Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for EPYZTEK

Active ingredient: Ustekinumab

Sponsor: Samsung Bioepis AU Pty Ltd

March 2026

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- 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.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The 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. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ADA	Anti-drug antibody
ARTG	Australian Register of Therapeutic Goods
AU	Australian
$AUC_{0\text{-}inf}$	Area under the concentration time curve from 0 to infinity
CI	Confidence interval
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
COVID-19	Coronavirus disease 2019
DP	Drug product
DS	Drug substance
EMA	European Medicines Agency
EU	European Union
IL	Interleukin
LSM	Least square means
PASI	Psoriasis Area and Severity Index
PFS	Pre-filled syringe
PI	Product Information
PK	Pharmacokinetic(s)
PPS	Per-protocol set
RMP	Risk management plan
SAE(s)	Serious adverse event(s)
SB17	Ustekinumab
SD	Standard deviation
TEAE(s)	Treatment emergent adverse event(s)
TGA	Therapeutic Goods Administration
US	United states (of America)

Product submission

Submission details

Type of submission:	New biosimilar medicine
Product name:	Epyztek
Active ingredient:	Ustekinumab
Decision:	Approved
Date of decision:	26 September 2024
Date of entry onto ARTG:	21 October 2024
ARTG numbers:	423022, 423023 and 423024
▼*Black Triangle Scheme*	Yes
for the current submission:	
Sponsor's name and address:	Samsung Bioepis AU Pty Ltd Suite 1, Level 11, 66 Goulburn Street Sydney NSW 2000 Australia
Dose forms:	Solution for injection and solution for infusion
Strengths:	45 mg/0.5 mL, 5 mg/1 mL and 90 mg/1 mL
Containers:	Syringe and vial
Pack size:	One
Approved therapeutic use for the current submission:	**Plaque Psoriasis** *Adults* Epyztek 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. *Paediatric population, 6 years and older* Epyztek is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from 6 years of age who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. **Psoriatic Arthritis (PsA)** Epyztek, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) where response to previous non-biological DMARD therapy has been inadequate.

Crohn's Disease

Epyztek is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative Colitis

Epyztek is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

Routes of administration: Subcutaneous and intravenous

Dosage:

Plaque Psoriasis

Adults

For the treatment of plaque psoriasis, Epyztek is administered by subcutaneous injection. The recommended dose of Epyztek is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg administered over Weeks 0 and 4, then every 12 weeks thereafter may be used in patients with a body weight greater than 100 kg.

Paediatric population, 6 years and older

For the treatment of plaque psoriasis, Epyztek should be administered by subcutaneous injection. The recommended dose of Epyztek is based on body weight. Epyztek should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Psoriatic Arthritis

For the treatment of psoriatic arthritis, Epyztek is administered by subcutaneous injection. The recommended dose of Epyztek is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Some patients with a body weight greater than 100 kg received a 90 mg dose in clinical trials and observed a clinical benefit.

Treatment should be discontinued in patients who have shown no response after 28 weeks of treatment.

Crohn's Disease and Ulcerative Colitis

For the treatment of Crohn's disease and ulcerative colitis, the recommended treatment regimen is to initiate Epyztek with a single intravenous tiered dose based on body weight.

For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category:	B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Samsung Bioepis AU Pty Ltd (the sponsor) to register Epyztek (ustekinumab) 45 mg/0.5 mL solution for injection pre-filled syringe, 5 mg/1 mL solution for intravenous infusion injection vial, and 90 mg/1 mL solution for injection pre-filled syringe for the following proposed indication:[1]

> *Epyztek is proposed as a biosimilar to the reference product Stelara, for the same indications that are currently approved in Australia for Stelara, as follows:*
>
> *- treatment of moderate to severe plaque psoriasis*
>
> *- treatment of signs and symptoms of active psoriatic arthritis*
>
> *- treatment of moderately to severely active Crohn's disease*
>
> *- treatment of moderately to severely active ulcerative colitis.*

Ustekinumab is a fully human immunoglobulin G1κ monoclonal antibody that specifically binds to the shared p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

Epyztek (designated as SB17 during development) is a biosimilar to the ustekinumab innovator Stelara (Janssen-Cilag Pty Ltd). Epyztek is a recombinant protein with the same primary amino acid sequence as Stelara, produced in a Chinese hamster ovary cell system (Stelara utilises a murine cell line).

