well as neutralisation of its actions.
- Treatment-related effects associated with fortnightly injections were minimal and limited to injection site reactions, which were evident by microscopic evaluation only.
- Pregnancy Category B1 is considered appropriate.[6]
- Overall, there are no nonclinical objections to the registration of tildrakizumab (Ilumya).

Clinical

Clinical evaluators comments on the clinical dossier

The clinical dossier represents a clinical development program up to and including Phase III for a new biological entity. The dossier does not contain long-term safety data, beyond 1 year of continuous treatment. In the opinion of the clinical evaluator, the deferment of the paediatric studies is appropriate because of the potential risks of serious infectious disease and malignancy. The deferment will enable further safety data to be collected in the adult population prior to studies in children and adolescents.

Pharmacokinetics

Studies identified by the CE as providing pharmacokinetic (PK) data (general PK, PK in special populations, drug interactions PK and PopPK) in the submission are shown in Table 6.

Summary of pharmacokinetics

Physicochemical characteristics of the active substance

Ilumya (tildrakizumab) is a humanised IgG1/k monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. It is composed of two identical heavy chains of 446 amino acids each and two identical light chains of 214 amino acids each linked by interchain disulfide bonds, with an approximate molecular weight of 147.0 kDa.

Pharmacokinetics in healthy subjects

- Following SC administration and absorption, the T_{max} was 6 days as per Study P05776/P005
- As per Study P05776/P005, the mean (90% CI) absolute bioavailability for subcutaneous (SC) administration, compared to IV, was 80 (62 to103) % for the 50 mg dose and 73 (46 to 115) % for the 200 mg dose. CL/F was 197 to 282 mL/day. Mean (90% CI) bioavailability in volunteers who were ADA positive was similar: 85.8 (67.6 to 109) % for the 50 mg dose and 64.7 (35.7 to 117) % for the 200 mg dose.
- Regarding the bioequivalence of clinical trial and proposed market formulations, the Phase IIa and III clinical trial formulation is the same as that proposed for marketing.
- Regarding the bioequivalence of different dosage forms and strengths, in Study P08630/P009, there was no significant difference in exposure to tildrakizumab by PFS compared to PFS with AI. The GMR (90% CI) for $AUC_{0-\infty}$ PFS + AI/PFS was 1.17 (0.81 to 1.70) and for C_{max} was 1.08 (0.79 to 1.47).
- Dose proportionality:
  - In Study P05661/P004, the PK of tildrakizumab were dose-proportional (linear) in the dose range 0.1 to 10 mg/kg).
  - In Study P05776/P005, with SC dosing there was dose proportionality for AUC and C_{max}.
  - In Study P06306/P007, tildrakizumab was dose-proportional for C_{max} and AUC when administered SC in the dose range 50 mg to 400 mg.
  - In Study P05495/P003, in the dose range 5 mg to 200 mg, exposure to tildrakizumab was dose proportional).
- Volume of distribution (V_d)

  - In Study P05661/P004, the plasma concentration versus time profile was consistent with a two-compartment model with rapid redistribution and V_d was 75.6 to 106 mL/kg.
  - In Study P05776/P005, mean (CV %) V_d/F was 6600 (17) mL for the 50 mg SC dose and 10400 (105) mL for the 200 mg SC dose.
- In terms of plasma protein binding, tildrakizumab is an antibody and would not be expected to have protein binding.
- Tildrakizumab is an antibody which is distributed mainly in the plasma. Distribution in either the erythrocyte or tissue is not expected.
- Metabolism: tildrakizumab is an antibody and is eliminated through catabolism.
- Excretion:
  - In Study P05661/P004, in the dose range 0.1 to 10 mg/kg by IV administration, the CL of tildrakizumab was in the range 2.04 to 2.52 mL/day/kg and t½ was 24.6 to 29.7 days. CL was not increased in the volunteers who were ADA positive: 1.96 to 2.52 mL/day/kg.
  - In Study P05776/P005 CL/F was 197 to 282 mL/day for the 50 mg and 200 mg SC doses respectively.
- Mass balance studies were not performed. Tildrakizumab is an antibody and is eliminated through catabolism.
- Renal clearance: tildrakizumab is not cleared via the renal route.
- Intra and inter individual variability of pharmacokinetics:
  - in Study P05661/P004 intra-individual variability was low: CV% for CL was in the range 5 to 23%, CV% for V_d was 10 to 37%, CV% for C_{max} was 4 to 9% and CV% for t½ was 12 to 44%;
  - in Study P05776/P005, variability expressed as CV% was 26 to 38 % for C_{max}, 12 to 22% for t½, 20 to 46% for AUC, 27 to 119% for CL/F and 19 to 107% for V_d/F for the 50 mg and 200 mg SC doses respectively.
- Pharmacokinetics in the target population
- In Study P05382/P001, in the dose range 0.05 to 10 mg/kg by IV administration mean t½ ranged from 20.2 to 26.9 days, CL from 1.57 to 2.50 mL/kg/day, and V_d from 58.3 to 91.6 mL/kg in the dose range 0.05 to 10 mg/kg. Accumulation ratios after the third dose ranged from 0.959 to 1.08 for AUC and 1.04 to 1.06 for C_{max}. These parameters were all similar to those in healthy volunteers.
- In Study P05839/006, in patients with Crohn's disease, in the dose range 0.5 to 10 mg/kg IV, mean CL ranged from 2.55 to 3.27 mL/kg/day, t½ from 20.6 to 25.0 days, and V_d from 77.5 to 103 mL/kg.

Pharmacokinetics in special populations

- The sponsor does not have data for PK in subjects with impaired hepatic function.
- The sponsor does not have data for PK in subjects with impaired renal function (Note: Tildrakizumab is not cleared via the renal route).
- Pharmacokinetics according to age:
  - In the population pharmacokinetic analysis, age had statistically significant effects on CL and V, but these effects were not clinically significant.
- Pharmacokinetics related to genetic factors:

  - The sponsor does not have data for PK related to genetic factors.

- Pharmacokinetics in other special population / with other population characteristic
  - In Study P06306/P007, there was no significant difference between the PK parameters in Japanese, Chinese and Caucasian volunteers. The PK parameters for IV tildrakizumab in Japanese volunteers were similar to those in other populations.

Population pharmacokinetics

- The sponsor provided one population pharmacokinetic analysis (PopPK analysis MK-3222-PPK). The structural model was one compartment with first order absorption and elimination. The typical values for CL and V were 0.297 L/day and 10.7 L respectively. Variability, expressed as CV%, for CL and V were 29% and 21% respectively. The final covariate model included effects on CL for age, weight, albumin, gender, race and ethnicity, effects on bioavailability for healthy volunteer status and formulation; and effects on V for age, weight and gender. The only clinically significant effect on exposure was for weight.

Pharmacokinetic interactions

- In Study P08630/P009, which used a CYP substrate cocktail to investigate the effects of tildrakizumab on CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP1A2, there were no clinically significant effects demonstrated.
- There was no clinically significant difference in exposure to CYP probe substrate when co-administered with tildrakizumab:
  - The GMR (90% CI) for $AUC_{0-\infty}$ midazolam +tildrakizumab/midazolam was 1.11 (0.94 to 1.32) and for C_{max} was 1.06 (0.86 to 1.29).
  - The GMR (90% CI) for $AUC_{0-\infty}$ s-warfarin +tildrakizumab/s-warfarin was 1.07 (0.98 to 1.17) and for C_{max} was 0.99 (0.95 to 1.03).
  - The GMR (90% CI) for $AUC_{0-\infty}$ dextromethorphan +tildrakizumab/dextromethorphan was 1.20 (1.00 to 1.45) and for C_{max} was 1.17 (0.96 to 1.43).
  - The GMR (90% CI) for $AUC_{0-\infty}$ caffeine +tildrakizumab/caffeine was 1.14 (1.01 to 1.28) and for C_{max} was 0.96 (0.88 to 1.05).
  - The GMR (90% CI) for $AUC_{0-\infty}$ omeprazole +tildrakizumab/omeprazole was 1.05 (0.83 to 1.32) and for C_{max} was 0.87 (0.69 to 1.10).
- There was no clinically significant difference in parent/substrate ratio for the CYP probe substrates when co-administered with tildrakizumab:
  - The GMR (90% CI) for 1-OH-midazolam/midazolam $AUC_{0-\infty}$ midazolam +tildrakizumab/midazolam was 0.88 (0.73 to 1.05) and for C_{max} was 0.88 (0.73 to 1.05).
  - The GMR (90% CI) for 7-OH-warfarin/s-warfarin $AUC_{0-\infty}$ s-warfarin +tildrakizumab/s-warfarin was 1.01 (0.59 to 1.73) and for C_{max} was 1.06 (0.92 to 1.22).
  - The GMR (90% CI) for dextrorphan/dextromethorphan $AUC_{0-\infty}$ dextromethorphan +tildrakizumab/dextromethorphan was 0.95 (0.81 to 1.11) and for C_{max} was 0.98 (0.82 to 1.16).
  - The GMR (90% CI) for paraxanthine/caffeine $AUC_{0-\infty}$ caffeine +tildrakizumab/caffeine was 1.05 (0.85 to 1.30) and for C_{max} was 1.12 (0.98 to 1.27).

  - The GMR (90% CI) for 5-OH-omeprazole/omeprazole $AUC_{0-\infty}$ omeprazole +tildrakizumab/omeprazole was 0.96 (0.77 to 1.19) and for C_{max} was 0.99 (0.85 to 1.15).
- Clinical implications of in vitro findings
  - There were no additional clinical implications of in vitro findings.

Clinical evaluator's overall conclusions on pharmacokinetics

- The PK of tildrakizumab has been adequately characterised.
- Tildrakizumab has the typical PK characteristics of an antibody based drug.
- The absorption characteristics after a SC dose are suitable for the proposed indication: T_{max} of 6 days and absolute bioavailability of 73% at the 200 mg dose level.
- V_d reflects intravascular plasma, indicating tildrakizumab is predominantly intravascular and not distributed to the tissues.
- The $t^{½}$ is 25 to 30 days.
- There is little inter-individual and intra-individual variability in PK.
- There are no significant interactions with CYP enzymes.
- The PK section of the proposed PI is supported by the PK data submitted by the sponsor.

Pharmacodynamics

Studies identified by the clinical evaluator as providing pharmacodynamic (PD) information in the submission as shown in Table 6.

Summary of pharmacodynamics

Mechanism of action

- Tildrakizumab is a humanised IgG1/κ monoclonal antibody that specifically binds to the p19 protein subunit of the interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor.
- IL-23 is a naturally occurring cytokine composed of 2 subunits (IL-23p19 and IL-12/23p40), that is involved in inflammatory and immune responses.
- Tildrakizumab inhibits the release of pro-inflammatory cytokines and chemokines. In in vitro models, tildrakizumab was shown to disrupt IL-23 mediated signalling and cytokine cascades by disrupting the interaction of IL-23 binding to its specific receptor, IL-23R without binding to IL-12 (composed of 2 subunits IL-12p35 and IL-12/23p40).

Primary pharmacodynamic effects

- In Study P05382/P001, in the dose range 0.05 to 10 mg/kg by IV administration, improvement in PASI appeared to plateau at the 3.0 mg/kg dose level. There were three patients with IL-23 above the level of detection. There were no clinically meaningful trends in IL-22, calprotectin, immunoglobulins, ESR or cytokines.
- In the active treatment groups, the Histopathologic Psoriasis Severity Score (HPSS) was significantly reduced: mean (95% CI) reduction 67.1 (53.3 to 80.9) %. By immuno-histochemistry, the dermal inflammatory exudate predominantly consisted of CD3+, CD4+ and CD68+ leukocytes. BDCA-2+ plasmacytoid dendritic cells, CD11c+ myeloid dendritic cells, CD15+ neutrophils and CD8+ cytotoxic T cells were represented to a lesser extent. After active treatment the infiltrates resolved.

- In Study P05495/P003, in the dose range 5 mg to 200 mg, PASI-75 response rates at Week 16 increased with dose: 14 (33.33%) at 5 mg, 58 (64.44%) at 25 mg, 59 (66.29%) at 100 mg, 64 (74.42%) at 200 mg and 2 (4.44%) with placebo. PASI-75 response rates at Week 12 increased with dose: 10 (23.81%) at 5 mg, 53 (58.89%) at 25 mg, 54 (60.67%) at 100 mg, 62 (72.09%) at 200 mg and 2 (4.44%) with placebo). PGA response (proportion of patients with PGA 'cleared' or 'minimal') rates at Week 16 increased with dose: 14 (33.33%) at 5 mg, 52 (57.78%) at 25 mg, 55 (61.80%) at 100 mg, 64 (74.42%) at 200 mg and one (2.22%) with placebo. PASI-90 response rates at Week 16 were: 5 (12.50%) at 5 mg, 22 (25.29%) at 25 mg, 34 (38.64%) at 100 mg, 44 (52.38%) at 200 mg and one (2.44%) with placebo. PASI-100 response rates at Week 16 were: 2 (5.00%) at 5 mg, 8 (9.20%) at 25 mg, 13 (14.77%) at 100 mg, 14 (16.67%) at 200 mg and none (0.00%) with placebo. PASI-50 response rates at Week 16 were: 24 (57.14%) at 5 mg, 74 (82.22%) at 25 mg, 73 (82.02%) at 100 mg, 79 (91.86%) at 200 mg and four (8.89%) with placebo. Response rates increased to Week 16. The proportion of patients with DLQI score of 0 or 1 at Week 16 were: 13 (32.50%) at 5 mg, 50 (57.47%) at 25 mg, 46 (52.37%) at 100 mg, 48 (57.83%) at 200 mg. There was no association between IL-22, miRNA or blood mRNA gene expression and PASI response. Changes in IL-23 and IL-12 signalling pathways were not dose-related.

Secondary pharmacodynamic effects

- In Study P05839/006, in patients with Crohn's disease, in the dose range 0.5 to 10 mg/kg IV, there was a dose-related fall in serum calprotectin, and faecal calprotectin was decreased in all the tildrakizumab groups compared to placebo. There were no clear trends in IL-6, IL-17, IL-22, PAP, or CRP-HS.[17]
- Regarding the time course of pharmacodynamic effects, in the Phase III studies, the majority of effect was reached by Week 12, but there was some ongoing improvement to Week 28.
- For the relationship between drug concentration and pharmacodynamic effects, the Phase IIa and Phase III data were fitted to an E_{max} model which was used in the dosage selection.
- There were no significant gender or age related differences in pharmacokinetic parameters, or in efficacy parameters. Hence, these effects were also not observed in the PD responses.
- The sponsor did not present data on pharmacodynamic interactions.

Clinical evaluator's overall conclusions on pharmacodynamics

- The pharmacodynamics of tildrakizumab have been adequately characterised.
- There is a plateau of effect from the 50 g dose level, and the majority of effect is reached by Week 12. However, there is measurable improvement in effect up to the 200 mg dose level and up to Week 28.
- There were no suitable biomarkers for effect, but the clinical measures of effect were suitable for measuring response. Hence, biomarkers did not contribute to the monitoring of tildrakizumab.
- The pharmacodynamic information in the PI is supported by the data submitted in the dossier.

[17] CRP = C-reactive protein

Dosage selection for the pivotal studies

Studies identified by the clinical evaluator as providing dosage selection information for the pivotal studies

- Phase I (PK and PD dose finding) studies indicated good tolerability for tildrakizumab up to 10 mg/kg.
- Phase II dose finding study was based on the findings of Study P05495/P003. The sponsor performed a model-based analysis of dose response. This analysis indicated a plateauing of response from 50 mg, and little effect of body weight > 100 kg.
- Phase III pivotal studies investigating more than one dose regimen. The sponsor performed further exposure response analyses using the data from the Phase IIa and III studies. The data were modelled using an E_{max}, using the plasma concentration data and the efficacy outcome data from the studies. Using these data, the Sponsor performed a risk-benefit analysis that indicates no significant difference between the 100 mg dose level and the 200 mg dose level. Based on these analyses the Sponsor is recommending the 200 mg dose level because of a slightly greater benefit in responders, and a greater benefit in partial responders, over time.