The three proposed presentations of Epyztek correspond to approved presentations of Stelara, and the sponsor is seeking identical indications for their biosimilar.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

However, as Epyztek will not have a presentation suitable for administering doses less than 45 mg, the sponsor proposes to restrict the use of Epyztek in paediatric patients with psoriasis to those with body weight of 60 kg or more.

There are currently two ustekinumab biosimilars registered in Australia (Wezlana and Ajemnye, Amgen Australia Pty Ltd).

Disease or condition

The pivotal Phase III study included in the submission was in psoriasis. The sponsor considered psoriasis the most appropriate indication to demonstrate clinical equivalence with the innovator. Psoriasis outcomes would be the most sensitive for detecting any differences between Epyztek and Stelara.

Psoriasis is a common chronic inflammatory skin disease. The most common subtype is plaque psoriasis, which is characterised by scaly erythematous plaques. Other subtypes include guttate psoriasis, pustular psoriasis and erythrodermic psoriasis. Psoriasis can also affect tissues other than the skin, including joints (that is, psoriatic arthritis).

Current treatment options

Ustekinumab is a human monoclonal antibody that has been widely used in clinical practice for the treatment of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Stelara, the Australian registered innovator product, is approved for use in all the proposed indications for Epyztek. Stelara has been widely used in clinical practice since its approval, with a well characterised pharmacological, efficacy, and safety profile.

Clinical rationale

The clinical development of Epyztek is aimed at comparing the pharmacokinetics (PK), efficacy, safety, and immunogenicity of Epyztek against the reference product, Stelara. The comparative clinical studies for Epyztek were designed to demonstrate similarity between Epyztek and Stelara in terms of clinical efficacy and safety, and not to establish patient benefit per se as this has previously been established for the reference product.

Throughout the development program, European Union (EU) sourced Stelara was used in lieu of Australian (AU) sourced Stelara as the main comparator in clinical studies. The sponsor has provided justification for this by providing additional bridging comparability study results between AU-sourced Stelara and EU-sourced Stelara in the 130 mg/26 mL intravenous vial drug product only. At the time of the bridging comparability study, no pre-filled syringe (PFS) drug product was available in the Australian market, and subsequently no bridging comparability studies were performed using these drug product presentations.

Regulatory status

Australian regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been approved in the United States of America in June 2024, Republic of Korea in April 2024, the European Union (EU) in April 2024, Canada in August 2024, and the United Kingdom in May 2024. A similar submission was under consideration in Switzerland (submitted on 12 July 2024).

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Timeline for Submission PM-2023-04204-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 October 2023
Evaluation completed	11 July 2024
Registration decision (Outcome)	26 September 2024
Registration in the ARTG completed	21 October 2024
Number of working days from submission dossier acceptance to registration decision*	160

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- TGA: Guideline on biosimilar medicines regulation by Australian Government Department of Health, Version 2.2.

  Last updated April 2018

- European Medicines Agency (EMA): Guideline on similar biological medicinal products. (CHMP/437/04 Rev. 1).

  TGA-adopted, effective date: 25 May 2015.

- EMA: Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

  TGA-adopted, effective date: 17 August 2015

- EMA: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

  TGA-adopted, effective date: 1 July 2015.

- EMA: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/2012)

TGA-adopted, effective date: 1 December 2014

- EMA: Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins (CHMP/EWP/89249/2004).

  TGA-adopted, effective date: 6 January 2006.

- EMA: Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006).

  TGA-adopted, effective date: 22 June 2009

- EMA: Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010)

  TGA-adopted, effective date: 1 December 2012

- EMA: Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)

  TGA-adopted, effective date: 1 October 1999

- EMA: Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (CHMP/EWP/2454/02 corr.)

  TGA-adopted, effective date: June 2005.

Quality evaluation summary

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product were assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopeial standards and the technical guidelines adopted by the TGA.

The ustekinumab (SB17) drug product (DP) for subcutaneous injection is a clear, colourless to light yellow, sterile and preservative-free solution. Both SB17 45 mg DP and 90 mg DP have the same composition as the SB17 drug substance (DS: 90 mg/mL ustekinumab, histidine, sucrose, and polysorbate 80). The same formulation has been used throughout product development.

The container closure system (pre-filled syringe (PFS)) of SB17 DP for subcutaneous use consists of a clear glass syringe with staked needle, rigid needle shield, and a plunger stopper. The PFS is assembled into the secondary packaging components which include a safety shield and plunger rod.

Ustekinumab (SB17) DP for intravenous use is a clear, colourless to light yellow solution. The formulation of the DP contains 5 mg/mL ustekinumab in histidine, methionine, disodium edetate, sucrose, and polysorbate 80. The 130 mg/26 mL presentation is packaged in a 30 mL Type I clear glass vial, with a 20 mm rubber stopper and aluminium flip-off cap.

The manufacturing process and process controls for both DS and DP have been sufficiently addressed. The steps, methods, equipment, reagents, critical process parameters and non-critical process parameters selected are typical of monoclonal manufacturing.

Characterisation studies were performed in accordance with ICH Guideline Q6B. The characterisation studies examined the structures (primary, post-translational modification, glycan profile, and higher-order) of SB17, purity/impurities, charge heterogeneity, quantity, cellular potency, and binding activity.

The quality attributes, including critical quality attributes and non-critical quality attributes were determined as per the ICH Guideline Q8 (R2) based on a risk assessment plan.

The sponsor provided two separate data sets to support the biosimilarity of PFS (45 mg/0.5 mL and 90 mg/1 mL) and vial (130 mg/26 mL) presentations of SB17 to EU-sourced Stelara. The characterisation for the similarity assessment involved the determination of physicochemical and biological properties of SB17 and Stelara. The primary structure and post-translational modifications of the two molecules were identical or substantially similar. The evaluation agreed that this difference is unlikely to be significant in terms of immunogenicity, pharmacokinetics, and biological activity of the two molecules. Purity was examined using multiple processes including chromatography and the two molecules were considered similar. Multiple assessments of higher-order structure (folding, secondary and tertiary structure, conformational changes etcetera) concluded similarity between the two molecules. Protein concentration results of all SB17 batches were within range. Biological properties including IL-12 and IL-23 neutralisation, IL-12 and IL-23 binding, and various FC receptor binding were comparable.

The evaluation noted that similar findings were reported for the vial presentation of SB17, except FC receptor-n binding. This was not considered relevant, as this has minimal effect on biological activity.

Comparative stability studies (forced degradation studies) were performed under heat stress condition, basic stress condition, acidic stress condition, oxidative stress condition, and photo stress condition. Results of all comparative stability studies showed similar degradation profiles supporting similarity between SB17 and Stelara.

A bridging study comparing vial formulations of AU-sourced Stelara with EU-sourced Stelara was also provided to support the use of the overseas reference product in clinical studies. The sponsor stated that at the time of the bridging study PFS formulations of Stelara were not available in Australia. Australian-sourced Stelara and EU-sourced Stelara were found to be comparable in all aspects examined, except for minor differences in the N-glycan profile of one AU-sourced batch, and micro-flow imaging (for visualisation of subvisible particles). These minor differences were justified by the sponsor and accepted.

Nonclinical evaluation summary

The nonclinical evaluation had no objection to registration of Epyztek, noting the following:

- The scope of the nonclinical program is adequate under the relevant EU guideline. The set of pharmacological assessments performed across the quality data with Epyztek and EU- and United States (US)-sourced Stelara is considered acceptable to cover all proposed indications. A slight glycosylation difference between the EU-sourced Stelara and Epyztek was identified, however, no meaningful differences were observed in the comparative pharmacology. No nonclinical data were provided to verify the comparability of the EU-sourced and AU-sourced Stelara.
- No nonclinical studies were submitted. Therefore, adequate comparability and determination of biosimilarity will need to rely upon quality and clinical evaluations.