Clinical evaluator's overall conclusions on dose finding for the pivotal studies

The sponsor has provided sufficient justification for the dosage regimens selected for the pivotal studies.

Efficacy

Studies identified by the clinical evaluator as providing evaluable efficacy data in the submission

As per the clinical evaluation, the sponsor provided two Phase III studies in support of efficacy; these were:

- Study 010: a placebo controlled study, with two dose levels for tildrakizumab.
- Study 011: a placebo and comparator (etanercept) controlled study, with two dose levels for tildrakizumab.

Study P010

Study P010 was a Phase III, multicentre, randomised, double blind, placebo controlled parallel group trial to evaluate the efficacy, safety and tolerability of subcutaneous tildrakizumab in patients with moderate-to-severe chronic plaque psoriasis.

Inclusion and exclusion criteria

The inclusion criteria were:

- Patient must be ≥ 18 years of age, of either sex and of any race/ethnicity.
- Diagnosis of predominantly plaque psoriasis for ≥ 6 months.
- Patient is considered to be a candidate for phototherapy or systemic therapy.
- Psoriasis body surface area (BSA) involvement ≥ 10% at baseline.
- Psoriasis Area and Severity Index (PASI) score ≥ 12 at baseline.
- Physician's Global Assessment (PGA) of at least moderate disease (≥ 3) at baseline.
- Patient is considered to be eligible according to the following tuberculosis (TB) screening criteria:

- Has no history of untreated latent or active TB prior to screening. Prophylactic treatment for latent TB (as per local guidelines) must be initiated at least 4 weeks prior to first administration of study medication.
- Has no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
- Has had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB at least 4 weeks prior to the first administration of study medication.
- Within 4 weeks prior to first administration of study medication, either has negative diagnostic TB test results (defined as a negative tuberculin skin test or a negative QuantiFERON-TB Gold test.
- A subject who has a positive intradermal skin test or positive QuantiFERON-TB Gold test, or who has had recent close contact with a person with active TB, or has signs or symptoms suggestive of active TB upon medical history and/or physical examination, or if required by local guidelines or regulations as part of routine TB screening, must have a negative chest radiograph (both posterior-anterior and lateral views) or chest computed tomography (CT) scan taken within 4 weeks prior to first administration of study medication. The radiograph or scan must be read by a qualified radiologist, and must have no evidence of current active TB or old inactive TB.
- Patient is unlikely to conceive.
- For women of childbearing potential, a negative serum pregnancy test at screening and a negative urine pregnancy test within 24 hours prior to the first dose of study medication.
- Patient must have clinical laboratory tests within the following parameters prior to the first dose of study medication:
- ALT, aspartate transaminase (AST) or alkaline phosphatase (ALP) ≤ 1.5 x upper limit of normal (ULN)
- Creatinine < 133 μmol/L
- Haemoglobin ≥ 10 g/dL
- Absolute neutrophil count ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm^3

- Subject must have results of a physical examination within normal limits or clinically acceptable limits to the investigator prior to the first dose of study medication.

The exclusion criteria included:

- Presence of predominantly non-plaque forms of psoriasis specifically erythrodermic psoriasis, predominantly pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new-onset guttate psoriasis.
- Patient with current, or history of, severe psoriatic arthritis and is well-controlled on current therapy.
- Patient who is expected to require topical therapy, phototherapy, or systemic therapy for psoriasis during the trial.
- Women of childbearing potential who are pregnant, intend to become pregnant (within 6 months of completing the trial), or are lactating.

- Positive human immunodeficiency virus (HIV) test result, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) test result.
- Prior malignancy or concurrent malignancy (excluding successfully treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma with no evidence of recurrence within 5 years, or carcinoma in situ of the cervix that has been adequately treated).
- Patient with any previous use of tildrakizumab or other IL-23/Th-17 pathway inhibitors, including p40, p19 and IL-17 antagonists.
- Patient has received any of the following treatments within the indicated washout period prior to randomisation:
  - Topical psoriasis treatment (within 2 weeks)
  - Conventional systemic psoriasis therapy (for example, cyclosporine, methotrexate, acitretin, fumaric acid esters) or phototherapy (for example, ultraviolet (UV)-B light phototherapy, psoralen-UVA (PUVA) therapy, tanning salon or home-administered UVB) (within 4 weeks)
  - Treatment with injectable or oral corticosteroids (within 4 weeks)
  - Treatment with a biological agent (including monoclonal antibodies, alefacept) (within 12 weeks or 5 half-lives whichever is longer)
  - Treatment with a non-biological investigational agent (within 4 weeks or 5 half-lives, whichever is longer)
  - Treatment with a biological investigational agent (within 12 weeks or 5 half-lives, whichever is longer)

Study treatments

The study treatments consisted of three parts:

Part 1 (Weeks 0 to 12):

- Arm A: tildrakizumab 200 mg SC at Weeks 0 and 4
- Arm B: tildrakizumab 100 mg SC at Weeks 0 and 4
- Arm C: Placebo SC at Weeks 0 and 4

Part 2 (Weeks 12 to 28):

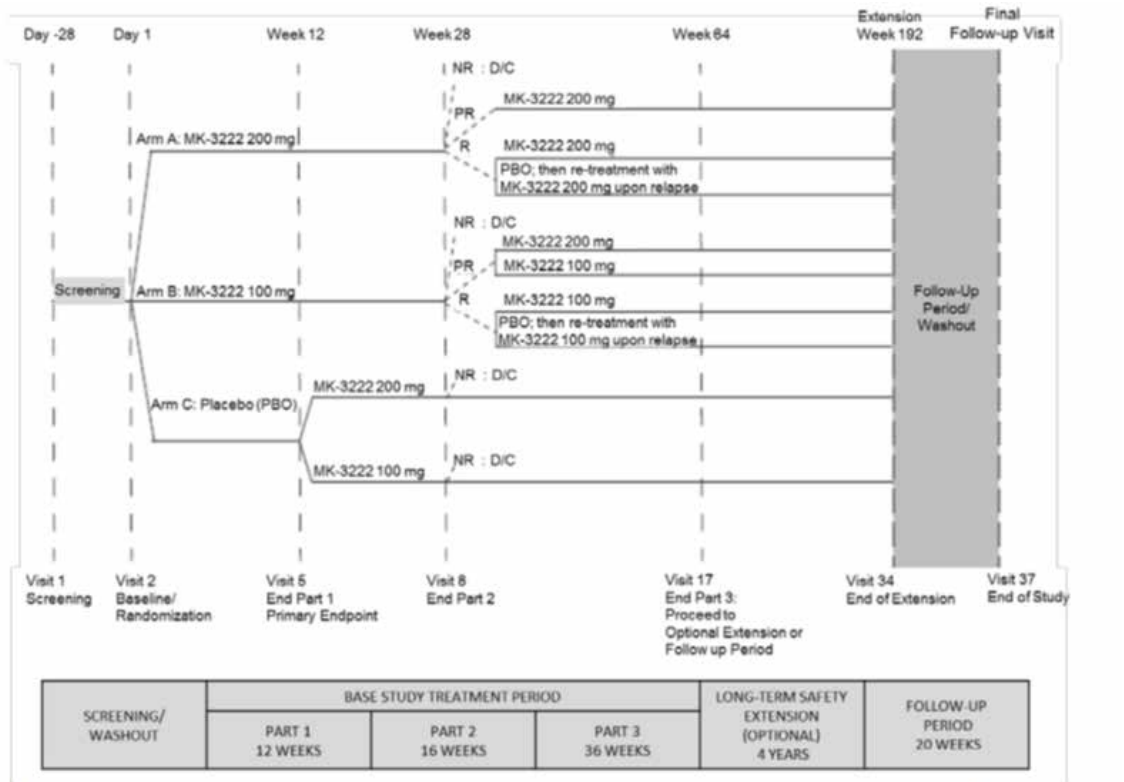
- Patients in Arms A and B received their corresponding tildrakizumab doses at Week 16 (that is 12 weeks after the last dose at Week 4)
- Patients in Arm C were re-randomised to either tildrakizumab 100 mg or 200 mg at Week 12 but received corresponding doses at Week 16

Part 3 (Weeks 28 to 64): Assessment was carried out at the end of Week 28 with reallocation of patients in Arm C to either Arm A or Arm B depending on previous dose.

- Full Responders (that is, Rs) (≥ 75% improvement in baseline PASI) were re-randomised to either their previous treatment or placebo:
  - Treatments were every 4 weeks, but patients receiving tildrakizumab received 12 weekly treatments with placebo for the 4 weekly intervals between active treatments.
  - Patients randomised to placebo received treatments every 4 weeks.
  - Patients randomised to placebo were recommenced on tildrakizumab (at their previous dose) if there was a reduction in maximum PASI response by 50%.

- Partial responders (that is. PRs)(PASI response ≥ 50% but < 75% improvement from baseline):
  - PRs in Arm A continued on tildrakizumab 200 mg.
  - PRs in Arm B were randomised to 100 mg or the higher 200 mg dose every 12 weeks.
  - PRs in Arm C continued on their current dose.
- Non-responders (NRs) from each arm (< 50% improvement in PASI from baseline) were discontinued from the study.
- The prohibited medications during the study were:
  - Topical psoriasis therapy (including topical corticosteroids except as rescue treatment during Part 3)
  - Conventional systemic psoriasis therapy or phototherapy
  - Treatment with injectable or oral corticosteroids
  - Treatment with a biological agent other than the study medication
  - Treatment with investigational agents other than the study medication. Bland emollients were allowed.

Figure 2: Schematic representation of Study P010



NR were subjects who achieved<50% improvement in PASI response frombaseline. At Week 28, NR were discontinued.
PR were subjects who achieved≥50% but <75% improvement in PASI response frombaseline.
R were subjects who achieved≥75% improvement in PASI response frombaseline.
D/C = discontinuation; NR = non-responders; PASI = Psoriasis Area and Severity Index; PR = partial responders; R = responders.

Efficacy outcome variables

For Part 1 treatment period, there were:

1. Two co-primary efficacy outcome measures:
    a. Proportion of subjects with PASI 75 response at Week 12
    b. Proportion of subjects with PGA score of clear or minimal with at least a 2 grade reduction from baseline at Week 12.
2. Key secondary efficacy outcome measures:
    a. Proportion of subjects with PASI 90 response at Week 12
    b. Proportion of subjects with PASI 100 response at Week 12.
3. Other efficacy outcome measures:
    a. Proportion of subjects with DLQI score of 0 or 1 at Week 12
    b. Proportion of subjects with ACR (20, 50, and 70) response at Week 12
    c. Change from baseline in DLQI at Week 12
    d. Change from baseline in health assessment questionnaire (HAQ) at Week 12
    e. Change from baseline in Patient Global Assessment of Pain (PGAP) (visual analogue scale (VAS) for pain) at Week 12
    f. Change and percent change from baseline in PASI at Week 12.

For Part 2 treatment period, efficacy outcome measures were:

1. Proportion of subjects with PASI (75, 90, and 100) response at Week 28
2. Proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 28
3. Proportion of subjects with DLQI score of 0 or 1 at Week 28
4. Proportion of subjects with ACR (20, 50, and 70) response at Weeks 16 and 28
5. Proportion of subjects with PASI (75, 90, and 100) response over time from randomisation to Week 28
6. Change and percent change from baseline in PASI score over time from randomization to Week 28
7. Change from baseline in DLQI at Week 28
8. Change from baseline in HAQ at Weeks 16 and 28
9. Change from baseline in PGAP (VAS for pain) at Weeks 16 and 28.

For Part 3 treatment period, efficacy outcome measures were:

1. Proportion of subjects with PASI 75 over time through Week 64
2. Change and percent change from baseline in PASI over time through Week 64
3. Proportion of subjects with PGA 'clear' or 'minimal' with at least a 2 grade reduction from baseline over time through Week 64
4. Proportion of subjects who relapse over time through Week 64
5. Proportion of subjects with rebound of disease
6. Proportion of subjects with PASI (75, 90, and 100) following 12 weeks of re-initiated tildrakizumab treatment over time

7. Proportion of subjects with PGA 'clear' or 'minimal' with at least a 2 grade reduction from baseline following 12 weeks of re-initiated tildrakizumab treatment over time
8. Proportion of subjects with PASI 75 response at Week 52 and 64
9. Proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Weeks 52 and 64
10. Change and percent change from baseline in PASI over time through Week 64
11. Proportion of subjects with PASI (75, 90 and 100) response at Weeks 40, 52 and 64
12. Proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Weeks 40, 52, and 64
13. Change and percent change from baseline in PASI over time through Week 64
14. Change from baseline in DLQI at Week 40, 52, and 64
15. Proportion of subjects with DLQI score of 0 or 1 at Weeks 40, 52, and 64
16. Proportion of subjects with ACR (20, 50, and 70) response at Weeks 40 and 64
17. Change from baseline in HAQ at Week 40 and 64
18. Change from baseline in PGAP (VAS for pain) at Weeks 40 and 64.

Note:

a. The PASI is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0-4 scale), weighed by the area of involvement. Such calculated PASI score ranges from 0 to 72, with higher score indicating more severe disease status.

b. PASI 75, PASI 90, and PASI 100 stand for the status (Yes/No) of achieving ≥ 75%, ≥ 90%, and ≥ 100% reduction from baseline in PASI score, respectively.

c. The Physician Global Assessment (PGA) version 2.0 is described below in Figure 3.

Figure 3: The Physician Global Assessment (PGA) version 2.0

Physician Global Assessment (PGA) –*version 2.0*

The PGA is used to determine the overall severity of a subject's psoriasis lesions at a given time point. Overall lesions will be graded for thickness, erythema, and scaling based on the scales below. The sum of the 3 scales will be divided by 3 to obtain the final PGA score.

Thickness (T) (averaged across all lesions)	
0 = no evidence of plaque elevation 1 = minimal plaque elevation (= 0.25 mm) 2 = mild plaque elevation (= 0.5 mm) 3 = moderate plaque elevation (= 0.75 mm) 4 = marked plaque elevation (= 1 mm) 5 = severe plaque elevation (= 1.25 mm or more)	T =
Erythema (E) (averaged across all lesions)	
0 = no evidence of erythema; hyperpigmentation may be present 1 = faint erythema 2 = light red coloration 3 = moderate red coloration 4 = bright red coloration 5 = dusky to deep red coloration	E =
Scaling (S) (averaged across all lesions)	
0 = no evidence of scaling 1 = minimal; occasional fine scale over less than 5% of the lesion 2 = mild; fine scale dominates 3 = moderate; coarse scale predominates 4 = marked; thick, nontenacious scale predominates 5 = severe; very thick tenacious scale predominates	S =
Total - Add T + E + S	**Total =**
Divide Total by 3	**Average =**
PGA (Round average to the nearest whole number) For example, if Average <1.49, PGA would be 1; if Average >1.50, PGA would be 2.	**PGA =**

Interpretation of PGA

0 = Cleared, except for residual discoloration
1 = Minimal – majority of lesions have individual scores for T+E+S / 3 that average 1
2 = Mild – majority of lesions have individual scores for T+E+S / 3 that average 2
3 = Moderate – majority of lesions have individual scores for T+E+S / 3 that average 3
4 = Marked – majority of lesions have individual scores for T+E+S / 3 that average 4
5 = Severe – majority of lesions have individual scores for T+E+S / 3 that average 5

d. The DLQI questionnaire consists of ten questions, where each question is scored from 0 (not affected at all) to 3 (very much affected). The DLQI score is the sum of the ten individual question scores and ranges from 0 to 30, with lower scores indicating better quality of life. If two or more questions are left unanswered, the DLQI score is set to missing.

e. Plasma samples were collected for pharmacokinetic observations and immunogenicity.

f. The safety outcome measures were: AEs, events of clinical interest (ECI), and vital signs.