Clinical evaluation summary

Summary of clinical studies

The clinical dossier included two studies to demonstrate similar pharmacokinetics (PK), efficacy, safety and immunogenicity of SB17 to the reference product Stelara.

Study SB17-1001 was a randomised, double blind, three arm, parallel group, single dose study which compared the pharmacokinetics, safety, tolerability, and immunogenicity of ustekinumab (SB17), EU-sourced Stelara, and US-sourced Stelara in healthy participants.

Study SB17-3001 was a Phase III, randomised, double blind, multi-centre clinical study which evaluated the efficacy, safety, tolerability, immunogenicity, and pharmacokinetics of SB17 compared to EU-sourced Stelara in participants with moderate to severe plaque psoriasis.

Pharmacology

Pharmacokinetics

In Study SB17-1001, 201 healthy volunteers were randomised in a 1:1:1 ratio to receive a single subcutaneous dose of SB17 45 mg, EU-sourced Stelara 45 mg, or US-sourced Stelara 45 mg following an 8 hour fast. Blood for PK analysis was sampled at a range of timepoints from Day 1 (0 hours) up to Day 99 (2352 hours) post dose.

The primary PK endpoints were area under the concentration time curve from 0 to infinity ($AUC_{0\text{-}inf}$) and maximum concentration (C_{max}). The difference in least square means (LSM) and the corresponding 90% confidence intervals (CI) between each of the treatment groups were estimated. The arithmetic mean values for each of the PK parameters for SB17, EU-sourced Stelara and US-sourced Stelara were generally comparable. Mean $AUC_{0\text{-}inf}$ values were 5143600 ng·h/mL, 5273000 ng·h/mL, and 5116600 ng·h/mL for SB17, EU-sourced Stelara, and US-sourced Stelara, respectively. Mean C_{max} were 5095 ng/mL, 5689 ng/mL, and 5420 ng/mL for SB17, EU-sourced Stelara, and US-sourced Stelara, respectively. Secondary PK parameters were comparable across all treatment groups. Additionally, concentration-time curves for each of the pairwise comparisons were essentially superimposable on both linear and semi-logarithmic scales.

The geometric LSM ratio (90% CI) for the comparison of SB17 and EU-sourced Stelara for $AUC_{0\text{-}inf}$ and C_{max} were 0.99 (0.90 to 1.08) and 0.90 (0.82 to 0.98), respectively. As the 90% CI for each of the PK parameters was within the pre-defined equivalence margin of 0.8 to 1.25, this indicated equivalence between the two treatments.

The geometric LSM ratio (90% CI) for the comparison of SB17 and US-sourced Stelara in $AUC_{0\text{-}inf}$ and C_{max} were 1.01 (0.93 to 1.10) and 0.94 (0.86 to 1.04), respectively. As the 90% CI for each of the PK parameters was within the pre-defined equivalence margin of 0.8 to 1.25, this indicated equivalence between the two treatments.

In Study SB17-3001, 503 adults with moderate-severe plaque psoriasis were randomised in a 1:1 ratio to receive either SB17 or EU-sourced Stelara (249 participants in the SB17 treatment group and 254 in the EU-sourced Stelara treatment group) for 28 weeks before reaching a transition period.

The evaluation of the PK of SB17 compared to EU-sourced Stelara in the first 28 weeks was a secondary objective of the study. Serum ustekinumab concentrations for 142 participants (71 in each of the SB17 and EU-sourced Stelara treatment groups) were measured at Week 0, 2, 4, 8, 12, 16, and 28. At Baseline, (pre-dose) ustekinumab concentrations were below the lower limit of quantitation for all but three participants (one in the SB17 group (concentration of 2919.4 ng/mL) and two in the EU-sourced Stelara group (concentrations of 2626 ng/mL and 158.5 ng/mL). Although the irregular results were thought to have been caused by contamination, the values were included in the PK analysis.

Mean serum concentrations of ustekinumab from Week 8 to 28 were generally comparable between the SB17 group and the EU-sourced Stelara group, but consistently higher in the SB17

group. Subgroup analysis was undertaken on the PK of ustekinumab by visit, treatment group, and overall anti-drug antibody (ADA) status up to 28 weeks. At Week 0, the mean serum ustekinumab concentration was above 0 in the SB17, ADA positive subgroup (mean = 364.9 ng/mL) and in the EU-sourced Stelara, ADA negative subgroup (mean = 75.3 ng/mL). The mean serum ustekinumab concentrations in the SB17, ADA negative subgroup and EU-sourced Stelara, ADA positive subgroup were both zero.

The mean ustekinumab concentrations for participants with an overall ADA negative status were comparable in the SB17 and EU-sourced Stelara groups up to 28 weeks. For ADA positive participants the mean ustekinumab concentrations from Week 8 onwards were generally higher in the SB17 group compared to the EU-sourced Stelara group.

Efficacy

Study SB17-3001 used a randomised, double-blind, multicentre study design.

The primary objective of the study was to demonstrate the equivalence of SB17 to EU-sourced Stelara, in terms of the percent change from Baseline in Psoriasis Area and Severity Index (PASI) at Week 12 in adults with moderate to severe plaque psoriasis. Both investigational products were presented as 45 mg/0.5 mL solution of ustekinumab in a PFS and administered as a subcutaneous injection. Several secondary objectives, including pharmacokinetic and immunogenicity outcomes, were also identified. Inclusion and exclusion criteria were appropriate and applied equally to both treatment groups.

A dose of 45 mg of SB17 or EU-sourced Stelara were administered at Week 0, 4, and then every 12 weeks up to Week 40. Participants who exceeded 100 kg body weight during the study were given a 90 mg dose in subsequent visits. At Week 28 of the study, participants who achieved a PASI50 response were considered eligible to enter the transition period. In the transition period, participants who received EU-sourced Stelara were re-randomised in a 1:1 ratio to continue EU-sourced Stelara or to switch to SB17 until Week 40. Participants who were already on SB17 continued to receive SB17 until Week 40.

The primary efficacy endpoint was the percent change from Baseline in PASI at Week 12. Primary efficacy analysis was undertaken on the per-protocol set (PPS) using Analysis of Covariance (ANCOVA) with the baseline value of PASI as a covariate and pooled centres (countries) and treatment group as factors.

Of the randomised participants, a total of 481 (95.6%) participants completed 28 weeks of the study, and 466 (96.9%) participants completed 52 weeks of the study. Ten participants (five participants in each of the treatment arms) had major protocol deviations that resulted in exclusion from the PPS for analysis. The reasons for exclusion were comparable between both treatment arms. The demographic characteristics were generally comparable across the different treatment groups. Mean age was 44.2 years (standard deviation (SD), 12.8) with more than half of the participants being male (312 out of 503, 62.0%). The mean weight was 80.3 kg (SD, 11.9 kg). Participants were predominately from Central-Eastern Europe, with most participants coming from Poland (243 out of 503, 48.3%), Ukraine (146 out of 503, 29.0%), and the Czech Republic (51 out of 503, 10.1%). The baseline disease characteristics were also generally comparable across the different treatment groups. The mean (SD) PASI score at baseline was 22.29 (7.7), mean total psoriasis body surface area involvement was 26.98 (13.6%) and the mean duration of psoriasis was 15.59 years. Almost all participants had used prior psoriasis topical treatment (466 out of 503, 92.6%), whilst there was a more balanced proportion of participants who had used prior conventional systemic treatment for psoriasis (250 out of 503, 49.7%) or who had used prior phototherapy (242 out of 503, 48.1%). A small proportion of participants reported use of prior biologic treatment (36 out of 503, 7.2%).