Analysis of populations

The efficacy analysis was based on the Full Analysis Set (FAS). The FAS included all randomised patients who received at least one dose of Part 1 or Part 2 study medication. The safety analysis was based on the All Subjects as Treated (ASaT) population, which included all randomised patients who received at least one dose of Part 1 or Part 2 study medication, based on the treatment received.

Sample size

The study was powered as a test of superiority. The intended samples size for Part 1 was 750 patients in total: 300 in the tildrakizumab 200 mg group, 300 in the tildrakizumab 100 mg group and 150 in the placebo. Assuming a placebo rate of 10% for both PASI 75 response rate and proportion of subjects with PGA 'clear' or 'minimal' with at least a 2 grade reduction from baseline, the trial had > 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response rate and to detect a 55% difference in proportion of subjects with PGA 'clear or 'minimal' with at least a 2 grade reduction from baseline, using 2-sided test at significance level of alpha = 0.05.

Statistical methods

The Cochran-Mantel-Haenszel test, stratified by body weight category and prior exposure to biologics treatment, was used to test for differences in proportions. Constrained longitudinal data analysis was used to test for differences in patient reported outcomes. Hypothesis tests were not performed for Part 2 or Part 3 and the outcome measures were analysed with descriptive statistics. Missing values were treated as non-responders for the primary analysis of efficacy. Multiplicity was addressed by using a hierarchical approach to hypothesis testing.

Major protocol violations/deviations

The commonest major protocol violation was in the informed consent category (32.1%) subjects.

Baseline data

There were 533 (69.0%) males, 239 (31.0%) females and the age range was 18 to 82 years. The treatment groups were similar in demographic characteristics.). There were 75 (9.7%) patients aged ≥ 65 years.

Baseline PASI scores were similar in the three treatment groups, but the baseline PGA scores were slightly lower in the placebo group.).

The pattern of previous medical conditions was similar for the three treatment groups except for infections and infestations which were more common in the placebo group: 39 (25.2%) patients compared to 53 (17.2%) in the tildrakizumab 100 mg group and 49 (15.9%) in the 200 mg).

Prior medications were used by 295 (95.5%) patients in the tildrakizumab 100 mg group, 296 (96.1%) in the 200 mg and 148 (95.5%) in the placebo. Immuno-suppressants had been used by 116 (37.5%) patients in the tildrakizumab 100 mg group, 112 (36.4%) in the 200 mg and 54 (34.8%) in the placebo. Topical corticosteroids had been used by 173 (56.0%) patients in the tildrakizumab 100 mg group, 166 (53.9%) in the 200 mg and 85 (54.8%) in the placebo.

The commonest concomitant medications were ibuprofen, paracetamol and aspirin. Concomitant antibacterials were used by 101 (32.7%) patients in the tildrakizumab 100 mg group, 93 (30.2%) in the 200 mg and 47 (30.3%) in the placebo.

Mean (standard deviation (SD)) treatment compliance was 99.42 (1.954) % in the tildrakizumab 100 mg group, 99.53 (1.771) % in the 200 mg group and 99.62 (1.747) % in the placebo.

Randomisation and blinding methods

Randomisation/re-randomisation was performed using Interactive web response system (IWRS). Randomisation was stratified by region (North America, EU and Japan), by body weight ≤ 90 kg or > 90 kg, prior exposure to biologics, and in Japan by psoriatic arthritis at baseline.

There were 772 patients randomised in the study (309 to tildrakizumab 100 mg, 308 to 200 mg and 155 to placebo as earlier stated). There were 638 (82.6%) patients who completed the study: 250 (80.9%) in the tildrakizumab 100 mg group, 250 (85.7%) in the 200 mg and 124 (80.0%) in the placebo. There were 506 (65.5%) patients who entered the long-term follow-up study.

Blinding was maintained by having placebo injections for the 4 week intervals between 12 weekly treatments.

Efficacy outcomes as per the clinical evaluator

Primary outcomes:

- Tildrakizumab was superior to placebo with similar efficacy for the 100 mg and 200 mg groups. PASI-75 at Week 12 was attained by 197 (63.8%) patients in the tildrakizumab 100 mg group, 192 (62.3%) in the 200 mg group and 9 (5.8%) in the placebo. Treatment difference (95% CI) tildrakizumab – placebo was 58.0 (51.0 to 64.1) % $p < 0.001$ for 100 mg and 56.6 (49.6 to 62.8) % $p < 0.001$ for 200 mg.
- PGA response at Week 12 was attained by 179 (57.9%) patients in the tildrakizumab 100 mg group, 182 (59.1%) in the 200 mg group and 11 (7.1%) in the placebo. Treatment difference (95% CI) tildrakizumab – placebo was 50.9 (43.6 to 57.4) % $p < 0.001$ for 100 mg and 52.1 (44.8 to 58.5) % $p < 0.001$ for 200 mg.
- Subgroup analysis for PASI-75 indicated efficacy in all subgroups, and no indication that patients > 90 kg had better response with 200 mg compared with 100 mg.
- Subgroup analysis for PASI-75 indicated efficacy in all subgroups, although there appears to be less chance of response if a patient has previously failed biological treatment, and no indication that patients > 90 kg had better response with 200 mg compared with 100 mg.

Key secondary outcomes:

For Part 1 treatment period:

- PASI-90 at Week 12 was attained by 107 (34.6%) patients in the tildrakizumab 100 mg group, 109 (35.4%) in the 200 mg group and 4 (2.6%) in the placebo. Treatment difference (95% CI) tildrakizumab – placebo was 32.1 (25.9 to 38.0), % $p < 0.001$ for 100 mg and 32.9 (26.8 to 38.8), % $p < 0.001$ for 200 mg.
- PASI-100 at Week 12 was attained by 43 (13.9%) patients in the tildrakizumab 100 mg group, 43 (14.0%) in the 200 mg group and two (1.3%) in the placebo. Treatment difference (95% CI) tildrakizumab – placebo was 12.7 (8.0 to 17.3), % $p < 0.001$ for 100 mg and 12.7 (8.3 to 17.2), % $p < 0.001$ for 200 mg.

Others outcomes:

For Part 1 treatment period:

- DLQI response (score of 0 or 1) at Week 12 PASI-90 at Week 12 was attained by 126 (41.5%) patients in the tildrakizumab 100 mg group, 132 (44.2%) in the 200 mg group and 8 (5.3%) in the placebo. Treatment difference (95% CI) tildrakizumab – placebo was 36.1 (29.3 to 42.5), % $p < 0.001$ for 100 mg and 38.9 (31.9 to 45.4), % $p < 0.001$ for 200 mg.
- Proportion of subjects with ACR (20, 50, and 70) response at Week 12 (in Japanese patients only) showed improvement in the active treatment groups relative to placebo, but no hypothesis tests were performed).
- The mean (SD) change from baseline in DLQI at Week 12 was -10.0 (6.66) for tildrakizumab 100 mg, -9.8 (6.63) for 200 mg and -2.1 (6.52) for placebo. Treatment

difference (95% CI) tildrakizumab – placebo was -7.4 (-8.3 to -6.5) p < 0.001 for 100 mg and -7.7 (-8.6 to -6.8) % p < 0.001 for 200 mg.

- The change from baseline in HAQ at Week 12 was analysed in Japanese patients only and showed no statistically significant difference between treatment groups.
- The change from baseline in PGAP (VAS for pain) at Week 12 was analysed in Japanese patients only and showed no statistically significant difference between treatment groups, or change from baseline in any treatment group.
- There was little change and percent change from baseline in PASI at Week 12 in the placebo group, but significant improvement in both treatment groups, with no apparent difference between the active treatment groups as per the figures below.

Figure 4: Change from Baseline in Psoriasis Area and Severity Index score and 95% confidence interval over time, (FAS)

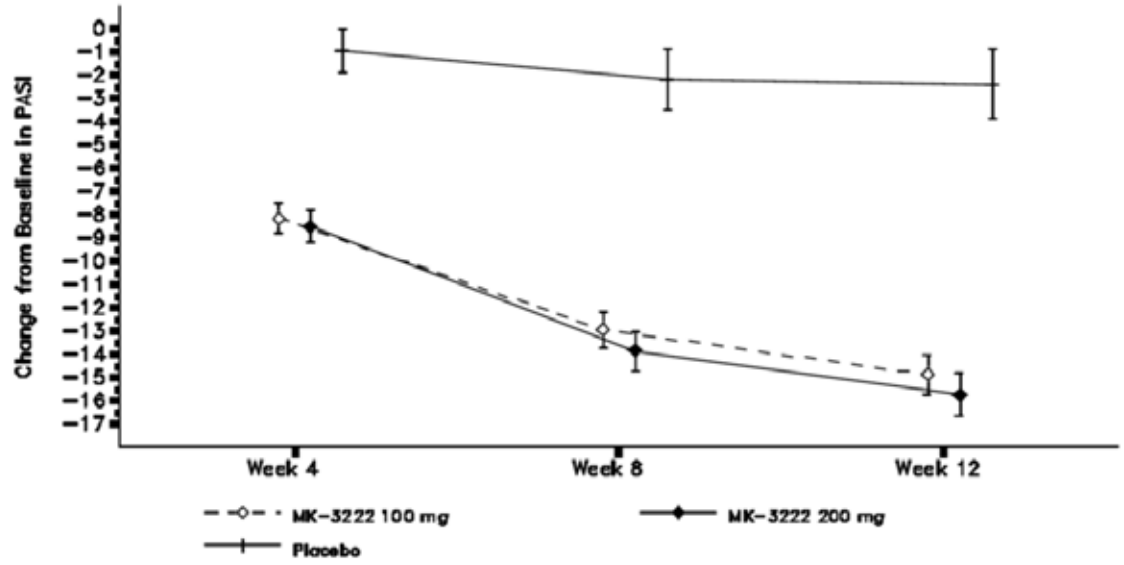
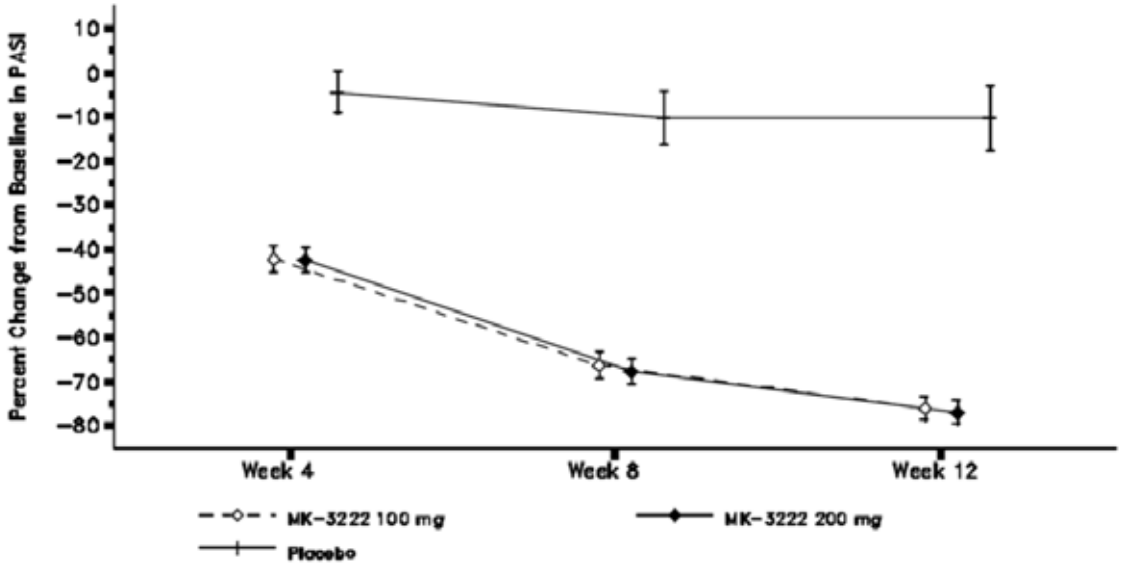


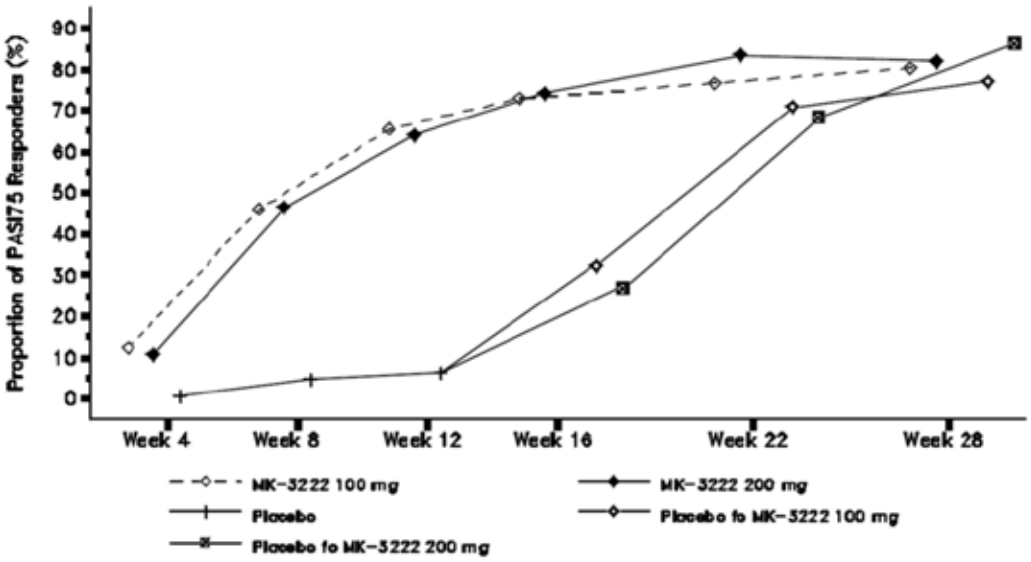
Figure 5: Percent change from Baseline in Psoriasis Area and Severity Index score and 95% confidence interval over time, (FAS)



Part 2 treatment period efficacy outcomes:

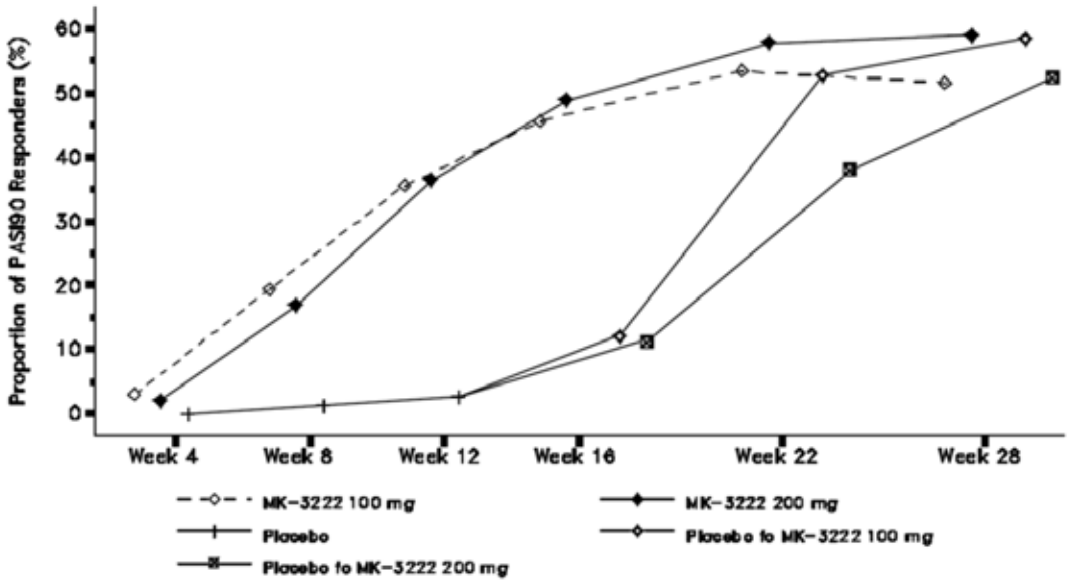
- The number (proportion) of patients with PASI-75 at week 28 was 54 (77.1%) in the placebo/100 mg group, 56 (86.2%) in the placebo/200 mg, 229 (80.4%) in the 100 mg and 236 (81.9%) in the 200 mg
- The number (proportion) of patients with PASI-90 at week 28 was 41 (58.6%) in the placebo/100 mg group, 34 (52.3%) in the placebo/200 mg, 147 (51.6%) in the 100 mg and 170 (59.0%) in the 200 mg
- The number (proportion) of patients with PASI-100 at week 28 was 22 (31.4%) in the placebo/100 mg group, 17 (26.2%) in the placebo/200 mg, 67 (23.5%) in the 100 mg and 91 (31.6) in the 200 mg
- Proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 28 was 53 (75.7%) in the placebo/100 mg group, 46 (70.8%) in the placebo/200 mg, 188 (66.0%) in the 100 mg and 199 (69.1) in the 200 mg
- Proportion of subjects with DLQI score of 0 or 1 at Week 28 was 37 (52.1%) in the placebo/100 mg group, 38 (55.9%) in the placebo/200 mg, 152 (52.4%) in the 100 mg and 164 (56.7) in the 200 mg
- Proportion of subjects with ACR (20, 50, and 70) response at Weeks 16 and 28 (Japanese patients only) showed improvement in the active treatment groups relative to placebo, but no hypothesis tests were performed).
- PASI 75 response rates improved to Week 22, and response was mirrored in the patients who switched from placebo to active treatment as per below figure.

Figure 6: Proportion of subjects with PASI-75 response over time (FAS) Part 1 and Part 2



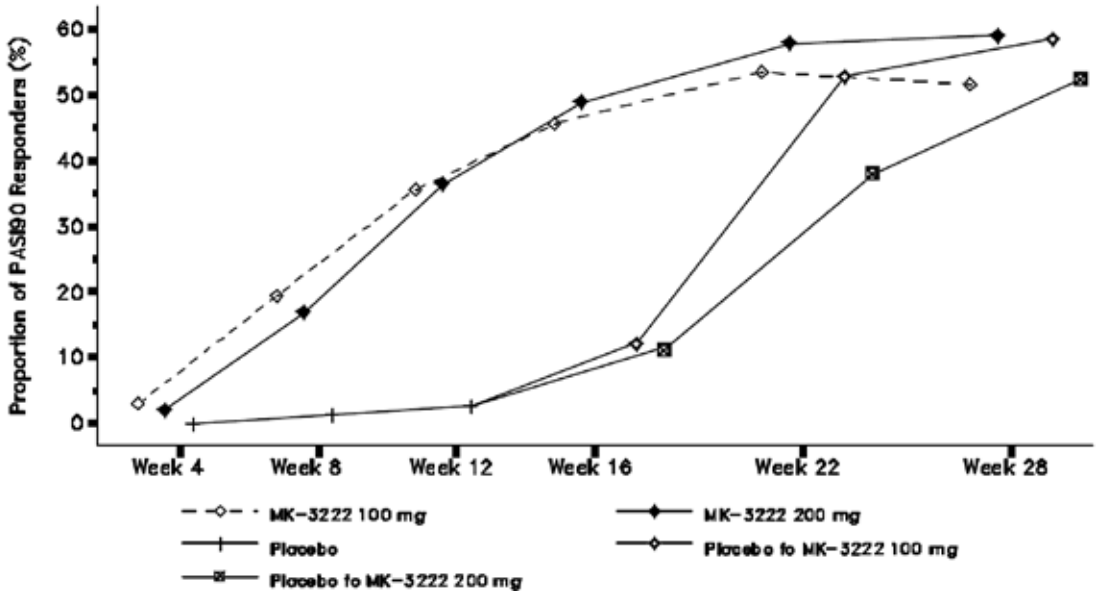
- PASI 90 response rates improved to Week 22, and response was mirrored in the patients who switched from placebo to active treatment as per the figure below.

Figure 7: Proportion of subjects with PASI90 response over time; FAS, Part 1 and Part 2



- PASI 100 response rates peaked at Week 22 in the 100 mg group, and increased to Week 28 in the 200 mg as per below figure.

Figure 8: Proportion of Subjects with PASI100 response over time FAS Part 1 and Part 2



- The change and percent change from baseline in PASI score over time from randomisation to Week 28 also indicate a plateauing of effect from Week 22 as per below figures.

Figure 9: Mean change from Baseline in PASI score over time; FAS, Part 1 and Part 2

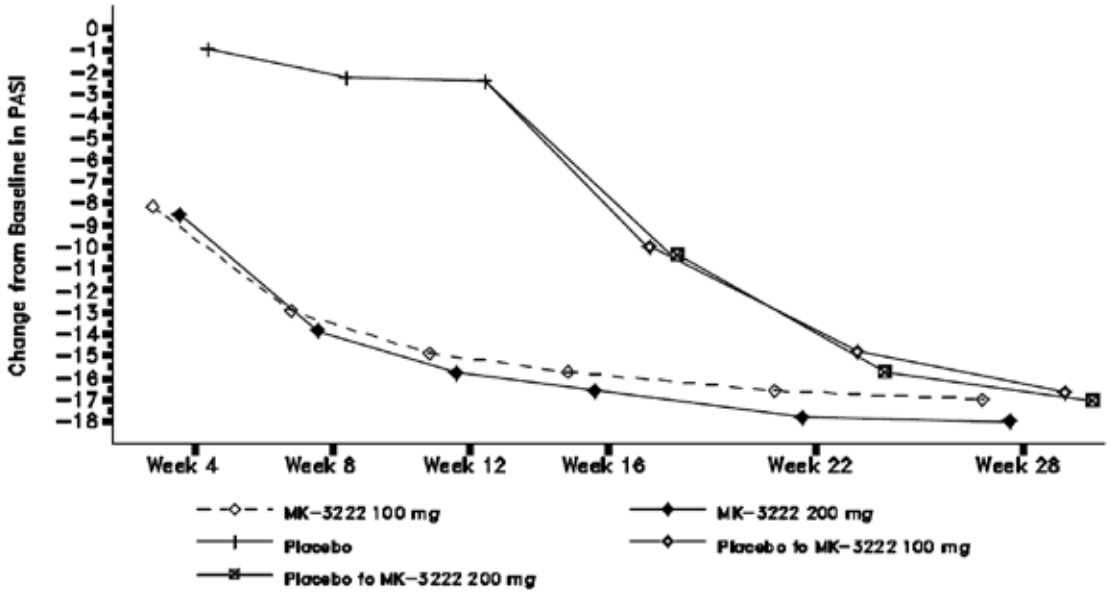
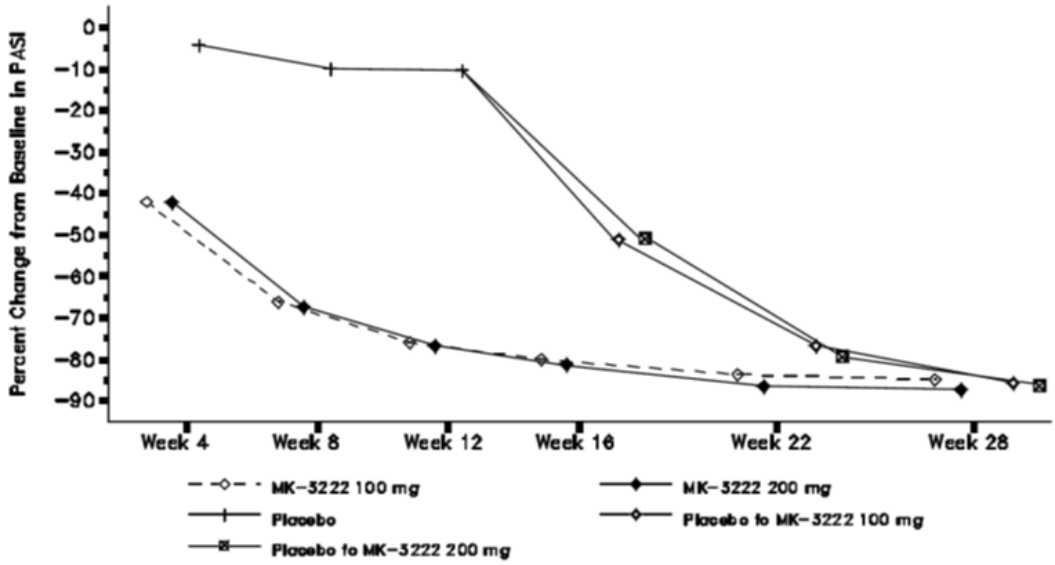


Figure 10: Mean percent change from Baseline in PASI score over time; FAS, Part 1 and Part 2



- The change from baseline in HAQ at Weeks 16 and 28 was analysed only in the Japanese patients and showed no statistically significant change from baseline.
- The change from baseline in PGAP (VAS for pain) at Weeks 16 and 28 was analysed in Japanese patients only and showed no statistically significant difference between treatment groups.

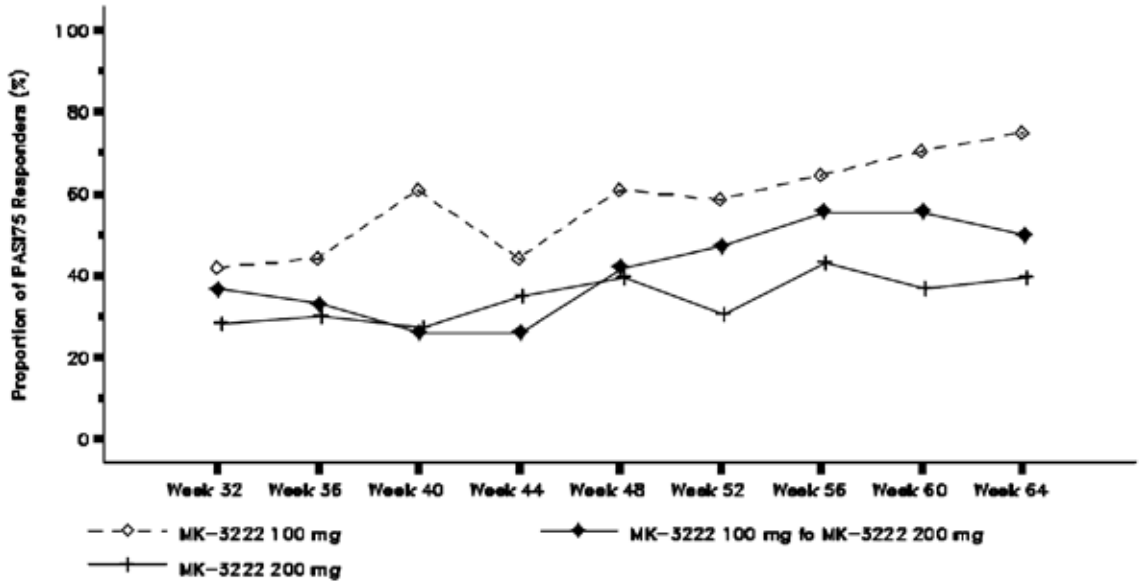
Part 3 treatment period efficacy outcomes:

- The number (proportion) of patients with PASI-75 at week 64 was 25 (49.0%) in the 100 mg to placebo group, 34 (56.7%) in the 200 mg to placebo, 98 (87.5%) in the 100 mg and 107 (93.9%) in the 200 mg, 30 (85.7%) in the placebo relapse/100 mg and 25 (83.3%) in the placebo relapse 200 mg
- The change (95% CI) in from baseline in PASI over time through Week 64 was -12.9 (-14.5 to -11.3) in the 100 mg to placebo group, -14.6 (-16.2 to -13.0) in the 200 mg to placebo, -17.7 (-19.0 to -16.3) in the 100 mg and -22.5 (-20.3 to -17.4) in the

200 mg, -18.7 (-21.8 to -15.5) in the placebo relapse/100 mg and -20.4 (-24.1 to -16.8) in the placebo relapse/200 mg

- Proportion of subjects with PGA 'clear' or 'minimal' with at least a 2 grade reduction from baseline over time through Week 64 was 16 (32.0%) in the 100 mg to placebo group, 25 (41.7) in the 200 mg to placebo, 69 (61.6%) in the 100 mg and 87 (76.3%) in the 200 mg, 21 (60.0%) in the placebo relapse/100 mg and 20 (66.7%) in the placebo relapse/200 mg
- The highest proportion of subjects with relapse was at Week 56: 12 (16.45) patients in the 100 mg group and 11 (13.1%) in the 200 mg group
- No patients experienced rebound of disease in Part 3
- Change from Baseline in DLQI at Week 40, 52, and 64 was preserved in patients treated with both 100 mg and 200 mg tildrakizumab.
- DLQI response was preserved in those patients who continued on tildrakizumab 100 mg and 200 mg.
- There were insufficient data on the proportion of subjects with ACR (20, 50, and 70) response at Weeks 40 and 64 to provide comment.
- The change from baseline in HAQ at Week 40 and 64 was analysed only in the Japanese patients and showed no statistically significant change from Baseline.
- The change from baseline in PGAP (VAS for pain) at Weeks 40 and 64 was analysed in Japanese patients only and showed no statistically significant difference between treatment groups.
- In patients who were patrial responders, there appeared to be increasing effect over time up to Week 64 as the figure below.

Figure 11: PASI 75 response over time: Part 3 FAS, subjects randomised to MK-3222 (tildrakizumab) 100 mg or MK-3222 200 mg in Part 1 who were PASI-75 partial responders at Week 28



For exploratory endpoints:

- SF-36 scores improved relative to placebo in both active treatment groups.
- EQ-5D scores improved relative to placebo in both active treatment groups.

Clinical evaluator's comments

- Study 010 was designed to answer a number of questions and as a consequence was complicated, and difficult to interpret. However, the study used appropriate endpoints, the study populations are generalisable to the patients intended in the proposed indication and the range of doses studied is sufficient to demonstrate the appropriate dosing regimen.
- Tildrakizumab has superior efficacy to placebo in the treatment of moderate to severe chronic plaque psoriasis over a 12 week period. Efficacy was demonstrated for PASI-75 response, PASI-90 response and PASI-100 response.
- There was no apparent difference in efficacy between the 100 mg dose and the 200 mg dose in establishing response. There may be some benefit of the 200 mg dose over the 100 mg dose in maintaining response, but this was not demonstrated to be significant in Study 010. There appeared to be some additional benefit in PASI-100 with the 200 mg dose level up to Week 28.
- There was significant benefit demonstrated for dermatology specific patient reported outcomes (DLQI), and an indication of benefit for general patient reported outcome (SF-36, EQ-5D).
- Efficacy was not demonstrated for psoriatic arthritis, but the analysis was underpowered because it was only applied to a subset of patients.
- In patients who cease tildrakizumab and relapse, response is regained with both the 100 mg and 200 mg dose levels, with no apparent effects on response rates.
- There was no indication of rebound effects when treatment was ceased.
- Efficacy is maintained for up to 64 weeks with no loss of response rates.
- There were no subgroup effects on efficacy. Efficacy has been demonstrated in Caucasian and Asian patients in Study 010 but there were few Black patients, and efficacy has not been demonstrated in this population.
- In patients who are partial responders, there appears to be benefit in continuing treatment because in this group response rates increased up to Week 64.