Clobetasol propionate was the most common reported prior medication by preferred term (SB17: 109 (43.8%) participants and EU-sourced Stelara overall: 109 (42.9%) participants).

Equivalence between SB17 and EU-sourced Stelara was established. The results were supported by pre-specified secondary outcomes, sensitivity analyses, and subgroup analyses.

Table 2: Study SB17-3001, primary efficacy analysis of percent change from baseline in PASI at Week 12, per-protocol set

				Difference (SB17 − Stelara)	
Timepoint	**Treatment**	**n**	**LSMeans (SE)**	**LSMeans (SE)**	**95% CI**
Week 12	SB17 (N=243)	243	85.7 (2.53)	−0.6 (1.62)	[−3.780, 2.579]
	Stelara (N=249)	249	86.3 (2.41)	-	-

CI: Confidence interval; LSMeans: Least Squares Means; N: Total number of subjects in the Per-Protocol Set in each treatment group; n: Number of subjects with available data at Week 12; PASI: Psoriasis Area and Severity Index; SE: Standard error
Inferential statistics for percent change from baseline in PASI at Week 12 were based on analysis of covariance model with the baseline value of PASI as a covariate and pooled centres (country) and treatment groups as factors.
Therapeutic equivalence is declared if the two-sided 95% CI of the LSMeans difference of percent changes from baseline at Week 12 between SB17 and Stelara lies within the pre-defined equivalence margin of [−15%, 15%].

Table 3: Study SB17-3001, primary efficacy analysis of percent change from baseline in PASI at Week 12, full analysis set

				Difference (SB17 − Stelara)	
Timepoint	**Treatment**	**n**	**LSMeans (SE)**	**LSMeans (SE)**	**95% CI**
Week 12	SB17 (N=249)	246	85.7 (2.42)	−0.7 (1.60)	[−3.836, 2.456]
	Stelara (N=254)	252	86.3 (2.31)	-	-

CI: Confidence interval; LSMeans: Least Squares Means; N: Total number of subjects in the Full Analysis Set in each treatment group; n: Number of subjects with available data at Week 12; PASI: Psoriasis Area and Severity Index; SE: Standard error
Inferential statistics for percent change from baseline in PASI at Week 12 were based on analysis of covariance model with the baseline value of PASI as a covariate and pooled centres (country) and treatment groups as factors.
Therapeutic equivalence is declared if the two-sided 95% CI of the LSMeans difference of percent changes from baseline at Week 12 between SB17 and Stelara lies within the pre-defined equivalence margin of [−15%, 15%].

The immunogenicity of SB17 appeared to be lower (that is, lower ADA) compared to EU-sourced Stelara overall and at each timepoint up to Week 52. However, in subgroup analysis of the primary efficacy endpoint by overall ADA status up to Week 52, there was no significant or clinically meaningful difference in efficacy between SB17 and EU-sourced Stelara for both ADA positive and negative subgroups, with the LSM difference and corresponding 95% CIs falling entirely within pre-defined equivalence margins.

The overall conclusion is that despite small differences in measurable concentrations of ustekinumab in patients treated with SB17 and EU-sourced Stelara, equivalent efficacy was demonstrated.

Safety

The safety data for this application arise only from the two clinical studies. In Study SB17-1001, 67 (33.3%) healthy participants were exposed to a single 45 mg dose of SB17, administered subcutaneously. The remaining study population (n = 138) was exposed to single doses of either EU-sourced Stelara or US-sourced Stelara. Reports of any adverse events were common in all three groups (ranging from 109 reports from 46 patients in the SB17 group to 80 reports from 39 patients in the EU-sourced Stelara group), most were not considered treatment related. In the SB17 group 46.3% (31 out of 67) were considered to have experienced moderate severity adverse events, compared to 37.3% (25 out of 67) in the EU-sourced Stelara group and 22.4% (15 out of 67) in the US-sourced Stelara group.

There were no deaths, severe treatment-emergent adverse events (TEAE) or serious TEAE reported in any group. Almost all discontinuations were associated with COVID-19 diagnoses (discontinuations per protocol). When grouped by preferred term, the most frequent TEAEs were headache (46 events total in 36 participants), nasopharyngitis (27 events total in 25 participants) and COVID-19 (14 events total in 14 participants). This reflects the known adverse event profile of ustekinumab.

In Study SB17-3001, 249 (49.5%) participants received approximately five subcutaneous injections of SB17 during the duration of the study. A further 122 participants initially treated with EU-sourced Stelara for 28 weeks were re-randomised to receive five subcutaneous injections of SB17 up until the end of the study. Total exposure to ustekinumab (SB17 or EU-sourced Stelara) was comparable in both treatment groups.

While adverse events during the main treatment period (0 to 28 weeks) were reported by around half of all participants in this study, reports were similar for each of the three treatment groups. Most were mild or moderate and considered unrelated to study treatment. Infections were the most frequently reported TEAEs (28.1 to 29.5% of reports). This pattern was also reflected in the summary of adverse events in the transition period and in the overall study period (0 to 52 weeks). There were no deaths reported during the trial period, and reports of serious adverse events were low, none were considered related to investigational product.

During the overall study period, there were a total of 13 participants (2.6%) who reported 14 treatment-emergent serious adverse events (SAEs). This comprised 7 (2.8%) participants in the SB17 and 6 (2.4%) participants in the EU-sourced Stelara overall group. In the SB17 group, one participant each reported the following preferred terms for SAEs: acute myocardial infarction, fibula fracture, joint dislocation, meniscus injury, musculoskeletal chest pain, ischaemic stroke and prerenal failure. In the EU-Sourced Stelara overall group, one participant each reported the following preferred terms for SAEs: atrial fibrillation, salivary gland calculus, pneumonia, tibia fracture, prostate cancer, and ovary cyst torsion and pelvic adhesions.

Systemic hypersensitivity, infections, pulmonary events, and injection site reaction were considered adverse events of special interest. Regarding infections, 79 (31.7%) participants in the SB17 group and 83 (32.7%) participants in the EU-sourced Stelara overall group reported infections during the overall study period, whereas no participant in any group reported pulmonary events. Systemic hypersensitivity and injection site reactions were reported by two participants in the EU-sourced Stelara groups and none in the group only exposed to SB17.

In both clinical studies, participants exposed to SB17 had lower rates of developing ADAs and neutralising antibodies than those exposed to EU-sourced Stelara alone or EU-sourced Stelara and SB17.

The overall conclusion was that the safety profile of SB17 appears to be similar to that of EU-sourced Stelara. There were no new safety issues with SB17 based on the two clinical studies provided with the submission.

Extrapolation to other indications and patient groups

In alignment with published guidance, the sponsor of a biosimilar medicine is not required to perform clinical trials in each of the populations for which the innovator medicine has been approved, subject to providing an acceptable justification for extrapolation. The sponsor for Epyztek provided the following evidence in support of extrapolation:

- The mechanism of action of ustekinumab is the same across the approved indications of psoriasis, psoriatic arthritis, Crohn’s disease and ulcerative colitis.

- The role of IL-23/IL-12 mediated inflammation in these diseases is supported by the data summarised in the Stelara Product Information (PI) and published scientific literature.
- The various structural assessments of SB17 undertaken demonstrate its similarity to Stelara.
- PK similarity between SB17 and Stelara has been demonstrated in a Phase I study which showed the 90% confidence intervals for the geometric mean ratios of $AUC_{0\text{-}inf}$ and C_{max} to be within the prespecified range of 0.8 to 1.25.
- Stelara is known to show similar PK characteristics across its different indications, thus supporting extrapolation for SB17.
- The safety profile of SB17 was found to be comparable to Stelara, further supporting an extrapolation across indications.

The differences in incidence of both binding and neutralising ADAs between SB17 and Stelara have been described. It is not possible to confidently extrapolate what may be expected (for example incidence and clinical/safety effects) with ADAs in non-psoriasis indications for SB17. This uncertainty is noted and should be addressed in the post market space.