Study P011

Study P011 was a Phase III, randomised, double blind, active-comparator and placebo controlled parallel group multicentre study of the efficacy and safety of tildrakizumab SC.

The inclusion and exclusion criteria were the same as for Study 010, with the additional exclusion of previous treatment with etanercept.

As per the schematic study design below, the study treatments also consisted of Three Parts:

Part 1 (Weeks 0 to 12)

- Arm A: tildrakizumab 200 mg SC at Weeks 0 and 4
- Arm B: tildrakizumab 100 mg SC at Weeks 0 and 4
- Arm C: Placebo SC at Weeks 0 and 4
- Arm D: etanercept 50 mg SC twice weekly

All patients received the alternative placebos (double dummy blinding) to take care of the varied dosing regimen.

Part 2 (Weeks 12 to 28)

- Treatments for Arms A, B and C were as for Study P010.

- Arm D patients continued on their Part 1 treatments.

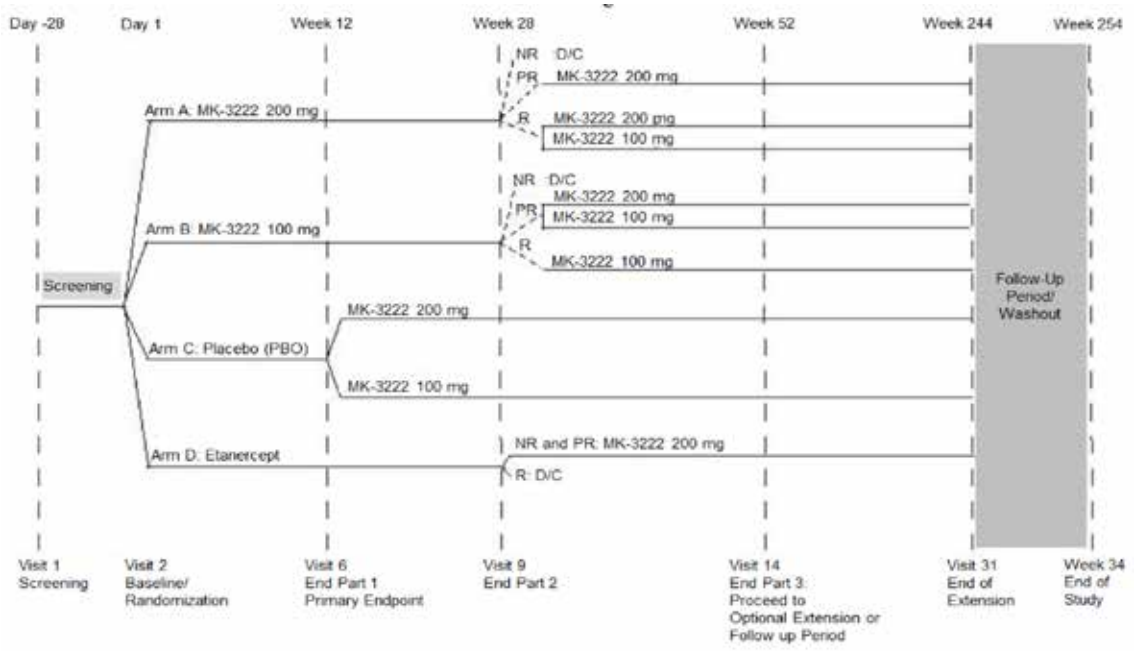
Part 3 (Weeks 28 to 52)

As in Study P010, assessment was done at the end of Week 28 with reallocation of patients in Arm C to either Arm A or Arm B depending on previous dose.

- Arm A: patients who achieved PASI-75 were re-randomised to either continue on 200 mg or reduce to 100 mg. Patients who achieved PASI-50 but not PASI 75 continued on 200 mg, and those that did not achieve PASI-50 were discontinued.
- Arm B: patients who achieved PASI-75 continued on 100 mg, patients who achieved PASI-50 but not PASI 75 were re-randomised to either continue on 100 mg or increase to 200 mg, and those that did not achieve PASI-50 were discontinued.
- Arm C: continued with their Part 2 treatment.
- Arm D: Patients who achieved PASI-75 on etanercept were discontinued, those who did not were commenced on tildrakizumab 200 mg at Week 32, Week 36 and Week 48.

The prohibited medications were the same as for Study 010 as shown below.

Figure 12: Study schema for Study PO11



SCREENING/ WASHOUT	BASE STUDY TREATMENT PERIOD			LONG-TERM SAFETY EXTENSION (OPTIONAL) 4 YEARS	FOLLOW-UP PERIOD 20 WEEKS
	PART 1 12 WEEKS	PART 2 16 WEEKS	PART 3 24 WEEKS		

Non-responders (NR) were subjects who achieved <50% improvement in PASI response from baseline.
At Week 28, non responders from Arms A and B were discontinued.
Partial responders (PR) were subjects who achieved ≥50% but <75% improvement in PASI response from baseline.
Responders (R) were subjects who achieved ≥75% improvement in PASI response from baseline.
D/C = discontinuation; PASI = Psoriasis Area and Severity Index.

Efficacy outcome variables:

For Part 1 treatment period, there were:

1. Two co-primary efficacy outcome measures:
    a. Proportion of subjects achieving PASI 75 response at Week 12.
    b. Proportion of subjects achieving a PGA score of 'clear' or 'minimal', with at least a 2 grade reduction from baseline, at Week 12.

2. Key secondary efficacy outcome measures were:
    a. Proportion of subjects achieving PASI 90 response at Week 12.
    b. Proportion of subjects achieving PASI 75 response at Week 28.
    c. Proportion of subjects achieving a PGA score of 'clear' or 'minimal', with at least a 2 grade reduction from baseline, at Week 28.
    d. Proportion of subjects with PASI 100 response at Week 12.
3. The other secondary efficacy outcome measures were:
    a. Proportion of subjects with PASI 90 response at Weeks 28, 40, and 52.
    b. Proportion of subjects with PASI 100 response at Weeks 28, 40, and 52.
    c. Proportion of subjects with PASI 75 response at Weeks 40 and 52.
    d. Proportion of subjects achieving a PGA score of 'clear' or 'minimal', with at least a 2 grade reduction from baseline, at Weeks 40 and 52
    e. Change from baseline in DLQI at Weeks 12, 28, 40, and 52.
    f. Proportion of subjects with DLQI score of 0 or 1 at Weeks 12, 28, 40, and 52.
    g. Proportion of subjects with PASI 75 response and proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 52, among partial responders who increased their dose of tildrakizumab (from 100 mg to 200 mg) at Week 28.
    h. Proportion of subjects with PASI 75 response and proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 52, among responders who decreased their dose of tildrakizumab (from 200 mg to 100 mg) at Week 28.
    i. Proportion of subjects with PASI 75 response and proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 52 among etanercept non-responders (subjects who achieve PASI response < 75% at Week 28) who crossed over to tildrakizumab.
    j. Change and percent change from baseline in PASI score over time.
4. The exploratory efficacy outcome measures were:
    a. Proportion of subjects with DLQI score < 5 at Weeks 12, 28, 40, and 52.
    b. Proportion of subjects with a reduction of 5 points or more in DLQI score from baseline at Weeks 12, 28, 40, and 52
    c. Correlation between PASI and PGA responses.

Note:

- Observations for population pharmacokinetic analyses and health economics analyses were collected for separate analysis.
- The safety endpoints were AEs, laboratory parameters and vital signs.

Analysis of populations

The FAS (efficacy) included all randomised patients who received at least one dose of Part 1, Part 2 or Part 3 study treatment, based on the treatment assigned. The ASaT population (safety) included all randomised patients who received at least one dose of study treatment, based on the treatment received.

Sample size

The sample size was 1050 patients, randomised in a 2:2:1:2 ratio for Part 1 A:B:C:D. Assuming a placebo rate of 10% for both PASI 75 response and PGA 'clear' or 'minimal' with at least a 2 grade reduction from baseline, the trial had more than 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response and to detect a 55% difference in PGA 'clear' or 'minimal' with at least a 2 grade reduction from baseline.

Statistical methods

Hypothesis tests were performed using the Cochran-Mantel-Haenszel test, stratified by body weight category (≤ 90 kg, > 90 kg) and prior exposure to biologic therapy for psoriasis. Subjects with missing data were treated as non-responders. Change from baseline in DLQI was tested using a constrained longitudinal data analysis (cLDA). Multiplicity was addressed by using a hierarchical approach to hypothesis testing.

Major protocol violations/deviations

The most common protocol deviations were regarding informed consent (29.9% of deviations), investigational product administration or study treatment (22.0%) and procedures or tests (19.4%).

Baseline data

There were 779 (71.5%) males, 311 (28.5%) females and the age range was 19 to 81 years. The treatment groups were similar in demographic characteristics). There were 97 (8.9%) patients aged ≥ 65 years. The treatment groups were similar in baseline efficacy outcome measures.

More patients in the etanercept group had a prior history of neoplasia: 24 (7.7%) compared with tildrakizumab 100 mg 15 (4.9%), 200 mg 12 (3.8%) and placebo 9 (5.8%).

Prior immunosuppressants had been used by 73 (23.8%) in the tildrakizumab 100 mg group, 60 (19.1%) in the 200 mg, 61 (19.5%) in the etanercept and 28 (17.9%) in the placebo. Prior adalimumab had been used by 13 (4.2%) in the tildrakizumab 100 mg group, 12 (3.8%) in the 200 mg, 16 (5.1%) in the etanercept and eight (5.1%) in the placebo.

The most common concomitant medications were ibuprofen 17%, paracetamol 10.8% and aspirin 10.4%. Mean (SD) compliance was 99.24 (3.096) % for tildrakizumab 100 mg and 99.51 (2.152) % for 200mg, 96.23 (6.401) for etanercept and 100.41 (11.536) for placebo.

Randomisation and blinding methods

Randomisation was performed using interactive voice response system (IVRS)/IWRS. As previously stated, randomisation was stratified by:

- Body weight ≤ 90 kg or > 90 kg
- Failure to respond to at least one traditional systemic medication
- Prior exposure to biologics therapy for psoriasis.

There were 1090 patients randomised to treatment: 307 to tildrakizumab 100 mg, 314 to 200 mg, 313 to etanercept and 156 to placebo. There were 756 patients who completed: 241 (78.5%) in the 100 mg group, 270 (86.0%) in the 200 mg, 114 (36.4%) in the etanercept and 131 (84.0%) in the placebo. The majority of the etanercept subjects were discontinued by the Sponsor at the end of Part 2.

Blinding was maintained by using double dummies for each corresponding dose.

Primary efficacy outcome as per the clinical evaluator

- Tildrakizumab 100 mg and 200 mg were both superior to placebo with similar efficacy.
- Tildrakizumab 200 mg was superior to etanercept, but although by PASI-75 tildrakizumab 100 mg was superior to etanercept there was no significant difference in PSA response.
- PASI-75 at Week 12 was attained by 188 (61.2%) patients in the tildrakizumab 100 mg group, 206 (65.6%) in the 200 mg group, 9 (5.8%) in the placebo and 151 (48.2%) in the etanercept. Treatment difference (95% CI) tildrakizumab – placebo was 55.5 (48.3 to 61.8) % $p < 0.001$ for 100 mg and 59.8 (52.9 to 65.9) % $p < 0.001$ for 200 mg. Treatment difference (95% CI) tildrakizumab – etanercept was 13.1 (5.3 to 20.7) % $p < 0.001$ for 100 mg and 17.4 (9.7 to 24.9) % $p < 0.001$ for 200 mg. The subgroup analysis indicated similar efficacy for subgroups, but in patients > 90 kg body weight, the 200 mg dose level appeared to have greater efficacy than the 100 mg.
- PGA response (score clear or minimal with a ≥ 2 grade reduction form baseline) at Week 12 was attained by 168 (54.7%) patients in the tildrakizumab 100 mg group, 186 (59.2%) in the 200 mg group, 7 (4.5%) in the placebo and 149 (47.6%) in the etanercept. Treatment difference (95% CI) tildrakizumab – placebo was 50.2 (43.2 to 56.5) % $p < 0.001$ for 100 mg and 54.7 (47.9 to 60.8) % $p < 0.001$ for 200 mg. Treatment difference (95% CI) tildrakizumab – etanercept was 7.3 (-0.5 to 15.0) % $p = 0.066$ for 100 mg and 11.7 (4.0 to 19.3) % $p = 0.003$ for 200 mg. There was similar efficacy for subgroups with no clinically significant differences between 100 mg and 200 mg.

Key secondary outcomes

- The number (proportion) of subjects achieving PASI-90 response at Week 12 was 119 (38.8%) patients in the tildrakizumab 100 mg group, 115 (36.6%) in the 200 mg group, 2 (1.3%) in the placebo and 67 (21.4%) in the etanercept. Treatment difference (95% CI) tildrakizumab – placebo was 37.5 (31.3 to 43.4) % $p < 0.001$ for 100 mg and 35.3 (29.2 to 41.1) % $p < 0.001$ for 200 mg. Treatment difference (95% CI) tildrakizumab – etanercept was 17.4 (10.3 to 24.4) % $p < 0.001$ for 100 mg and 15.2 (8.3 to 22.1) % $p < 0.001$ for 200 mg.
- The number (proportion) of subjects achieving PASI-75 response at Week 28 was 216 (73.5%) patients in the tildrakizumab 100 mg group, 217 (72.5%) in the 200 mg group and 155 (53.6%) in the etanercept. Treatment difference (95% CI) tildrakizumab – etanercept was 20.1 (12.4 to 27.6) % $p < 0.001$ for 100 mg and 19.0 (11.3 to 26.5) % $p < 0.001$ for 200 mg.
- Proportion of subjects achieving a PGA score of 'clear' or 'minimal', with at least a 2 grade reduction from baseline, at Week 28, was 190 (64.6%) patients in the tildrakizumab 100 mg group, 207 (69.2%) in the 200 mg group and 131 (45.3%) in the etanercept. Treatment difference (95% CI) tildrakizumab – etanercept was 19.6 (11.7 to 27.3) % $p < 0.001$ for 100 mg and 24.1 (16.2 to 31.7) % $p < 0.001$ for 200 mg.
- Proportion of subjects with PASI 100 response at Week 12 was 38 (12.4%) patients in the tildrakizumab 100 mg group, 37 (11.8%) in the 200 mg group, 0 (0%) in the placebo and 15 (4.8%) in the etanercept. Treatment difference (95% CI) tildrakizumab – placebo was 12.4 (8.5 to 16.6) % $p < 0.001$ for 100 mg and 11.7 (7.8 to 16.0) % $p < 0.001$ for 200 mg. Treatment difference (95% CI) tildrakizumab – etanercept was 7.6 (3.3 to 12.3) % $p < 0.001$ for 100 mg and 7.0 (2.8 to 11.6) % $p < 0.001$ for 200 mg.

Other secondary outcomes

- The proportion of subjects with PASI 90 response at Week 28 was 161 (55.5%) patients in the tildrakizumab 100 mg group, 169 (57.7%) in the 200 mg group and 85 (30.7%) in the etanercept. Treatment difference (95% CI) tildrakizumab – etanercept was 24.9 (17.0 to 32.6) % $p < 0.001$ for 100 mg and 27.1 (19.1 to 34.7) % $p < 0.001$ for 200 mg. PASI-90 response rates in the tildrakizumab groups were maintained to Week 52.
- The proportion of subjects with PASI 100 response at Week 28 was 66 (22.8%) patients in the tildrakizumab 100 mg group, 79 (27.0%) in the 200 mg group and 31 (11.2%) in the etanercept. Treatment difference (95% CI) tildrakizumab – etanercept was 11.7 (5.6 to 17.9) % $p < 0.001$ for 100 mg and 15.7 (9.4 to 22.1) % $p < 0.001$ for 200 mg. PASI-100 response rates in the tildrakizumab groups were maintained to Week 52.
- PASI-75 response rates in the tildrakizumab groups were maintained to Week 52.
- The proportion of subjects achieving a PGA score of 'clear' or 'minimal', with at least a 2 grade reduction from baseline, at Weeks 40 and 52 was maintained in the tildrakizumab groups.
- The mean (SD) change from baseline in DLQI at Week 12 was -10.6 (7.00) for tildrakizumab 100 mg, -9.7 (6.81) for 200 mg, -1.6 (5.97) for placebo and -9.1 (7.38) for etanercept. There were statistically significant improvements in the tildrakizumab groups relative to both placebo and etanercept. The mean (SD) change from baseline in DLQI at Week 28 was -11.7 (7.00), $p < 0.001$ compared to etanercept, for tildrakizumab 100 mg, -10.9 (6.81), $p < 0.001$ compared to etanercept, for 200 mg and -9.8 (7.30) for etanercept. The response for tildrakizumab was maintained to Weeks 40 and 52.
- The number (proportion) of subjects with DLQI score of 0 or 1 at Week 12 was 119 (40.2%) patients in the tildrakizumab 100 mg group, 145 (47.4%) in the 200 mg group, 12 (8.0%) in the placebo and 108 (35.5%) in the etanercept. Treatment difference (95% CI) tildrakizumab – placebo was 32.1 (24.5 to 39.1) % $p < 0.001$ for 100 mg and 39.3 (31.8 to 46.1) % $p < 0.001$ for 200 mg. Treatment difference (95% CI) tildrakizumab – etanercept was 4.8 (-2.9 to 12.5) % $p = 0.221$ for 100 mg and 11.9 (4.1 to 19.5) % $p < 0.001$ for 200 mg. The number (proportion) of subjects with DLQI score of 0 or 1 at Week 28 was 157 (54.1%) patients in the tildrakizumab 100 mg group, 193 (65.0%) in the 200 mg group and 111 (39.4%) in the etanercept. Treatment difference (95% CI) tildrakizumab – etanercept was 15.0 (6.9 to 22.9) % $p < 0.001$ for 100 mg and 25.7 (17.7 to 33.4) % $p < 0.001$ for 200 mg. The response rates for tildrakizumab were maintained to Weeks 40 and 52.
- The number (proportion) of subjects with PASI 75 response and proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 52, among partial responders who increased their dose of tildrakizumab (from 100 mg to 200 mg) at Week 28 was 11 (57.9%) in patients on 100 mg who remained on 100 mg, 8 (42.1%) in those who increased from 100 mg to 200 mg and 30 (50.8%) in those on 200 mg who remained on 200 mg.
- The number (proportion) of subjects with PASI 75 response at Week 52, among responders who decreased their dose of tildrakizumab (from 200 mg to 100 mg) at Week 28 was 98 (94.2%) compared with 191 (93.6%) of those who remained on 100 mg and 102 (97.1%) of those who remained on 200 mg.
- The number (proportion) of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 52, among responders who decreased their dose of tildrakizumab (from 200 mg to 100 mg) at Week 28 was 80 (77.7%)

compared with 162 (79.4%) of those who remained on 100 mg and 89 (84.8%) of those who remained on 200 mg.

- The number (proportion) of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 52 among etanercept non-responders (subjects who achieve PASI response < 75% at Week 28) who crossed over to tildrakizumab was 92 (81.4%).
- The number (proportion) of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from baseline at Week 52 among etanercept non-responders (subjects who achieve PASI response < 75% at Week 28) who crossed over to tildrakizumab was 76 (68.5%).
- Change and percent change from baseline in PASI score over time indicate preservation of effect in all the active treatment groups as per the figures below.

Figure 13: Change from Baseline in Psoriasis Area and Severity Index score over time; FAS,) Part 1 and Part 2

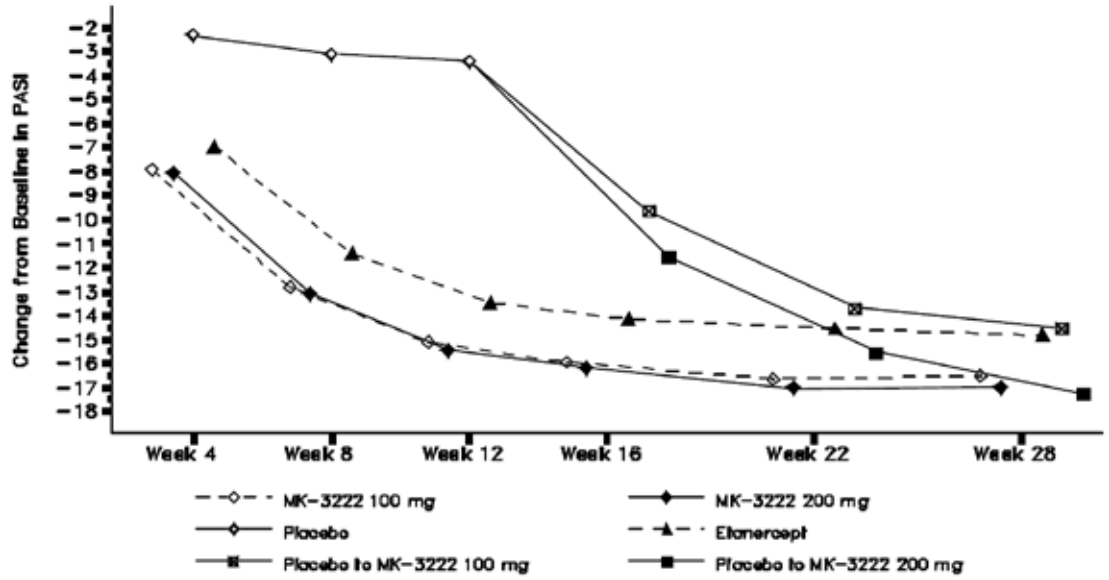
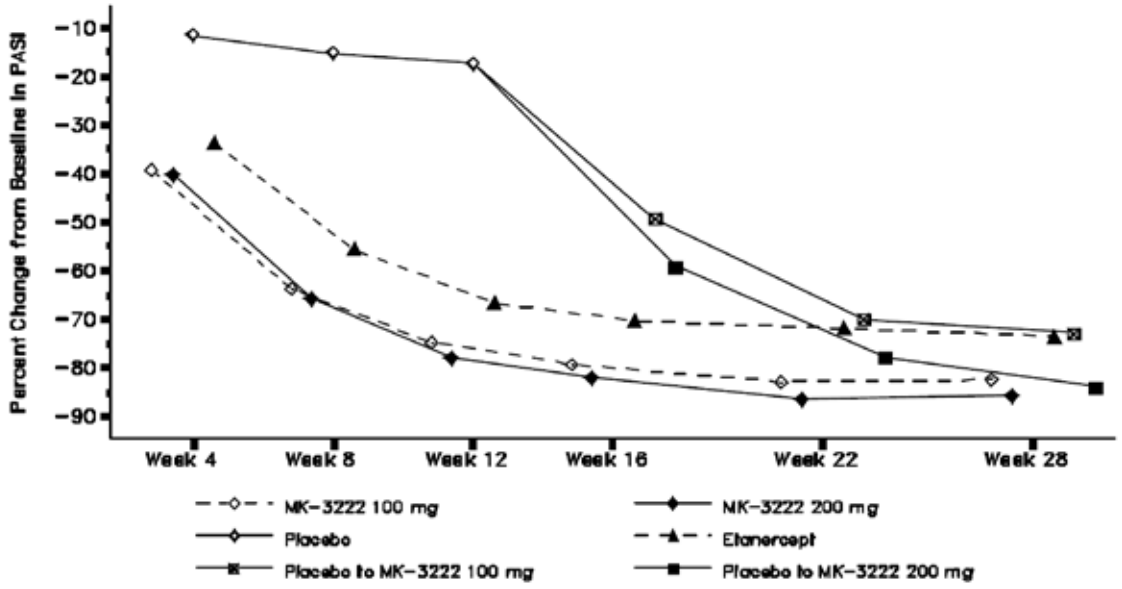


Figure 14: Percent change from baseline in psoriasis area and severity index score over time (full analysis set) Part 1 and Part 2



Exploratory efficacy outcomes

- The proportion of subjects with DLQI score < 5 at Week 12 was higher in the tildrakizumab than the placebo groups and this was maintained to Week 28. The proportion of patients with DLQI < 5 at Weeks 40 and 52 were preserved in the tildrakizumab groups.
- The proportion of subjects with a reduction of 5 points or more in DLQI score from baseline at Weeks 12 was higher in the tildrakizumab groups and was maintained through to Week 52.
- For the relationship between % change in PASI and change in PGA, in the tildrakizumab 100 mg, tildrakizumab 200 mg, placebo, and etanercept groups, the coefficient of correlation was 0.7141, 0.6641, 0.6052, and 0.6704, respectively.

Clinical evaluator's comment

- The study was appropriately designed to test for superiority in comparison with active comparator and placebo. The study conformed with the guideline.[18] The study population was well defined and consistent with the target population in Australia. The outcome measures, PASI and PGA, were appropriate. There were intra-individual and inter-individual comparisons. The sample size was appropriate and the statistical procedures were appropriate.
- The active comparator (etanercept) is approved in Australia for the following related indication: Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy. Hence, etanercept is an appropriate comparator. The recommended dose for plaque psoriasis in Australia is 50 mg once weekly; however, 50 mg twice weekly for the first 12 weeks may achieve higher responses. Hence the dosing regimen for the active comparator used in the study is consistent with use in Australia.
- Tildrakizumab was superior to both placebo and etanercept over a 12 week period. Tildrakizumab was superior to etanercept over a 28 week period. The treatment benefit from tildrakizumab was maintained for up to 52 weeks. Partial responders had improvement over the 52 week treatment period. Patients who did not respond to etanercept showed response when switched to tildrakizumab. There was no significant difference between the two dose levels of tildrakizumab, and there was no change in response when switched between dose levels.
- There was clinically and statistically significant benefit demonstrated for tildrakizumab for both clinical measures (PASI and PGA) and patient reported outcomes (DLQI).

Analyses performed across trials: pooled and meta analyses

- In the Integrated Analysis of Efficacy, there were 355 patients treated with placebo, 705 with tildrakizumab 100 mg, 708 with 200 mg and 313 with etanercept 50 mg.
- At Week 12, PASI-75 was recorded for 439 (62.3%) patients with tildrakizumab 100 mg, 459 (64.8%) with 200 mg, 20 (5.6%) with placebo and 151 (48.2%) with etanercept. The treatment difference (95% CI) tildrakizumab – placebo was 56.4 (51.8 to 60.7) % for 100 mg and 59.3 (54.8 to 63.4) % with 200 mg. The treatment difference (95% CI) tildrakizumab – etanercept was 13.1 (5.3 to 20.7) % for 100 mg and 17.4 (9.7 to 24.9) % with 200 mg.
- The proportion (%) of patients with PGA 'clear' or 'minimal' at Week 12 was 403 (57.2%) patients with tildrakizumab 100 mg, 425 (60.0%) with 200 mg, 20 (5.6%)

[18] CHMP/EWP/2454/02 corr. Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis.

with placebo and 149 (47.6%) with etanercept. The treatment difference (95% CI) tildrakizumab – placebo was 51.3 (46.7 to 55.7) % for 100 mg and 54.4 (49.8 to 58.6) % with 200 mg. The treatment difference (95% CI) tildrakizumab – etanercept was 7.3 (-0.5 to 15.0) % for 100 mg and 11.7 (4.0 to 19.3) % with 200 mg.

- At Week 12, PASI-90 was recorded for 253 (35.9%) patients with tildrakizumab 100 mg, 262 (37.0%) with 200 mg, seven (2.0%) with placebo and 67 (21.4%) with etanercept. The treatment difference (95% CI) tildrakizumab – placebo was 33.8 (29.7 to 37.8) % for 100 mg and 35.0 (30.9 to 38.9) % with 200 mg. The treatment difference (95% CI) tildrakizumab – etanercept was 17.4 (10.3 to 24.4) % for 100 mg and 15.2 (8.3 to 22.1) % with 200 mg.
- At Week 12, PASI-100 was recorded for 93 (13.2%) patients with tildrakizumab 100 mg, 91 (12.9%) with 200 mg, two (0.6%) with placebo and 15 (4.8%) with etanercept. The treatment difference (95% CI) tildrakizumab – placebo was 12.6 (9.8 to 15.4) % for 100 mg and 12.2 (9.6 to 15.4) % with 200 mg. The treatment difference (95% CI) tildrakizumab – etanercept was 7.6 (3.3 to 12.3) % for 100 mg and 7.0 (2.8 to 11.6) % with 200 mg.
- There were no subgroup effects on efficacy.

Clinical evaluator's conclusions on clinical efficacy

- The two Phase III efficacy and safety studies were designed and conducted in accordance with the Guideline.[18] The study populations were similar to the intended target population in Australia. The outcome measures were appropriate. The comparators were appropriate, and were used at effective doses.
- Both Study 010 and Study 011 were designed to answer a number of questions and as a consequence were complicated, and difficult to interpret. However, because of the study designs the results also answer a number of clinically relevant questions.
- Tildrakizumab has superior efficacy to placebo in the treatment of moderate to severe chronic plaque psoriasis over a 12 week period. Efficacy was demonstrated for PASI-75 response, PGA, PASI-90 response and PASI-100 response. There was clinically and statistically significant benefit demonstrated for tildrakizumab for both clinical measures (PASI and PGA) and patient reported outcomes (DLQI).
- Tildrakizumab was superior to etanercept over a 28 week period. This was demonstrated for PASI-75 for both tildrakizumab doses, but only for the 200 mg dose level for PGA response.
- The treatment benefit was maintained for up to 64 weeks of continuous treatment with no loss of response rates.
- There was no apparent difference in efficacy between the 100 mg dose and the 200 mg dose in establishing response. There may be some benefit of the 200 mg dose over the 100 mg dose in maintaining response, but this was not demonstrated to be significant in Study 010. There appeared to be some additional benefit in PASI-100 with the 200 mg dose level up to Week 28.
- There was significant benefit demonstrated for dermatology specific patient reported outcomes (DLQI), and an indication of benefit for general patient reported outcome (SF-36, EQ-5D).
- In patients who cease tildrakizumab and relapse, response is regained with both the 100 mg and 200 mg dose levels, with no apparent effects on response rates.
- There was no indication of rebound effects when treatment was ceased.

- There were no subgroup effects on efficacy. Efficacy has been demonstrated in Caucasian and Asian patients in Study 010 but there were few Black patients, and efficacy has not been demonstrated in this population.
- In patients who are partial responders, there appears to be benefit in continuing treatment because in this group response rates increased up to Week 64.
- Patients who did not respond to etanercept showed response when switched to tildrakizumab.
- There was no significant improvement in response when the dose was increased from 100 mg to 200 mg in patients previously treated with 100 mg.
- Efficacy was not demonstrated for psoriatic arthritis, but the analysis was underpowered because it was only applied to a subset of patients.

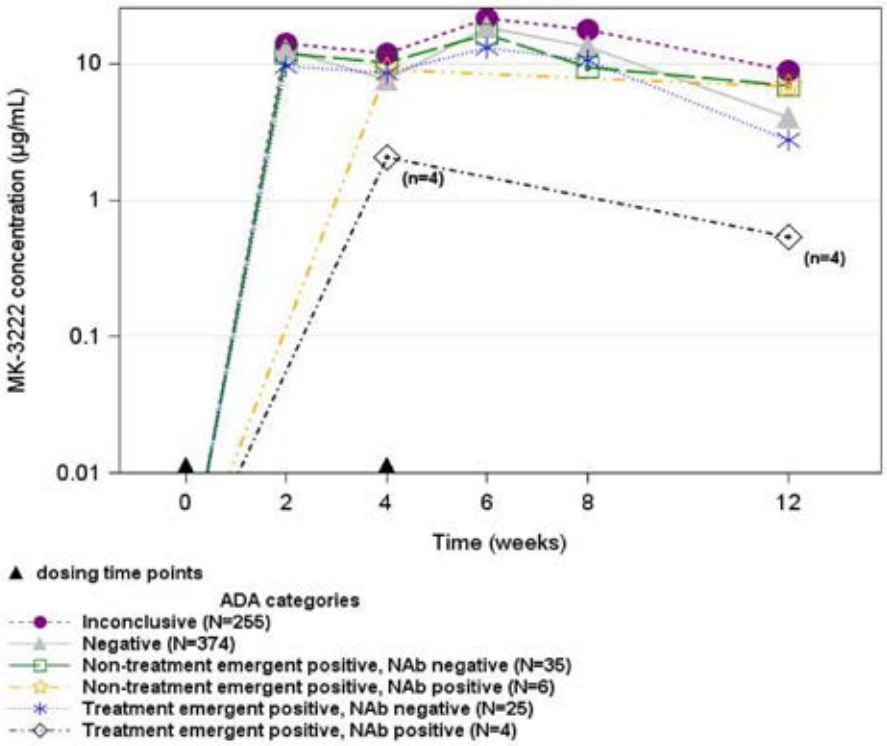
Safety

Regarding the overall conclusions on clinical safety, the CE stated that:

- Tildrakizumab (Ilumya) appears to have a favourable safety profile. There is no apparent difference in the safety profile of the 200 mg dose level compared to the 100 mg.
- The overall rate of TEAEs is similar with either tildrakizumab 100 mg or 200 mg compared to either placebo or etanercept. In the placebo controlled safety pool (to Week 12), TEAEs were reported in 48.2% patients with tildrakizumab 100 mg, 47.9% with 200 mg, 54.0% with etanercept and 53.8% with placebo.
- There were few deaths in the development program, and when adjusted for duration of exposure to treatment there does not appear to be an excess in the tildrakizumab groups. The following deaths were reported:
  - In Study 010) there was one death in the tildrakizumab 200 mg group (aneurysm – femoral and aortic).
  - In Study 011) there were four deaths (0.9 /100 patient years) in the tildrakizumab 100 mg group (steatohepatitis/alcoholic cardiomyopathy, acute myeloid leukaemia, respiratory arrest, myocardial infarction) and one (0.2 /100 patient years) in the 200 mg after being randomised from etanercept (sepsis).
  - In Study P05495/P003), in Part 1, there was one death in the 100 mg group (unknown cause).
- SAEs were reported at similar rates for tildrakizumab, placebo and etanercept. In the placebo controlled safety pool (to Week 12) SAEs were reported in ten (1.4%) patients with tildrakizumab 100 mg, 16 (2.3%) with 200 mg, seven (1.1%) with etanercept and six (1.7%) with placebo. In Study 010, SAEs were reported in 20 patients (5.1 /100 patient years) during tildrakizumab 100 mg, 35 patients (8.4 /100 patient years) with 200 mg and nine (5.3 /100 patient years) with placebo. In Study 011, SAEs were reported in 30 patients (6.6 /100 patient years) in the tildrakizumab 100 mg group, 26 (6.2 /100 patient years) in the 200 mg, four (11.5 /100 patient years) in the placebo and 20 (13.0 /100 patient years) in the etanercept.
- Discontinuation due to AE occurred at a similar rate with tildrakizumab, placebo and etanercept. In the placebo controlled safety pool (to Week 12) DAE were reported for four (0.6%) patients with tildrakizumab 100 mg, nine (1.3%) with 200 mg, six (1.9%) with etanercept and four (1.1%) with placebo.
- There were no safety issues identified with regard to DILI or renal injury. There were no safety issues identified with regards to haematology.

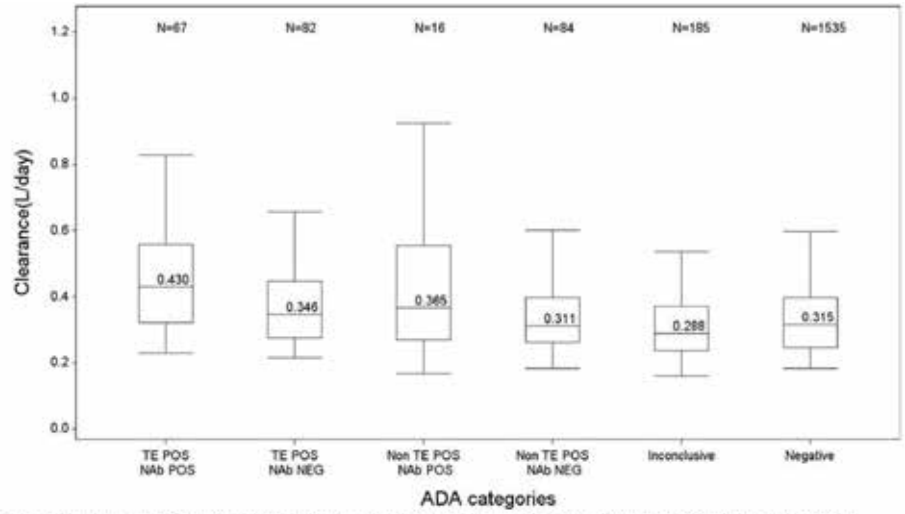
- The rates of minor and/or serious infections were not increased with tildrakizumab relative to placebo.
- The dossier complies with the Note for guidance on population exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95). A total of 1994 volunteers and patients have been exposed to tildrakizumab, with 1391 exposed for ≥ 52 weeks. There were 1041 patients exposed to the proposed 200 mg dose level.
- The dossier complies with the Committee for Medicinal Products for Human Use (CHMP) Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. EMA/CHMP/BMWP/86289/2010 (24 May 2012):
  - The immunogenicity report states an overall rate of treatment emergent ANA of 7.6% and of neutralising antibodies of 3.4% in the Phase IIa and III studies.
  - In patients with treatment emergent neutralising antibodies, there was a decrease in mean tildrakizumab concentrations as per the figure below.

Figure 15: Mean tildrakizumab concentration-time profiles of subjects treated with 200 mg tildrakizumab by ADA subject category through Week 12 in Phase IIb and Phase III



  - CL of tildrakizumab was increased in the presence of treatment emergent neutralising antibodies, but not by the presence of ANA alone as per the box plot below.

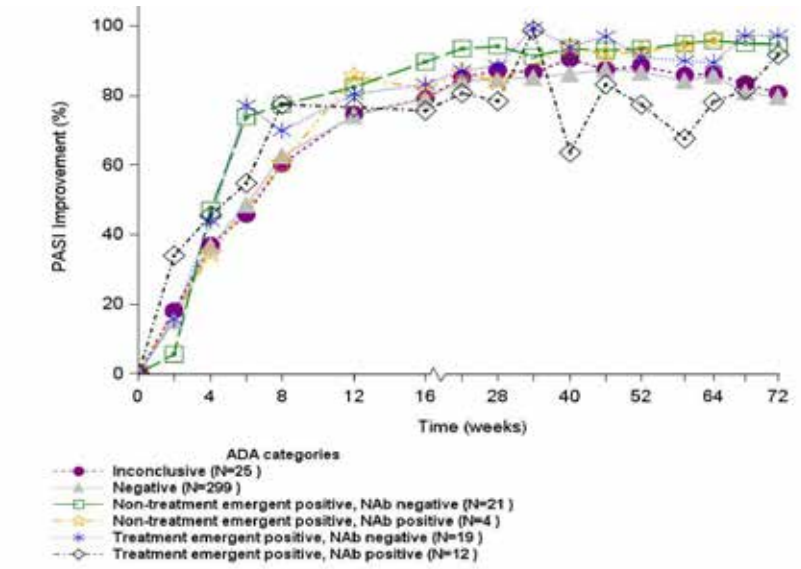
Figure 16: Distribution of clearance for all evaluable subjects by ADA subject category through the end of the trial in Phase IIb and Phase III



The boxes represent 25th to 75th percentiles, the line in the box is the median and whiskers are 5th and 95th percentiles.
TE-POS = treatment emergent positive
NAb NEG = neutralizing antibodies negative
NAb POS = neutralizing antibodies positive

– Efficacy was reduced in patients who were treatment emergent neutralising antibody positive, but not to the extent where it would restrict the use of tildrakizumab in this group as per the figure below.

Figure 17: Effect of ADA on percent PASI improvement in subjects on 200 mg tildrakizumab for the full duration of the trials by ADA subject category in Phase IIb and Phase III



ADA = anti-drug antibody; NAb = neutralizing antibodies; PASI = psoriasis area and severity index
One Non-TE-POS subject in P05495,did not have a NAb result and hence is not in the figure.
Data source: [04FCNM: analysis-ada], script:an0ada.sas

- There did not appear to be any effect of ADA or neutralising antibodies on immunological AEs or AEs overall.
- However, there does appear to be an excess of malignancies reported with tildrakizumab. In the Integrated Analysis of Safety, the sponsor reported malignancy in two (0.3%) patients with tildrakizumab 100 mg, one (0.1%) with 200 mg, three (0.2%) with 100/200 mg, none with placebo and one (0.3%) with etanercept. The following malignancies were reported in the individual studies:

  - In Study 010 malignancies were reported in five patients (1.3 /100 patient years) during tildrakizumab 100 mg, six patients (1.4 /100 patient years) with 200 mg and two patients (1.2 /100 patient years) with placebo.
  - In Study 011) malignancies were reported in eight patients (1.8 /100 patient years) in the tildrakizumab 100 mg group, four (1.0 /100 patient years) in the 200 mg and four (2.6 /100 patient years) in the etanercept and none in the placebo).
  - In Study P05495/P003), there were three malignancies reported as SAEs: malignant melanoma in the 25 mg group; malignant melanoma in situ and rectal cancer in the 100 mg group.
- In the opinion of the evaluator, there are insufficient data to conclude that tildrakizumab is associated with malignancy because of the much longer duration of treatment exposure relative to placebo in the clinical trials. The sponsor has included malignancy in the safety specification as an 'Important Potential Risk'.

Risk management plan

For evaluation of the RMP please see *Section VI*.

Comments on the draft RMP (Summary of Safety Concerns) as detailed by the clinical evaluator

In the RMP, the sponsor does not adequately describe the measures that will be taken to monitor the long-term risks of malignancy. The sponsor proposes to use routine pharmacovigilance which relies on spontaneous reporting. Spontaneous reporting would identify at best only 10% of relevant cases, which in the opinion of the clinical evaluator is inadequate. The sponsor also proposes establishing a registry of patients that have used tildrakizumab, but does not describe how patients who subsequently develop malignancy will be identified. Clarification was sought from the sponsor. The sponsor's response has provided adequate clarification and the proposed monitoring for this safety concern is considered adequate from an RMP perspective. The results of this study and any safety concerns identified in the study should be reported to the TGA in an RMP update.

Risk-benefit analysis

Delegate's considerations

It is noted that none of the evaluators raised objection to the approval of tildrakizumab (Ilumya), a new biological entity, in this submission for the proposed indication of:

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

However, the clinical evaluator has flagged concern about tildrakizumab's potential to cause malignancies (Studies 010, 011, and P0595/P003). The latter had been echoed by the RMP evaluator. In that regard, the clinical evaluator stated that the '*potential for increased malignancy with tildrakizumab will require prospective monitoring and that the decision, to authorise Ilumya (tildrakizumab) should take into consideration the measures the sponsor proposes (see sponsor's RMP response below) to monitor the long-term risk of malignancy with tildrakizumab (Ilumya)*'. In the same vein, the RMP evaluator recommended that:

- The Delegate should consider including a precautionary statement on the potential risk of malignancies in the PI and CMI (similar to some other biological immunosuppressive agents) and
- As Ilumya is a new biological entity, it should be included in the Black Triangle Scheme as a condition of registration. The latter is acceptable to the sponsor.

In terms of benefits, the clinical evaluator stated that there:

- 'was no apparent difference in efficacy between the 100 mg dose and the 200 mg dose in establishing response. There was no significant improvement in response when the dose was increased from 100 mg to 200 mg in patients previously treated with 100 mg
- may be some benefit of the 200 mg dose over the 100 mg dose in maintaining response, but this was not demonstrated to be significant in Study 010 (a pivotal study)
- appeared to be some additional benefit in PASI-100 with the 200 mg dose level up to Week 28
- are no apparent effects on response rates in patients who cease tildrakizumab and relapse with respect to recommencing Tildrakizumab. Response is equally regained at either the 100 mg or 200 mg dose level'.

Although the evaluated safety profiles of tildrakizumab 100 mg and 200 mg were similar, the above will lean towards initiating dose at 100 mg as per contemporary clinical practice, instead of the 200 mg currently stated in the draft PI. The latter is also on a background of potential for increased malignancy with tildrakizumab.

The sponsor needs to comply with recommendations made to the draft PI by the evaluator and fulfil the assurance given to update the ASA (RMP), once the approved versions of the PI and SmPC are available and acceptable.

Summary of issues

The Delegate draws the attention of the committee members to tildrakizumab's potential to cause malignancies and the sponsor's proposed 200 mg dosage regimenbased on the available evidence from the evaluated data, the Delegate was inclined at this stage to favour the approval of the application, subject to taking into account all issues arising from the ACM deliberations and finalising matters pertaining to the draft PI to the satisfaction of the TGA.

Request for ACM advice

Specific advice is sought on:

1. Approvability of the proposed indication.
2. Appropriateness or otherwise of the inclusion of malignancy in both the 'Precaution' and 'Adverse events' sections of the PI for tildrakizumab.
3. Recommendation for tildrakizumab dosage at 100 mg at Weeks 0, 4 and every 12 weeks thereafter.
4. Reinforcement for clarity of the Immunogenicity section of the PI for tildrakizumab.

Response from sponsor

The sponsor concurs with the Delegate's inclination to approve tildrakizumab for the treatment of psoriasis but disagrees with the Delegates comments that the proposed dose should be 100 mg. In alignment with the clinical evaluator and the RMP

evaluator the sponsor considers that the risk benefit profile of the 200 mg presentation is in fact superior to that of the 100 mg and is therefore the most appropriate posology.

Delegates summary of issues

The sponsor notes the Delegate's pre-ACM request for advice is seeking the Committee's input on the following issues:

- tildrakizumab's potential to cause malignancies; and
- the sponsor's proposed 200 mg dosage regimen [section redacted].

Provided below are the sponsor's comments on these 2 key issues.

Tildrakizumab's potential to cause malignancies

A low incidence of malignancy (including non-melanoma and melanoma skin cancer) was reported in general throughout the safety data pools. Although reported numerically less in the placebo-treated arms, it is important to note that there were twice as many subjects randomized to the treatment arms versus placebo in the 12 week placebo- controlled period. As patients in this initial 12 week period had only received two doses of study drug, it is also considered unlikely that the small absolute number of cases could be attributable to study drug. When these points are combined with the significantly shorter duration of treatment in the placebo-controlled component of the study designs, as concluded by the clinical evaluator, this finding should not be interpreted as an increased malignancy risk. Provided below as a table is a summary of the malignancy reports for the placebo-controlled periods, the active control periods, and the long-term open label extension (OLE) to the Phase III studies, including data from the most recent cut-off period for the open-label extensions.

The summary of the malignancy reports for the placebo-controlled periods, the active control periods, and the long-term open label extension (OLE) to the Phase III studies, including data from the most recent cut-off period for the open-label extensions is shown in the table below.

Table 11: Reports of malignancy; total data set

	Placebo-controlled Period[‡], n (%[*])				Controlled-Trial Period Based on 20 week follow-up[‡] n, (Exposure-Adjusted Rate[†])				5 Years Cumulative[§] Base and Extension Study n, (Exposure-adjusted rate[†])	
	TIL 200 mg (n=708)	TIL 100 mg (n=705)	Placebo (n=355)	ETN 50 mg (n=313)	TIL 200 mg (n=1041)	TIL 100 mg (n=1083)	Placebo (n=588)	ETN 50 mg (n=313)	TIL 200 mg (n=721)	TIL 100 mg (n=654)
Malignancies[^]	1 (0.1) [¥]	2 (0.3) [¥]	0	1 (0.3)	11 (1.2)	17 (1.7)	2 (0.9)	4 (2.6)	15 (0.7)	16 (0.8)
Non-melanoma skin cancer	1 (0.1) [¥]	2 (0.3) [¥]	0	1 (0.3)	8 (0.9)	11 (1.1)	2 (0.9)	2 (1.3)	8 (0.4)	6 (0.3)
Melanoma skin cancer	0[¥]	0[¥]	0	0	0	2 (0.2)	0	0	1 (<0.1)	1 (0.1)

[‡] Includes data from one Phase 2b and two Phase 3 studies.
[*] Patients/number of patients exposed.
[†] Patients/100 patient years of exposure
[¥] Difference from placebo not statistically significant based on the Miettinen & Nurminen method.
[^] Excluding carcinoma in situ of the cervix.
[§] Includes data from ongoing extensions up to cut-off date 19-Aug-2017 for study P010 and 27-May-2017 for study P011. Only includes subjects who took at least one dose of extension study medication based on the treatment actually received.
TIL: tildrakizumab; ENT: etanercept

As indicated in the table, the initial numerical differences identified in the placebo-controlled period were not encountered in the full controlled trial periods and this finding is also reflected in the safety information collected in the open-label extension data. It should also be noted that the incidence rate reported in the open-label extension patient population in the table excludes exposure from patients who participated in the controlled phases of the studies but did not continue into the extension period. Consequently, the incidence rate presented may in fact be an over-estimate of the actual malignancy rate.

Patients with psoriasis may also have an increased risk of some types of malignancies, possibly due to the underlying disease pathology, compared to the general population. In a retrospective cohort study utilising data from USA health insurance claims databases from 1 January 1995 to 31 December 2011, Kimball et al.;19 found that psoriasis patients appeared to have an increased risk of some solid cancers (respiratory tract cancer, upper aerodigestive tract cancer, urinary tract cancer, liver cancer), haematological cancers (non-Hodgkin lymphoma) and skin cancers (squamous cell carcinoma, basal cell carcinoma). Furthermore, some non-biological treatments for psoriasis also appear to increase the risk of malignancy, including phytochemotherapy (psoralens + UVA light treatment (PUVA), ciclosporin and possibly methotrexate. The table below lists the incidence rates for malignancy in the psoriasis population reported in the Kimball et al., analysis against the incidence rates calculated from the latest long term data from the open label extension studies. As can be seen from the table, the incidence of malignancy reported following up to 5 years cumulative exposure to tildrakizumab appears to be lower than would be expected in this historical patient population, providing further reassurance regarding the long-term malignancy risk.

Table 12: Incidence rate of malignancies

	Psoriasis*	Tildrakizumab 200 mg†	Tildrakizumab 100 mg†	Tildrakizumab† (Total across studies & dose groups)
Total Malignancies	(not reported)	73.5^	80.5^	77.0^
Malignancies (excluding NMSC)	142	34.3	50.3	42.2
Non-melanoma skin cancer (NMSC)	180	39.2	30.2	34.8

* Kimball 2015, incidence rate per 10,000 patient years observations
† incidence rate per 10,000 patient years exposure. Includes subjects who took at least one dose of extension study medication based on the treatment actually received.
^ Excluding carcinoma in situ of the cervix.

The totality of safety data collected to-date does not suggest that exposure to tildrakizumab represents an increased risk of malignancy in this patient population and this finding is not unexpected given the mechanism of action of tildrakizumab. Tildrakizumab specifically binds only to the p19 protein subunit of the interleukin 23 (IL-23) cytokine. Therapies which target IL-12/23p40 (such as ustekizumab), have demonstrated efficacy in patients with chronic plaque psoriasis however current data suggest that this efficacy is driven by the ability to neutralize IL-23 rather than IL-12. While IL-12 promotes interferon γ (IFNγ)-producing T helper 1 (Th1) cells, which are known to enhance antimicrobial and cytotoxic responses, IL-23 promotes the pro-inflammatory Th17 cells that produce IL-17. In addition, IL-23 has been found to be up-regulated in many human carcinomas from various organs but not in the surrounding normal tissue, while the expression of IL-12 was similar in both tumours and adjacent normal tissues. By selectively blocking IL-23, tildrakizumab has the potential for a more favorable safety profile as it does not prevent the anti-tumour activity of IL-12 but does prevent the tumorigenic response of IL-23.[20,21.] This effect was demonstrated in nonclinical investigations submitted with the application. Study SN 08221 using tildrakizumab in mice and genetically engineered IL-23 null mice reported that treatment with a therapeutic agent specifically inhibiting IL 23p19 is not associated with increased

[19] Kimball, A. B., et al. 'Cohort study of malignancies and hospitalized infectious events in treated and untreated patients with psoriasis and a general population in the United States.' *British Journal of Dermatology* 2015; 173.5: 1183-1190.
[20] Tausend, W et al. 'Systematic review of interleukin-12, interleukin-17, and interleukin-23 pathway inhibitors for the treatment of moderate-to-severe chronic plaque psoriasis: ustekinumab, briakinumab, tildrakizumab, guselkumab, secukinumab, ixekizumab, and brodalumab.' *Journal of cutaneous medicine and surgery* 2014; 18.3: 156-169.
[21] Koutruba, N et al. 'Review of ustekinumab, an interleukin-12 and interleukin- 23 inhibitor used for the treatment of plaque psoriasis.' *Therapeutics and clinical risk management* 2010; 6: 123.

cancer risk. In contrast, a majority of tumour models demonstrated that dual IL-12 and IL-23 blockade with an anti-IL-12/23 ablating therapy resulted in impaired tumour surveillance and increased tumour burden. Furthermore, histopathological analysis of tissues from the submitted 3 and 9 month repeat dose toxicity studies did not indicate any evidence for pre-neoplastic changes. Taken together the weight of evidence supports the position that mechanistically tildrakizumab is unlikely to be associated with an increased carcinogenic risk.

TNF-α inhibitors have been associated with a malignancy risk;[22,23] driven by the role this cytokine plays in immunologic surveillance and angiogenesis and the impact of its blockade. Evaluation of patients with psoriasis in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) by Fiorentino et al., found that long term (≥ 12 months) treatment with TNF-α inhibitors yielded a statistically significant higher risk for malignancy development. Further, analysis conducted by Quarterwatch found that ustekinumab, also has an association with reported cancers. As there is a relatively clear signal of an increased incidence of malignancy with combined IL-12/23 inhibitors and TNF-α inhibitors, one that can be explained by their mechanisms of action, statements to this effect have been included in the TGA-approved PI documents for these products. However, an increased risk of malignancy has not been reported with selective inhibitors of other cytokines used for the treatment of psoriasis where a tumorigenic mechanism of action has not been identified, including the recently approved selective IL-23 antibody Tremfya (guselkumab) and the IL-17 antibody, Cosentyx (secukinumab).

The sponsor the Delegate's suggestion that the Product Information document should be aligned to that of other biological therapies however the most appropriate documents to compare with are those with the same or similar cytokine selectivity. Therefore, instead of making reference to the warnings contained in the PI documents for ustekizumab and etanercept (IL-12/23 and TNFα antibodies), alignment with the PI for guselkumab (as a specific inhibitor of IL-23) or secukinumab (as a specific inhibitor of IL-17) are considered to be more appropriate. As the clinical trial data with tildrakizumab do not identify an increased risk of malignancy, similar to the PI documents for guselkumab and secukinumab, inclusion of specific precautions and statements in the adverse events sections are not currently warranted.

Although the data collected to-date are reassuring, the potential for an increased risk of malignancy associated with tildrakizumab treatment will be further investigated through activities outlined in the submitted Risk Management Plan (RMP). As an increased rate of malignancy, should one exist, is most likely to be detected following longer-term use, SUN proposes to continue to monitor the potential risk of malignancies via two ongoing open-label extension Phase III studies (Studies PN10 and PN11) which will provide data from patients experiencing up to 5 years of additional open-label treatment; and, in addition, a prospective observational registry study, which will collect data for up to 8 years. Malignancy data will be collected as a part of the history of comorbidities at enrolment and subsequently as an adverse event. Patients with a malignancy will have a detailed data collection guided by a targeted event questionnaire specific to malignancy and appropriate for all types of haematologic, solid and cutaneous cancers. Additionally, information on malignancies will be collected in targeted follow-up questionnaires as part of the routine pharmacovigilance in Australia. These commitments were considered by both the clinical and RMP evaluators to be of sufficient duration, and sufficient sample size, to capture a clinically significant increase in malignancy risk should one exist.

[22] Fiorentino, D, et al. 'Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry.' *Journal of the American Academy of Dermatology* 2017; 77.5: 845-854.
[23] ISMP QuarterWatch, April 2, 2016 – Data from 2015 Quarter 3. Available from: https://www.ismp.org/sites/default/files/attachments/2018-01/2015Q3R1.pdf, last accessed 11-Jul-2018

In summary, the available evidence collected with tildrakizumab does not suggest an increased malignancy risk, which is as expected based on knowledge of the mechanism of action. Consequently, and similar to the PI documents for the other approved IL-23 antibody, inclusion of warning statements in the PI in this regard are not considered appropriate. Robust post-market plans for assessing the malignancy risk have been established and the results of these investigations will be provided to the TGA when available.

Sponsor's proposed 200 mg dose[24]

[Information redacted]

In their pre-ACM response the sponsor included and updated version of the PI and CMI in accordance with the recommendations proposed by the Delegate.

Advisory committee considerations[25]

The Advisory Committee on Medicines (ACM) taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Ilumya (injection) pre-filled syringe containing 100 mg in 1 mL of tildrakizumab to have an overall positive benefit-risk profile for the amended indication:

> *Ilumya is indicated for the treatment of adults patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.*

In providing this advice the ACM noted the following:

- Two Phase III studies were provided in support of efficacy of tildrakizumab: Study 010 (reSURFACE1 trial) was a placebo controlled study, with two dose levels for tildrakizumab (200 mg and 100 mg); and Study 011 (reSURFACE2 trial) was a placebo and comparator (etanercept) controlled study, with two dose levels for tildrakizumab (200 mg and 100 mg). The primary outcome measures in both trials were:
  - the proportion of subjects with PASI 75 response at Week 12; and
  - the proportion of subjects with PGA score of 'clear' or 'minimal' with at least a 2 grade reduction from Baseline at Week 12.
- Superior efficacy of tildrakizumab over placebo (in Study 010 and 011) for the co-primary outcomes was significantly demonstrated.
- Superior efficacy of tildrakizumab over etanercept (in Study 011) for PASI 75 response at Week 12 was significantly demonstrated.
- Efficacy was similar between the 100 mg and 200 mg tildrakizumab dose groups. A significant and clinically meaningful benefit was not demonstrated for the 200 mg dose over the 100 mg dose of tildrakizumab, in either establishing response or maintaining response.

[24] The sponsor withdrew the 200 mg dose after the ACM.

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

- FDA approval for tildrakizumab in moderate to severe plaque psoriasis is for a recommended dose of 100 mg.

Proposed conditions of registration

The ACM agreed with the delegate on the proposed conditions of registration.

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

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

- As patients recently vaccinated with a live vaccine were excluded in the clinical trials, the ACM suggested giving consideration to listing recent live vaccination as a contraindication rather than a precaution. Further, the ACM advised that the definition of a live vaccine with examples be included in the CMI.
- Statements in the 'Precautions' and 'Adverse Effects' sections of the PI on the potential risk of malignancies. The CMI should also have statements reflecting the potential risk of malignancies.

Specific advice

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

1. Approvability of the proposed indication

The ACM advised that for consistency with the indication wording for similar agents, such as guselkumab and ustekinumab, the indication for tildrakizumab should read:

> *'Ilumya is indicated for the treatment of adults, patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.'*

The ACM considered that tildrakizumab was approvable based on demonstrated efficacy and a favourable benefit-risk profile.

2. Appropriateness or otherwise of the inclusion of malignancy in both the Precaution and Adverse sections of the PI for tildrakizumab

The ACM were in favour of including statements in the 'Precautions' and 'Adverse Effects' sections of the PI and CMI on the potential risk of malignancies.

3. Recommendation for tildrakizumab dosage at 100 mg at Weeks 0, 4 and every 12 weeks thereafter

The ACM noted that there was no significant or clinically meaningful benefit shown for the 200 mg dose over the 100 mg dose of tildrakizumab in the course of the pivotal trials. The safety profile appeared similar in both dose groups. It was noted that tildrakizumab 100 mg did not demonstrate a significant difference in PGA response at Week 12 over etanercept (whereas tildrakizumab 200 mg did). However, the ACM did not consider this to be clinically significant, noting that tildrakizumab 100 mg was similar to tildrakizumab 200 mg in PASI 75 response at Week 12.

The ACM therefore, were of the view that 100 mg should be the recommended tildrakizumab dose for registration.

4. Reinforcement for clarity of the Immunogenicity section of the PI for tildrakizumab

The ACM considered that the inclusion of the wording for the 'Immunogenicity' section of the PI as proposed in the pre-ACM response was mostly appropriate, with corrections as per the following:

> *'In the Phase 2 and Phase 3 psoriasis clinical studies 7.6% of Ilumya-treated patients developed antibodies to Ilumya. In the subset of these patients with treatment emergent neutralising antibodies, a small decrease in serum tildrakizumab concentrations and a corresponding increase in clearance were observed. Those patients who developed neutralising antibodies reported minor decreases in some efficacy parameters. No apparent association between the development of antibodies to Ilumya and the development of treatment emergent adverse events was seen.'*

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

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Ilumya (injection) pre-filled syringe containing 100 mg in 1 mL of tildrakizumab, indicated for:

> *Ilumya is indicated for the treatment of adults patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.*

Specific conditions of registration applying to these goods

- Ilumya (tildrakizumab) is to be included in the Black Triangle Scheme. The PI and CMI for Ilumya must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Ilumya EU-Risk Management Plan (RMP) (version 0.1, dated 28 February 2017, data lock point 16 April 2017), with Australian Specific Annex (version 0.2, dated 5 February 2018), included with submission PM-2017-02274-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.
- All batches of Ilumya tildrakizumab solution for injection 100 mg/1 mL pre-filled syringe imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).[26]

Attachment 1. Product Information

The PI for Ilumya 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>.

[26] This condition of registration was included following notification post approval

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au