The use of psoriasis as the population in which to demonstrate comparable efficacy is appropriate given the expected robust treatment effects. Furthermore, the lack of comorbidities and other immunosuppressant use compared with the other indications, makes the psoriasis population sensitive for detecting safety signals and immunogenicity.

Real world data were not included in this submission.

Recommendation following the clinical evaluation

The clinical evaluation recommended approval of all three presentations of the biosimilar ustekinumab Epyztek for injection for the same indications approved for the innovator in psoriasis (including only children ≥ 6 years, weighing ≥ 60kg), psoriatic arthritis, Crohn's disease and ulcerative colitis. The evaluation noted that in the absence of an appropriate presentation, Epyztek would not be suitable for smaller paediatric patients.

Risk management plan

The sponsor submitted an EU risk management plan (RMP), Version 1.0, data lock point 22 March 2023, and an Australian Specific Annex, Version 1.0, dated 8 September 2023. These documents did not require evaluation but may be reviewed at a later date if indicated.

The clinical evaluation did not raise any issues with the summary of safety concerns based on the innovator.

The sponsor is required to comply with product vigilance and risk minimisation requirements.

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

The application for Epyztek 5 mg/1 mL (130 mg/26 mL) ustekinumab concentrate for solutions for intravenous infusion in a vial, and for 90 mg/1 mL and 45 mg/0.5 mL ustekinumab solution for subcutaneous injection in a pre-filled syringe is supported by the submitted data. Based on the Phase I PK Study SB17-1001, Epyztek and EU-sourced Stelara were considered to have similar PK profiles. Based on the Phase III clinical equivalence efficacy Study SB17-3001, Epyztek and EU-sourced Stelara were considered equivalent based on pre-defined equivalence margins. The safety profile of Epyztek is similar to that of the reference product, Stelara. No new safety concerns were raised in the studies submitted. A risk management plan will be implemented for the product.

Justification for extrapolation to indications other than psoriasis in adults has been provided and is based on a combination of quality, nonclinical, historical and current clinical data.

The sponsor has provided a bridging study report for the comparability of the Australian reference product Stelara to EU-sourced Stelara. The suitability of using the vial presentation for the bridging study is based on extrapolation of evidence provided by the sponsor to demonstrate comparability between the vial and PFS presentation of Epyztek, as well as between Epyztek and EU-sourced Stelara for each presentation.

Proposed action

The benefit-risk profile of Epyztek (ustekinumab) in the proposed indication is considered favourable. The Delegate proposed to approve Epyztek for the indications:

Plaque Psoriasis

Adults

Epyztek 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.

Paediatric population, 6 years and older

Epyztek is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from 6 years of age who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Psoriatic Arthritis (PsA)

Epyztek, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) where response to previous non-biological DMARD therapy has been inadequate.

Crohn's Disease

Epyztek is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative Colitis

Epyztek is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Epyztek (ustekinumab) 45 mg/0.5 mL solution for injection pre-filled syringe, 5 mg/1 mL solution for intravenous infusion injection vial, and 90 mg/1 mL solution for injection pre-filled syringe indicated for:

Plaque Psoriasis

Adults

Epyztek 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.

Paediatric population, 6 years and older

Epyztek is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from 6 years of age who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Psoriatic Arthritis (PsA)

Epyztek, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) where response to previous non-biological DMARD therapy has been inadequate.

Crohn's Disease

Epyztek is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative Colitis

Epyztek is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

Specific conditions of registration

- Epyztek (ustekinumab) is to be included in the Black Triangle Scheme. The PI and CMI [Consumer Medicines Information] for Epyztek 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.
- Laboratory testing & compliance with Certified Product Details (CPD)
  - All batches of Epyztek ustekinumab supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Please note that outcomes of laboratory testing may be published on the TGA website.
- Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change. A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website [for the form] https://www.tga.gov.au/form/certified-productdetails-cpd-biological-prescription-medicines [for the CPD guidance] https://www.tga.gov.au/guidance-7-certified-product-details.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #