

Pharmaceutical Benefits Scheme

Post-market Review

The use of biologics in the treatment of severe chronic plaque psoriasis

Term of Reference 2

DRAFT REPORT

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Abbreviations

Abbreviation	Full Name / Wording
AAD	American Academy of Dermatology
ACD	Australasian College of Dermatologists
ACR	American College of Rheumatology
AGREE	Appraisal of Guidelines for Research and Evaluation
AS	ankylosing spondylitis
BAD	British Association of Dermatology
CASPAR	The Classification Criteria for Psoriatic Arthritis
CDA	Canadian Dermatology Association
CPP	chronic plaque psoriasis
DHS	Department of Human Services
DLQI	Dermatology Life Quality Index
DoH	Department of Health
EACV	European Association for Dermatology and Venereology
EDF	European Dermatology Forum
EU	European Union
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IPC	International Psoriasis Council
NICE	National Institute for Health and Care Excellence
NPF	National Psoriasis Foundation
PASI	Psoriasis Area and Severity Index
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PGA	Physician's Global Assessment
PsA	psoriatic arthritis
PUVA	psoralen and ultraviolet A
RA	rheumatoid arthritis
SCD	standard coverage days
SIGN	Scottish Intercollegiate Guidelines Network
ToR	term of reference
tx	treatment
UK	United Kingdom
US	United States

Section 2: Term of Reference (ToR) 2

Efficacy and safety of biologics used in the treatment of severe chronic plaque psoriasis (CPP)

ToR 2: Review and evaluate recent clinical evidence on the efficacy and safety of biologics used in the treatment of severe CPP and compare to the evidence considered by the Pharmaceutical Benefits Advisory Committee (PBAC) in previous sponsor submissions.

2.1 Key findings for ToR 2

Evaluation of clinical evidence

A systematic literature review and network meta-analysis was conducted to analyse the comparative effectiveness and safety of the biologics listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of severe CPP.

Direct comparisons

The searches identified 67 trials and four observational studies in total. The majority of RCTs were placebo controlled (43) and there were five studies identified that included etanercept as the comparator to infliximab (PIECE), Ixekinumab (UNCOVER 2 & 3) secukinumab (FIXTURE) and ustekinumab (ACCEPT) and one trial that compared secukinumab versus ustekinumab (CLEAR). Overall the quality of the methods for the RCTs was high, but the overall risk of bias was generally unclear. Trials were similar with regards recruitment processes, trial implementation, and placebo response (only four of the 67 trials had a placebo response greater than 10%).

On a whole biologics demonstrated that they provided much greater PASI response than placebo with an acceptable safety profile. In the direct RCTs infliximab, Ixekinumab, secukinumab and ustekinumab had greater PASI 75 response rates than etanercept.

Indirect comparison

Based on a comparison of all trials measuring PASI 75% response rates at 12 weeks the network meta-analysis found that all biologics were superior to placebo in terms of efficacy, with ixekizumab having the greatest point estimate PASI 75 response rate compared to placebo and etanercept had the lowest point estimate PASI 75 response rate compared to placebo.

Safety was assessed by comparing the proportion of patients who experienced any adverse event at 12 weeks; etanercept and ustekinumab were ranked the safest of the PBS-listed biologics.

New evidence compared to evidence previously presented to the PBAC

New evidence for each biologic was compared with that previously seen by the PBAC in terms of the proportion of patients achieving a PASI 75 response and mean change in the Dermatology Life Quality Index (DLQI) score.

In general, the trials that were seen previously were comparable in terms of inclusion criteria, disease severity (baseline BSA and PASI) and quality. For each PBS-listed biologic the

new efficacy and quality of life evidence was highly consistent with that previously considered by the PBAC.

Recent safety findings concerning longer-term use of the PBS-listed biologics

In the longer-term (up to five years) studies the proportions of patients experiencing any adverse event was relatively unchanged when compared to the comparator-controlled randomised controlled trials (RCTs) (up to 24 weeks). Approximately 10% of patients experienced a severe adverse event. The incidence of cardiovascular disease, serious infection and malignancy was consistently very low across all studies.

Efficacy and safety of the PBS-listed biologics in patients with mild-to-moderate CPP

It was not possible to evaluate the PBS-listed biologics in patients with mild-to-moderate CPP, as only one trial was identified that considered the efficacy of etanercept in patients with moderate CPP. The results of this small trial suggested that etanercept might have been marginally less effective in patients with less severe disease.

Effectiveness of the PBS-listed biologics in patients with severe CPP and other comorbidities

Evidence was found for the use of etanercept, infliximab and secukinumab in the treatment of patients with severe CPP (for this analysis, severe CPP was defined as a baseline PASI score of greater than 10) and psoriatic arthritis (PsA). In terms of treating PsA, these biologics appeared to have an effect, with over half of all treated patients meeting the American College of Rheumatology 20% (ACR 20) improvement criteria for joint response. In terms of treating CPP, the proportions of patients achieving PASI 75 responses were marginally lower than in patients that were treated for severe CPP alone.

Of the PBS-listed biologics for the treatment of severe CPP in adults, only etanercept is listed on the PBS for the treatment of severe CPP in children. The systematic literature review identified three trials, with five related publications, relating to the use of the PBS-listed biologics for the treatment of severe CPP in children: one trial each considering adalimumab, etanercept and ustekinumab. The biologics were superior in terms of efficacy to placebo.

Comparative effectiveness of the PBS-listed biologic agents in hand, face, and/or feet psoriasis

There was limited evidence for the treatment CPP with hands, face and/or feet involvement. In the systematic literature review, small trials were identified for the use of adalimumab (one trial), infliximab (one trial) and secukinumab (one trial) in this population. Each trial assessed the proportion of patients achieving a score of clear or almost clear on the hand and/or feet Physician's Global Assessment (hf PGA) tool. Each drug appeared to have an effect compared to placebo.

Stakeholder views (Public consultation and stakeholder forum)

Stakeholder consultation phase

During the consultation phase Janssen-Cilag Pty Ltd, Eli Lilly Pty Ltd, Abbvie Pty Ltd and Pfizer Australia provided substantial valuable information and data from trials and observational studies in support of the safety and efficacy of the various biologics being used in severe CPP. Those studies that were identified in the systematic review and met the inclusion criteria that were also provided sponsors were included in the review of the

evidence. Those studies provided by Sponsors that fell outside the systematic review protocol were not included in the network meta-analysis.

Patient-relevant outcomes

Clearing of psoriasis was identified as the primary focus for most patients. It was noted that psoriasis clearance may lead to an improvement in self-confidence, workforce participation, mental health and wellbeing and social participation. Choice of clothes patients wear (e.g. shorts, T-shirts, bikinis) and successful management of their CPP influences their employment options. Workforce participation and productivity can be significantly impacted by psoriasis, particularly in industries such as hospitality. This also has economic impacts in absenteeism and presenteeism (i.e. present, but not focused on work).

The reduction of fatigue was considered an important outcome, particularly for patients who also have psoriatic arthritis. It was also noted that co-morbidities that are inflammatory in nature may also improve when biologics are used to treat psoriasis.

Effectiveness of biologics

Clinicians at the stakeholder meeting noted that there are some efficacy differences between biologics and individual patient variations with respect to biologic efficacy. Clinicians reported that the IL-17 class of biologics (e.g. ixekizumab) consistently achieves a PASI 90 response in 60 to 80% of patients, while the TNF inhibitor class (e.g. adalimumab, etanercept and infliximab) consistently achieves a PASI 75 response in 60 to 80% of patients.

The difference to patients may not be large and they may be happy with a PASI 75 response. However, most patients say they want the best response. It was noted that new drug classes may be more effective. Etanercept has a particular role due to its long-term safety data, short half-life and use in paediatric populations. Additionally, consumers were concerned about waning effectiveness of biologics over time.

It was noted that there are very limited options for treating psoriasis in children and this is a group with high unmet need. There is not much data in this population. Additional research is required to understand if treating early influences the course of psoriasis.

It was noted that the lower the baseline PASI score (e.g. PASI 10-12), the harder it is to achieve a 75% reduction in PASI score (PASI 75). This creates issues with using PASI 75 as a measure of treatment response in these patients. The baseline PASI score in most clinical trials is 10 to 12.

Safety of biologics

Biologics were considered to be generally well tolerated, with adverse events such as infections consistent with those reported in the clinical trials. It was noted that psoriasis and comorbidities can be sufficiently severe that many patients are willing to accept any risk for successful treatment. Most patients reported that improved quality of life outweighs the risk of adverse effects with biologics.

The stakeholders noted that there is now over 10 years' experience in using biologics in psoriasis. Registry data indicate there is no increase in malignancies in age matched cohorts. Clinicians are getting better at managing (predicting and planning) biologic side effects, in particular for planning around times when a biologic must be stopped such pre and post-

surgery and identifying patients with higher risk of infection. Cancer diagnoses require patients and clinicians to weigh up the risks and benefits whether to stop or continue biologics. Side-effects associated with injections are a concern for some patients, but the prospect of effective treatment outweighs the risk. It was noted there some unanswered questions with respect to the safety of biologics such as whether the adverse event profile is dose-dependent or whether adverse events differ by patient age.

2.2 Systematic literature review

2.2.1 Methods

A systematic literature review of PBS-listed biologics used the treatment of severe CPP was conducted. Relevant publications on the efficacy and safety of the biologics used in the treatment of severe CPP were identified. New evidence identified was compared with that considered by the PBAC in previous sponsor submissions. Detailed methods and search terms are presented in Appendix A – ToR2:

In addition to identifying relevant publications and comparing new evidence with that previously considered by the PBAC (Sections 2.3 and 2.4), the systematic review aimed to:

- identify and describe any recent findings concerning safety associated with longer-term use of the PBS-listed biologics (Section 2.5);
- compare evidence on the efficacy and safety of biologics for CPP in mild-to-moderate disease versus severe disease (Section 2.7);
- consider any evidence on the effectiveness of biologics for severe CPP on other comorbidities, such as PsA (Section 2.8); and
- consider evidence on comparative effectiveness of classes of biologic agents in populations with hands, face and/or feet psoriasis (Section 2.9).

Trials were included in the review if they measured outcomes previously accepted by the PBAC or any other clinical outcomes suggested by the Reference Group. The included trials and observational studies were assessed in terms of quality and any limitations are discussed.

Briefly, bibliographic databases were searched for the following PBS-listed biologics: adalimumab, efalizumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab. Although efalizumab was removed from the PBS in May 2009 due to safety concerns, it was included in the literature search as it formed the basis of a number of comparative analyses and was included in the network meta-analysis for completeness.

The searches were carried out by one staff member and the results extracted and imported into the bibliographical software Endnote X8 (Thomson Reuters). Endnote was used to automatically remove any duplicates from the database searches by matching title and author. The dataset was then visually scanned and any duplicates not found by Endnote were identified and removed. Articles that did not meet the inclusion criteria, assessed first by their title, and secondly by their abstract, were removed.

Trials were included in the final analysis if they met the following inclusion criteria:

- English language;
- Patients with severe CPP;
- Published since 2003;
- RCTs or large observational studies (i.e. > 200 patients);
- Included at least one of the PBS-listed biologics; and
- Provided efficacy, quality of life or safety outcomes.

In the event of disagreement regarding inclusion of a publication, the publication was read in full and resolved by consensus (two staff). If there was still uncertainty after this point, a third reviewer assessed the study independently and a decision was made by consensus or majority vote.

A multiple-treatments network meta-analysis was undertaken to summarise the results of the PBS-listed biologics for each of the outcomes where common treatment arms existed (PASI 75 and adverse events) using the trial data in the clinical evidence base.

2.2.2 Included trials and studies

Table 54 and Figure 7, Appendix A present the number of studies identified, included and excluded during the systematic review. A total of 86 relevant publications were identified in the systematic literature review. These publications related to 58 trials and four large observational studies (N > 200, which included longer-term outcomes, i.e. longer than one year).

In response to public consultation on the terms of reference, additional information was provided by sponsors and peak bodies. This information has been evaluated, where appropriate; the data provided was included if it was also identified in the systematic review and appropriate to the systematic review protocol.

A list of all identified trials and studies and the related publications for each biologic is presented at the beginning of each relevant section of this document (see Sections 2.3 to 2.10). The list for each biologic includes the primary outcome measures and an indication of whether the PBAC has previously seen the evidence. The information on trials previously seen by the PBAC was derived from the 'Review of the current restrictions and clinical guidelines of PBS-listed biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) for psoriasis', which was a 2016 report included at the first Reference Group Meeting and the relevant Public Summary Documents.

Table 1 provides a brief summary of the number of trials and large observational studies for each PBS-listed biologic included in this review.

Table 1: Trials and large observational studies investigating the use of PBS-listed biologics for the treatment of CPP: overall summary

Biologic	Publication date		CPP	CPP in children	Mild-to-moderate CPP	CPP + PsA	CPP + hands, face and/or feet	Total
	Earliest	Latest						
Trials								
Adalimumab	2005	2017	7	1	0	0	1	9
Efalizumab	2003	2008	5	0	0	0	0	5
Etanercept	2003	2017	11	1	1	2 ^b	0	15
Infliximab	2001 ^a	2017	8	0	0	1	1	10
Ixekizumab	2012	2016	3	0	0	0	0	3
Secukinumab	2013	2016	6	0	0	1	1	8
Ustekinumab	2007	2015	8 ^c	1	0	0	0	8
TOTAL			48	3	1	3	3	58
Observational Studies								
Etanercept	2003	2017	4	0	0	0	0	4

CPP = chronic plaque psoriasis; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PsA = psoriatic arthritis

^a One trial published prior to 2003 was included as it was used in a PBAC application

^b Included 1 trial which was also used in the analysis of etanercept for the treatment of CPP

^c Included 1 trial which was also included in the analysis of secukinumab for the treatment of CPP

Data from the identified RCTs are used in the analysis of efficacy and safety for each biologic in the treatment of severe CPP (see Sections 2.3.1 to 2.3.8) and in the network meta-analyses (see Section 2.4). These RCTs are summarised below.

Results from the four large observational studies identified in the systematic literature review are used in the analysis of longer-term safety of etanercept (see Section 2.5). A number of the trials had open-label extension studies and these were also considered in this section.

The use of the PBS-listed biologics in children with severe CPP was assessed for efficacy and safety (see Section 2.6). The use of the biologics was also assessed in terms of effectiveness in mild-to-moderate psoriasis (Section 2.7), for the treatment of patients with severe CPP and associated PsA (see Section 2.8) and the treatment of CPP with hands, face, feet and/or genital involvement (see Section 2.9).

Data (risk of bias assessments, baseline characteristics, efficacy and quality of life outcomes and adverse event information) were extracted from the included publications into a template in Excel. Extraction was performed by two reviewers – one reviewer extracted the data and one reviewer checked the extracted data for consistency.

2.2.3 Risk of bias

To assess the risk of bias in the identified RCTs the Cochrane Collaboration's 'Risk of bias tool' (Chapter 8, Cochrane Handbook, v5.1.0) was used (1). A summary of the level of risk of bias for each included RCT is provided in Table 55 to Table 61, Appendix B.

Selection bias – random sequence generation and allocation concealment

The majority of the RCTs (36/48; 75%) had a low risk of selection bias, as a centrally located computer randomisation system or an adaptive treatment allocation based on a biased-coin minimization algorithm was used, and a low risk of allocation bias, with the use of interactive voice and/or web response systems. The remaining 12 trials (25%) had an unclear risk of selection and allocation bias, as although they were all described as randomised, the methods of randomisation and/or allocation concealment were not described.

Performance & detection bias – blinding of participants, personnel and outcome assessment

The majority of the included RCTs (45/48; 94%) were double blinded (patients and investigators) and had a low risk of performance and detection bias; three trials were open-label and had a high risk of performance and detection bias. Outcome assessors were described as being blinded in 23 trials (48%) and unblinded in two trials (4%); in 23 trials (48%) the blinding of outcome assessors was not described and therefore the risk of bias was unclear.

Attrition bias – incomplete outcome data

The RCTs analysed efficacy and quality of life using the intention-to-treat population and safety using the safety analysis set. Attrition bias was assessed as being low in all of the trials, with similar proportions of patients in all arms of the trials completing the randomised periods.

Reporting bias – selective outcome reporting

All of the trials were assessed as having a low risk of reporting bias.

Other biases

The majority of the RCTs identified in the systematic literature review (47/48; 98%) had a high risk of 'other' bias as they were funded or sponsored by pharmaceutical companies. Torii (2010), which examined the efficacy of infliximab in Japanese patients, had an unclear risk of bias as the publication did not state whether the authors had any conflicts of interest.

2.2.4 Trial characteristics

A summary of the characteristics of the trials identified in the systematic literature review for the treatment of severe CPP by PBS-listed biologics is presented in Table 2.

Table 2: Trials investigating the use of PBS-listed biologics for the treatment of severe CPP: characteristics

	Number of RCTs	Previously seen by PBAC	Double-blind	Placebo-controlled	PI recommended dose	Includes another PBS-listed biologic	Randomised time horizon
Adalimumab	7	4	6	6	7	0	12-16 weeks
Efalizumab	5	5	5	5	5	0	12 weeks
Etanercept	11	3	11	9	6	0	12-24 weeks
Infliximab	8	3	6	6	8	1	10-24 weeks
Ixekizumab	3	3	3	3	3	2	12 weeks
Secukinumab	6	4	6	4	6	2	12-16 weeks
Ustekinumab ^a	8	3	8	6	8	2	12-16 weeks

CPP = chronic plaque psoriasis; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; RCT = randomised controlled trial

^a Included 1 trial which was also included in the analysis of secukinumab for the treatment of CPP

The majority of the included trials were double-blinded (44/48; 92%) and/or placebo-controlled (38/48; 80%). Etanercept was identified as a comparator in trials for infliximab (1 trial), ixekizumab (2 trials), secukinumab (1 trial) and ustekinumab (1 trial) and these trials, plus the CLEAR trial which compared secukinumab and ustekinumab, are analysed in each section relating to the primary biologic and in Section 2.3.8: Direct comparisons of PBS-listed biologics.

The majority of the identified trials included at least one arm which utilised the approved Australian Product Information recommended dosing regimen.

The time horizons for the randomised periods of the trials varied from ten to 24 weeks. Twelve weeks was the most common time horizon, and available results for each biologic at this time point are used in the network meta-analyses.

2.2.5 Baseline characteristics

In addition to demographic characteristics, such as age, sex, race, weight, and disease duration, the following baseline characteristics, which are typical of severe CPP, are presented:

- Proportion of body surface area (BSA) affected –
 - determination of the area affected by psoriasis in relation to the whole body surface area. (2)
- Psoriasis Area and Severity Index (PASI) score –
 - evaluates lesions by their characteristics of erythema, induration and scaling, as well as by the surface area affected (2, 3);
 - score ranges from 0 to 72, with higher scores indicating more severe disease;
 - in the majority of the identified trials a PASI of < 10 represents mild disease and a PASI of ≥ represents moderate-to-severe psoriasis.
- Dermatology Life Quality Index (DLQI) score –
 - assesses the impact of psoriasis on the quality of life of the patient (2, 3);

- score ranges from 0 to 30, with higher scores indicating a worse quality of life;
- a DLQI score of ≥ 10 indicates a significant impact on quality of life. (2, 3)

Table 3 provides a summary of the baseline characteristics for patients in the identified trials for each PBS-listed biologic. Only arms receiving approved Product Information doses, commonly used doses or placebo were included.

Table 3: Trials investigating the use of PBS-listed biologics for the treatment of severe CPP: baseline patient characteristics^a

	Adalimumab	Efalizumab	Etanercept	Infliximab	Ixekizumab	Secukinumab	Ustekinumab
N, total	2,419	2,721	4,073	1,956	2,701	2,871	5,255
Mean Age, years	44.1	45.1	45.1	43.9	45.6	45.0	44.8
Male, %	68%	67%	66%	68%	68%	70%	70%
Caucasian, %	72%	91%	84%	82%	93%	76%	81%
Mean? Weight, kg	86	82	90	86	91	86	89
DoD, years	18	19	19	18	19	17	19
BSA, %	30%	30%	28%	31%	27%	33%	28%
Mean? Median PASI score	20.7	20.4	19.1	21.6	20.2	22.5	20.3
DLQI score	12.0	12.0	12.4	13.2	12.4	-	12.4

BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; DoD = duration of disease; PASI = Psoriasis Area and Severity Index

^a Calculations included means and medians

The results of 21,996 patients were included in this analysis of PBS-listed biologics for the treatment of severe CPP. Overall, the total patient groups for each biologic were homogeneous in terms of baseline demographics and disease characteristics. Slight differences between the groups included fewer Caucasian patients in the adalimumab and secukinumab trials and marginally heavier patients in the ixekizumab trials.

The literature review also identified a number of trials involving the PBS-listed biologics which included specific CPP patient groups: children with severe CPP; mild-to-moderate CPP, patients with severe CPP and PsA; and patients with hand, face and/or feet involvement. The baseline characteristics for trial patients in these population groups are presented in Table 4.

Table 4: Trials investigating the use of PBS-listed biologics for the treatment of specific patient groups with CPP: baseline patient characteristics

	Children with severe CPP	Mild-to-moderate CPP	Severe CPP plus PsA	CPP with hand, face and/or feet involvement
N	398	60	1,310	301
Age, years	13.8	54.6	46.8	51.0
Male, %	50%	55%	58%	50%
Caucasian, %	81%	NR	90%	95%
Weight, kg	60	79	87	NR
DoD, years	6	21	7	9
BSA, %	25%	12%	NR	NR
PASI score	18.1	11.1	16.2	7.9
DLQI score	9.5	NR	NR	NR

BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; DoD = duration of disease; PASI = Psoriasis Area and Severity Index; PBS = Pharmaceutical Benefits Scheme; PsA = psoriatic arthritis; NR = not reported

The effectiveness and safety of the PBS-listed biologics in the specific patient groups listed above are considered in Sections 2.6 to 2.9 of this report.

2.2.6 Outcomes assessed

Efficacy and quality of life

The following clinical efficacy and quality of life outcomes are presented for each of the PBS-listed biologics in the treatment of severe CPP, when possible, from the identified publications:

- Proportion of patients achieving a reduction in PASI score of 50%, 75%, 90% and 100% (PASI 50, 75, 90, 100) from baseline;
- Mean change in DLQI score (a negative change represents an improvement in quality of life).

The PBAC has previously considered PASI 75 to be a clinically important outcome. If this level of response is achieved following induction with a biologic, continuing with the treatment is recommended.

The network meta-analysis presents a comparison of the proportion of patients achieving a PASI 75 response at 12 weeks for each biologic.

Safety

The safety of the PBS-listed biologics in the treatment of severe CPP was assessed in terms of the following outcomes:

- Adverse events;
- Treatment emergent adverse events;
- Serious adverse events;
- Deaths;

- Patients discontinuing the trial due to adverse events; and
- Specific adverse events: infections, serious infections, malignancy, skin cancer, cardiovascular disease, upper respiratory tract infection, nasopharyngitis, changes in liver enzymes, headache, pruritus and administration site disorders.

The network meta-analysis presents a comparison of the proportion of patients experiencing an adverse event at 12 weeks for each biologic.

2.2.7 Methods of analysis

Analysis of the trial data for the PBS-listed biologics for the treatment of severe CPP was performed in two ways:

- i) Quantitative analyses of efficacy, quality of life and safety outcomes for each PBS-listed biologic including:
 - a. Direct analyses and indirect comparisons of the trials identified for each biologic;
 - b. Direct analysis of trials identified which compared two PBS-listed biologics;
 - c. Comparison of new evidence with that which the PBAC had seen previously; and
- ii) Network meta-analyses comparing:
 - a. Efficacy: the proportion of patients achieving a PASI 75 response at 12 weeks; and
 - b. Safety: the risk of any adverse event at 12 weeks.

2.3 Efficacy and safety results for the PBS-listed biologics in the treatment of severe CPP

2.3.1 Adalimumab

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody which binds to human tumour necrosis factor in psoriasis plaques, reducing the inflammatory response. Adalimumab was listed on the PBS for the treatment of adults with severe CPP in June 2009 based on indirect analyses comparing adalimumab to infliximab and efalizumab with placebo as the common comparator. In March 2013 the PBAC was asked to extend the listing to include moderate CPP; this submission was rejected on the basis of highly uncertain cost-effectiveness.

Publication details

Seven adalimumab trials, with 12 related publications, which assessed the efficacy, safety and/or quality of life of adalimumab in the treatment of moderate-to-severe CPP were identified in the systematic literature review. The citation details are presented below in Table 5 with a brief description of the outcomes and whether the trial had been previously considered by the PBAC.

Table 5: Adalimumab trials: publication details

Trial ID	Citation	Description	Seen by PBAC?
Adalimumab versus placebo			
REVEAL (4-6)	Menter A, Tying SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled Phase III trial. <i>Journal of the American Academy of Dermatology</i> . 2008; 58(1): 106-115.	RCT: efficacy, safety	Yes
	Revicki DA, Willian MK, Menter A, et al. Impact of adalimumab treatment on patient-reported outcomes: Results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis. <i>Journal of Dermatological Treatment</i> . 2007; 18(6): 341-350.	RCT: QoL	Yes
	Gordon K, Papp K, Poulin Y, et al. Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: Results from and open-label extension study for patients from REVEAL. <i>Journal of the American Academy of Dermatology</i> . 2012; 66(2): 241-251.	OL extension: longer-term safety	No
Asahina (2010) (7, 8)	Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: Efficacy and safety results from a Phase II/III randomized controlled study. <i>Journal of Dermatology</i> . 2010; 37(4): 299-310.	RCT: efficacy, safety, QoL	Yes
	Asahina A, Ohtsuki M, Etoh T, et al. Adalimumab treatment optimization for psoriasis: results of a long-term Phase II/III Japanese study. <i>Journal of Dermatology</i> . 2015; 42(11): 1042-1052.	OL extension: longer-term safety	No
Gordon (2006) (10)	Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. <i>Journal of the American Academy of Dermatology</i> . 2006; 55(4): 598-606.	RCT: efficacy, safety; OL extension: longer-term efficacy and safety	No
	Shikiar R, Heffernan M, Langley RG, et al. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a Phase II randomized controlled trial. <i>Journal of Dermatological Treatment</i> . 2007; 18(1): 25-31.	RCT: QoL	Yes
Cai (2017) (9)	Cai L, Gu J, Zheng J, Zheng M, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a Phase 3, randomized, placebo-controlled, double-blind study. <i>Journal of the European Academy of Dermatology and Venereology</i> . 2017; 31(1): 89-95.	RCT: efficacy, safety, QoL	No
Adalimumab versus methotrexate versus placebo			
CHAMPION (11, 12)	Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs, methotrexate vs. placebo in patients with psoriasis. <i>British Journal of Dermatology</i> . 2008; 158(3): 558-566.	RCT: efficacy, safety	Yes

Trial ID	Citation	Description	Seen by PBAC?
	Revicki D, Willian MK, Saurat JH, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. <i>British Journal of Dermatology</i> . 2008; 158(3): 549-557.	RCT: QoL	Yes
Adalimumab versus guselkumab versus placebo			
Gordon (2015) (13)	Gordon KB, Duffin KC, Bissonnette R, et al. A Phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. <i>New England Journal of Medicine</i> . 2015; 373(2): 136-144.	RCT: efficacy, safety, QoL; OL extension: longer term safety	No
Biosimilar trial			
Papp (2016) (15)	Papp K, Bachelez H, Costanzo A, et al. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: a randomized, double-blind, multicenter, Phase III study. <i>Journal of the American Academy of Dermatology</i> . 2016; 76(6): 1093-1102.	RCT: efficacy, safety; OL extension: longer-term safety	No

OL = open-label; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial; Shaded = previously considered by the PBAC

Longer-term safety data from the open-label extension studies of the REVEAL and Asahina (2010) trials are presented in Section 2.5.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the adalimumab trials are presented in Table 62, Appendix B.

Overall, the inclusion criteria for the identified adalimumab trials were very similar in terms of including adults who had moderate-to-severe CPP for at least six months and stable for at least two months. Five of the trials (REVEAL, Asahina 2010, CHAMPION, Gordon 2015, and Papp 2016) required patients to have a BSA affected of 10% or greater and a baseline PASI score of either 10 and above or 12 and above. The REVEAL, Gordon (2015) and Papp (2016) trials also required a Physician's Global Assessment (PGA) score of 3 or above. Cai (2017) did not specify the severity of the CPP beyond stating it had to be moderate-to-severe and Gordon (2006) only required a body surface area affected of 5% or greater.

In terms of prior therapies, the criteria differed between trials. CHAMPION required patients to be candidates for systemic or phototherapy; whereas Cai (2017) and Papp (2016) required patients to have been intolerant or contraindicated to one or more conventional systemic therapies. In general, prior exposure to another biologic resulted in exclusion from the trial.

The exclusion criteria also varied between the trials; however, patients were most often excluded if they were suffering from latent tuberculosis, another active skin disease or were immunocompromised.

Baseline characteristics

The within trial randomisation appeared to be successful in terms of patient demographics and disease characteristics, as summarised in Table 6. Characteristics for patients in arms receiving the approved Australian Product Information dose of adalimumab or placebo are presented.

Between trials, the baseline demographics and disease characteristics for patients from REVEAL, CHAMPION, Gordon (2015) and Papp (2016) were broadly homogeneous. Patients in these trials were predominantly Caucasian. Patients in the Gordon (2006) trial reported lower baseline PASI scores; Gordon (2006) did not include a minimum PASI score as an inclusion criteria.

Asahina (2010) and Cai (2017) both had trial populations consisting of only Asian patients. The patients in these two trials were more often male, had a lower body weight, a shorter duration of disease, and a lower DLQI score; however, patients appeared to have more severe disease, with a higher mean BSA affected and higher baseline PASI scores.

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Table 6: Adalimumab trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Adalimumab versus placebo										
REVEAL	Ada ¹	814	44.1 (13.2)	67%	C: 91%	92 (23)	18 (12)	26% (16)	19.0 (7.1)	11.4 (6.6)
	Pbo	398	45.4 (13.4)	65%	C: 90%	94 (23)	18 (12)	26% (15)	18.8 (7.1)	11.4 (7.0)
Asahina (2010)	Ada ¹	43	44.2 (14.3)	81%	A: 100%	67 (10)	14 (7)	48% (20)	30.2 (10.9)	8.5 (NR)
	Pbo	46	43.9 (10.8)	89%	A: 100%	71 (15)	16 (9)	47% (20)	29.1 (11.8)	8.4 (NR)
Gordon (2006)	Ada ¹	45	46 (NR)	71%	C: 89%	93 (NR)	21 (NR)	29% (NR)	16.7 (NR)	13.3 (NR)
	Pbo	52	43 (NR)	65%	C: 92%	94 (NR)	19 (NR)	28% (NR)	16.0 (NR)	12.2 (NR)
CHAMPION	Ada ¹	108	42.9 (12.6)	65%	C: 95%	82 (20)	18 (10)	34% (20)	20.2 (7.5)	11.8 (6.6)
	Pbo	53	40.7 (11.4)	66%	C: 93%	83 (20)	19 (9)	28% (16)	19.2 (6.9)	11.7 (7.0)
Cai (2017)	Ada ¹	338	43.1 (11.9)	75%	A: 100%	70 (12)	15 (10)	43% (22)	28.2 (12.0)	14.7 (7.1)
	Pbo	87	43.8 (12.5)	67%	A: 100%	67 (11)	16 (10)	39% (23)	25.6 (11.0)	13.4 (7.1)
Gordon (2015)	Ada ¹	43	50.0 (NR)	70%	C: 91%	92 (20)	19 (13)	27% (17)	20.2 (7.6)	NR
	Pbo	42	46.5 (NR)	67%	C: 93%	94 (22)	18 (13)	28% (19)	21.8 (10.0)	NR
Biosimilar trial										
Papp (2016)	Ada ¹	175	41 (33-56)	66%	C: 90%	NR	18 (10-28)	23% (15-40)	18.3 (14.4-24.7)	NR
	ABP 501 ¹	175	46 (35-54)	64%	C: 95%	NR	19 (11-27)	20% (15-32)	17.1 (13.8-22.7)	NR
AVERAGE OF ALL TRIALS^a										
N = 2,419	NR	NR	44.1	68%	C: 72%	86	18	30%	20.7	12.0

A = Asian; ABP 501 = adalimumab biosimilar; Ada = adalimumab; BSA = body surface area; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; IQR = interquartile range; NR = not reported; PASI = Psoriasis Area and Severity Index; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; *Italics = median (IQR)*; Shaded = previously considered by the PBAC

^a Arms presented above only

¹ Adalimumab 80 mg SC Week 0; 40 mg every other week from Week 1 or 2 (PI recommended dose)

The PBS criteria for initial treatment with adalimumab requires patients to have severe CPP, defined as a PASI score of greater than 15. When PASI inclusion was stipulated in the trials, inclusion required a PASI greater than 10 or 12. In general, patients treated in the adalimumab trials appeared to have severe CPP, with the average baseline PASI score in each of the identified trials exceeding 15. This situation was previously accepted by the PBAC when considering adalimumab for the treatment of severe CPP. Overall, the average adalimumab trial patient had 30% of their BSA affected and a baseline PASI score of 20.7. Patients were most commonly male, approximately 44.1 years old and had been suffering from psoriasis for an average of 18 years.

Treatment details

Table 63, Appendix B summarises the treatment regimens used in each trial and the length of the placebo- or comparator-controlled period.

All of the trials utilised in this review had a dosing regimen for adalimumab that is recommended in the approved Australian Product Information (i.e. 80 mg loading dose in Week 0, followed by 40 mg every other week from Week 1 (or Week 2)) in at least one treatment arm.

All trials had a placebo- and/or comparator-controlled period of 16 weeks, except Cai (2017) and Gordon (2006), which each had a placebo-controlled period of 12 weeks. Papp (2016) was the only non-placebo-controlled trial. It assessed the comparability of the originator brand of adalimumab with a biosimilar version.

Efficacy

Table 7 presents a summary of the trials included in the review of adalimumab and a comparison of those previously considered by the PBAC and those that were newly identified in the systematic literature review.

When compared, the trials previously considered by the PBAC were all randomised, double-blind, placebo-controlled and multi-centre. REVEAL and Gordon (2006) had an unclear risk of bias as blinding of outcome assessors was not described. Asahina (2010) did not describe the method of randomisation generation and allocation concealment or if outcome assessors were blinded. All four trials were funded by a pharmaceutical company and therefore may have had a high risk of bias, if this was taken into consideration. Gordon (2006) provided quality of life data for the July 2008 PBAC submission; this trial accepted patients with less severe CPP (BSA affected greater than 5%). Patients in the Asahina (2010) trial had more severe disease at baseline.

Of the trial identified in the systematic literature review, all were randomised and multi-centre. The adalimumab arm of Gordon (2015) was not blinded, resulting in a high risk of bias. Cai (2017) had an unclear risk of bias as the method of randomisation generation and allocation concealment and if outcome assessors were blinded was not described. Again, all trials were funded by a pharmaceutical company. Patients in the Cai (2017) had more severe disease at baseline.

Table 7: Adalimumab trials: comparison of trial characteristics

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	Outcomes	Other details
Adalimumab versus placebo								
REVEAL	Yes: Jul 2008	1,212	R, DB, PC, MC	16 weeks (52 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 16; Safety; QoL	-
Gordon (2006)	Yes: Jul 2008, QoL data	147	R, DB, PC, MC	12 weeks (60 weeks)	Unclear (High ^a)	≥ 5% BSA	% PASI 75 at Week 12; Safety; QoL	Less severe disease (PASI < 17); outcomes at 12 weeks
Asahina (2010)	Yes: Mar 2013	169	R, DB, PC, MC	16 weeks (24 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 16; Safety; QoL	Japanese patients only; more severe disease (BSA > 45%; PASI > 29)
CHAMPION	Yes: Mar 2013	271	R, DB, PC, MC	16 weeks	Low (High ^a)	≥ 10% BSA ≥ 10 PASI	% PASI 75 at Week 16; Safety; QoL	Adalimumab versus methotrexate
Cai (2017)	No	425	R, DB, PC, MC	12 weeks (24 weeks)	Unclear (High ^a)	Moderate to severe CPP	% PASI 75 at Week 12; Safety; QoL	Chinese patients only; more severe disease (BSA > 39%; PASI > 25); outcomes at 12 weeks
Gordon (2015)	No	293	R, PC, MC	16 weeks (40 weeks)	High (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 16; Safety; QoL	Adalimumab arm was not blinded
Biosimilar trial								
Papp (2016)	No	114	R, DB, MC	16 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 16	-

BSA = body surface area; CPP = chronic plaque psoriasis; DB = double blind; MC = multi-centre; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; PGA = Physicians Global Assessment; QoL = quality of life; R = randomised; Shaded = previously considered by the PBAC

^a Trial was funded by a pharmaceutical company, therefore risk of bias could be considered high

Overall, trials previously considered by the PBAC and those identified in the systematic literature review were similar in terms of design (with the exception of Gordon 2015), duration, risk of bias (with the exception of Gordon 2015), patient populations and outcomes.

Table 8 presents the key efficacy outcomes – the proportion of patients achieving a PASI 75 response and the mean change in DLQI scores – for patients who received the Product Information recommended dose of adalimumab or placebo. It also provides a comparison of results between trials considered by the PBAC previously with trials which were newly

identified in the systematic literature review. Overall, the efficacy of adalimumab in the newly identified trials was consistent with that considered previously.

In the large REVEAL trial, which was considered by the PBAC in July 2008, 71% of patients achieved a PASI 75 response when receiving the recommended dose of adalimumab at 16 weeks compared to 7% of placebo patients. This result was supported by the smaller Asahina (2010) and CHAMPION trials, which were considered by the PBAC in March 2013. Gordon (2006) had a lower rate of response.

The newly identified placebo-controlled trials, Cai (2017) and Gordon (2015), presented similar results with up to 78% of adalimumab patients and up to 12% of placebo patients achieving a PASI 75 response. The results from the Papp (2016) biosimilar trial reported similar proportions of patients achieving PASI 75 responses.

Table 8: Adalimumab trials: efficacy results – proportion of patients achieving a PASI 75 response and mean change in DLQI scores

Trial	Time horizon	PASI 75; n/N (%)		Δ DLQI; mean (SD)	
		Adalimumab ¹	Placebo	Adalimumab ¹	Placebo
Adalimumab versus placebo					
REVEAL	16 weeks	NR/814 (71%)	NR/398 (7%)	-8.2 (NR)	-1.7 (NR)
Asahina (2010)	16 weeks	27/43 (63%)	2/46 (4%)	-5.1 (5.7)	1.0 (7.0)
Gordon (2006)	12 weeks	NR/45 (53%)	NR/52 (4%)	-10.8 (-13.1, -8.5)	-1.3 (-3.3, 0.7)
CHAMPION	16 weeks	NR/108 (80%)	NR/53 (19%)	-9.1 (-10.4, -7.8)	-3.4 (-5.2, -1.6)
Cai (2017)	12 weeks	NR/338 (78%)	NR/87 (12%)	-9.1 (NR)	-4.2 (NR)
Gordon (2015)	16 weeks	30/48 (70%)	2/42 (5%)	-10.1 (9.0)	-2.3 (6.8)
Biosimilar trial			ABP 501¹		
Papp (2016)	16 weeks	NR/175 (83%)	NR/175 (74%)	NR	NR

ABP 501 = adalimumab biosimilar; DLQI = Dermatology Life Quality Index; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; *Italics = (95% confidence interval)*; Shaded = previously considered by the PBAC

¹ Adalimumab 80 mg SC Week 0; 40 mg every other week from Week 1 or 2 (PI recommended dose)

In terms of quality of life, adalimumab consistently resulted in reductions/improvements in mean DLQI scores at 12 to 16 weeks. The mean change in DLQI scores in the adalimumab arms of the REVEAL, Gordon (2006) and CHAMPION trials, -8.2, -10.8 and -9.1 respectively, were supported by the results from Cai (2017) and Gordon (2015), -9.1 and -10.1 respectively.

Overall, the results of the trials identified in the systematic literature review supported those previously considered by the PBAC.

Table 64 in Appendix B compares the efficacy results of the adalimumab trials in terms of the proportions of patients achieving PASI 50, 75, 90 and 100 responses.

In the largest adalimumab RCT, the REVEAL trial, the proportions of patients achieving a PASI 75, 90 and 100 response at 16 weeks were 71%, 45% and 20% with adalimumab

treatment and 7%, 2% and 1% with placebo. Adalimumab treatment was given at the recommended Product Information dose in this trial. The proportions of patients achieving these response rates in the other, smaller placebo-controlled trials were comparable to REVEAL.

Safety

A summary of the adverse events reported in each of the adalimumab trials is presented in Table 9.

Of the 12 and 16 week trials, the CHAMPION trial reported the highest incidence of adverse events for both the recommended dose of adalimumab (74%) and placebo (79%). In these trials, the proportions of patients who experienced a serious adverse event ($\leq 2\%$) and an adverse event resulting in discontinuation from the trial ($\leq 7\%$) was consistently low. No deaths were reported in any of the trials.

The Asahina (2010) trial reported adverse events at 24 weeks. The incidence of any adverse event in adalimumab patients utilising the recommended dose was 91% and 89% in the placebo arm. The rates of adverse events resulting in discontinuation from the trial were also slightly higher in this trial ($\leq 12\%$).

Table 9: Adalimumab trials: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Adalimumab versus placebo							
Cai (2017)	12 weeks	Ada ¹	338	158 (47%)	4 (1%)	0	2 (< 1%)
		Pbo	87	33 (38%)	3 (3%)	0	0
Gordon (2006)	12 weeks	Ada ¹	45	28 (62%)	1 (2%)	NR	2 (4%)
		Pbo	52	35 (67%)	0	NR	1 (2%)
REVEAL	16 weeks	Ada ¹	814	506 (62%)	15 (2%)	0	14 (2%)
		Pbo	398	221 (56%)	7 (2%)	0	8 (2%)
CHAMPION	16 weeks	Ada ¹	108	79 (74%)	2 (2%)	0	1 (1%)
		Pbo	53	42 (79%)	1 (2%)	0	1 (2%)
Gordon (2015)	16 weeks	Ada ¹	43	24 (56%)	1 (2%)	NR	3 (7%)
		Pbo	42	22 (52%)	1 (2%)	NR	3 (7%)
Asahina (2010)	24 weeks	Ada ¹	43	39 (91%)	3 (7%)	NR	5 (12%)
		Pbo	46	41 (89%)	2 (4%)	NR	5 (11%)
Biosimilar trial							
Papp (2016)	16 weeks	Ada ¹	175	110 (64%)	5 (3%)	0	5 (3%)
		ABP 501 ¹	175	117 (67%)	6 (3%)	0	7 (4%)

ABP 501 = adalimumab biosimilar; Ada = adalimumab; AE = adverse event; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SAE = serious adverse event; SC = subcutaneous; Shaded = previously considered by the PBAC

¹ Adalimumab 80 mg SC Week 0; 40 mg every other week from Week 1 or 2 (PI recommended dose)

Table 65 in Appendix B provides a summary of specific adverse events of interest including infection, serious infection, malignancy, skin cancer, cardiovascular disease, upper respiratory tract infection, liver enzyme changes, headache, pruritus and administration site disorders.

Infection was the most commonly reported adverse event, with up to 55% of adalimumab and 50% of placebo patients affected. The rate of serious infection, when reported, did not exceed 2% of patients and the incidence of malignancy, skin cancer and cardiovascular disease was equal to or less than 1% in all of the trials. Nasopharyngitis, headache and administration site disorders were other common adverse events for both adalimumab and placebo patients.

Only the REVEAL trial reported cardiovascular disease as an adverse event. The incidence was less than 1% in the adalimumab arm (n = 814) and nil in the placebo arm (n = 398).

2.3.2 Efalizumab

Efalizumab was the first biologic to be recommended for listing on the PBS for the treatment of severe CPP in November 2005. It had been considered twice previously, but rejected because of unacceptable cost-effectiveness. The submissions presented a comparison with placebo and presented the proportion of patients achieving a PASI 50 response at 12 and 24 weeks. Due to a risk of progressive multifocal leukoencephalopathy, efalizumab was withdrawn from the market and removed from the PBS in 2009.

Trials relating to the use of efalizumab for the treatment of CPP were identified and included in the network meta-analyses as efalizumab was a comparator in a number of the submissions considered previously by the PBAC.

The publication details, inclusion and exclusion criteria, baseline characteristics, treatment details, efficacy results and summary of adverse events of the identified efalizumab trials are presented in Table 66 to Table 71, Appendix B.

The PBAC had previously considered all of the five identified trials (with six publications).

The inclusion criteria for the efalizumab trials were very similar in terms of including adults of up to 70 to 75 years who had CPP for at least six months and that had been stable for at least three months. All of the trials required patients to have a BSA affected of 10% or greater and a baseline PASI score of 12 or above.

In terms of prior therapies, the criteria differed between trials. The Gordon (2003), Leonardi (2005) and Papp (2006) trials required patients to be candidates for systemic therapy, whereas CLEAR required patients to be unresponsive to at least two prior treatments. Patients were excluded from the Lebwohl (2003) and Papp (2006) trials if they had received prior efalizumab.

The exclusion criteria varied between the trials; however, most trials excluded patients if they were suffering from another active skin disease or were immunocompromised.

When comparable, the within trial randomisation appeared to be successful. The only exception was in terms of BSA affected in the CLEAR trial, with placebo patients having a

lower mean BSA affected (26%) compared to those who received efalizumab (37%). Between the efalizumab trials, the patients were highly homogeneous at baseline in terms of age, gender, duration of disease, BSA affected and PASI score. Race, weight and DLQI scores were rarely reported.

All five of the efalizumab trails were placebo-controlled (CLEAR, Gordon 2003, Lebwohl 2003, Leonardi 2005 and Papp 2006), and each of these included an arm which utilised the recommended dosing regimen (before it was deregistered) of 0.7 mg/kg in Week 0, then 1 mg/kg weekly from Week 1. All of the trials had a 12 week time horizon.

2.3.3 Etanercept

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein which was listed on the PBS for the treatment of severe CPP in August 2006 based on comparisons with placebo.

Publication details

For the treatment of CPP, 11 etanercept trials and 19 related publications for etanercept were identified. The citation details, a brief description of the publication, the outcomes, and whether the trial has been previously considered by the PBAC are presented below in Table 10.

Table 10: Etanercept trials: publication details

Trial ID	Citation	Description	Seen by PBAC?
Etanercept versus placebo			
Leonardi (2003) (16-19)	Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. <i>New England Journal of Medicine</i> . 2003; 349(21): 2014-2022.	RCT: efficacy, safety	Yes
	Feldman SR, Kimball AB, Krueger GG, et al. Etanercept improves the health-related quality of life of patients with psoriasis: results of a Phase III randomized clinical trial. <i>Journal of the American Academy of Dermatology</i> . 2005; 53(5): 887-889.	RCT: QoL	Yes
	Gordon KB, Gottlieb AB, Leonardi CL, et al. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. <i>Journal of Dermatological Treatment</i> . 2006; 17(1): 9-17.	OL extension: longer-term efficacy, safety	Yes
	Krueger GG, Elewski B, Papp K, et al. Patients with psoriasis respond to continuous open-label etanercept treatment after initial incomplete response in a randomized, placebo-controlled trial. <i>Journal of the American Academy of Dermatology</i> . 2006; 54(3 Suppl 2): S112-119.	OL extension: longer-term efficacy	Yes
Gottlieb (2003)(20)	Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. <i>Archives of Dermatology</i> . 2003; 139(12): 1627-1632.	RCT: efficacy, safety, QoL	Yes
Papp (2005) (21, 22)	Papp KA, Tyring S, Lahfa M, et al. A global Phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. <i>British Journal of Dermatology</i> . 2005; 152(6): 1304-1312.	RCT: efficacy, safety	Yes

Trial ID	Citation	Description	Seen by PBAC?
	Krueger GG, Langley RG, Finlay AY, et al. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized Phase III trial. <i>British Journal of Dermatology</i> . 2005; 153(6): 1192-1199.	RCT: QoL	No
van de Kerkhof (2008) (23, 24)	van de Kerkhof PC, Segaert S, Lahfa M, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. <i>British Journal of Dermatology</i> . 2008;159(5):1177-85.	RCT: efficacy, safety	No
	Reich K, Segaert S, Van de Kerkhof P, et al. Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis. <i>Dermatology</i> . 2009; 219(3): 239-249.	RCT: QoL	No
Tyring (2006) (25, 26)	Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised Phase III trial. <i>Lancet</i> . 2006; 367(9504): 29-35.	RCT: efficacy, safety, QoL	No
	Tyring S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. <i>Archives of Dermatology</i> . 2007; 143(6): 719-726.	OL extension: longer-term efficacy, safety	No
Etanercept versus tofacitinib versus placebo			
OPT COMPARE (27, 28)	Bachelez H, van de Kerkhof PC, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a Phase 3 randomised non-inferiority trial. <i>Lancet</i> . 2015; 386 (9993): 552-561.	RCT: efficacy, safety	No
	Valenzuela F, Paul C, Mallbris L, et al. Tofacitinib versus etanercept or placebo in patients with moderate to severe chronic plaque psoriasis: patient-reported outcomes from a Phase 3 study. <i>Journal of the European Academy of Dermatology and Venereology</i> . 2016; 30(10): 1753-1759.	RCT: QoL	No
Etanercept versus briakinumab versus placebo			
M10-114 (29)	Gottlieb AB, Leonardi C, Kerdel F, et al. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. <i>British Journal of Dermatology</i> . 2011; 165(3): 652-660.	RCT: efficacy, safety	No
M10-315 (30)	Strober BE, Crowley JJ, Yamauchi PS, et al. Efficacy and safety results from a Phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. <i>British Journal of Dermatology</i> . 2011; 165(3): 661-668.	RCT: efficacy, safety	No
Etanercept versus etanercept			
PRESTA (31, 32)	Sterry W, Ortonne JP, Kirkham B, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. <i>British Medical Journal</i> . 2010; 340: c147.	RCT: efficacy, safety	No
	Gniadecki R, Robertson D, Molta CT, et al. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. <i>Journal of the European Academy of Dermatology and Venereology</i> . 2010; 26(11): 1436-1443.	RCT: QoL	No

Trial ID	Citation	Description	Seen by PBAC?
PRISTINE (33)	Strohal R, Puig L, Chouela E, et al. The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). <i>Journal of Dermatological Treatment</i> . 2013; 24(3): 169-178.	RCT: efficacy, safety	No
Etanercept versus methotrexate			
Gottlieb (2012) (34)	Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. <i>British Journal of Dermatology</i> . 2012; 167(3): 649-657.	RCT: efficacy, safety	No

OL = open label; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial; Shaded = previously considered by the PBAC

The PRESTA trial is also included in the analysis of PBS-listed biologics in the treatment of patients with severe CPP and PsA.

As etanercept was one of the earlier biologics in treatment for severe psoriasis, it was used in the comparator arm of the newer biologics. These studies are explored in the individual biologics sections below and in Section 2.3.8. The citation details, a brief description of the publication, the outcomes, and whether the trial has been previously considered by the PBAC are presented below in Table 11.

Table 11: Etanercept trials with other PBS listed biologics: publication details

Trial ID	Citation	Description	Seen by PBAC?
Infliximab versus etanercept			
PIECE (47)	Vries A, Thio H, Kort W, et al. A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. <i>British Journal of Dermatology</i> . 2017; 176(3): 624-633.	RCT: efficacy, safety	No
Ixekizumab versus placebo			
UNCOVER 1 (50)	Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. <i>New England Journal of Medicine</i> . 2016; 375(4): 345-356.	RCT: efficacy, safety	Yes
Ixekizumab versus etanercept versus placebo			
UNCOVER 2, 3 (51)	Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two Phase 3 randomised trials. <i>Lancet</i> . 2015; 386(9993): 541-551.	RCT: efficacy, safety, QoL	Yes
Secukinumab versus etanercept versus placebo			
FIXTURE/ERASURE 2 (58)	Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis-results of two Phase 3 trials. <i>New England Journal of Medicine</i> . 2014; 371(4): 326-338.	RCT: efficacy, safety, QoL OL extension: longer-term efficacy	Yes
Ustekinumab versus etanercept			
ACCEPT (72)	Griffiths CEM, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. <i>New England Journal of Medicine</i> . 2010; 362 (2): 118-128.	RCT: efficacy, safety	Yes

OL = open label; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial; Shaded = previously considered by the PBAC

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the identified etanercept trials are presented in Table 72, Appendix B.

The inclusion criteria for the identified etanercept trials were very similar in terms of including adults who had active, but clinically stable plaque psoriasis for at least six months. Nine of the trials (Leonardi 2003, Papp 2005, van de Kerkhof 2008, Tying 2006, OPT COMPARE, M10-114, M10-315, PRISTINE and Gottlieb 2012) required patients to have a BSA affected of 10% or greater and a baseline PASI score of either 10 and above or 12 and above. The OPT COMPARE, M10-114 and M10-315 trials also required a PGA score of 3 or above. Gottlieb (2003) and PRESTA required patients to have a BSA affected of 10% or more, but no requirement regarding PASI score.

Leonardi (2003), Gottlieb (2003), Papp (2005), van de Kerkhof (2008), Tying (2006), OPT COMPARE, PRISTINE and Gottlieb (2012) all required patients to have either been candidates for or had previously received systemic or phototherapy. In general, prior

exposure to etanercept or another tumour necrosis factor resulted in exclusion from the trial.

The exclusion criteria varied between the trials; however, patients were excluded if they were suffering from latent tuberculosis, another active skin disease or were immunocompromised.

Baseline characteristics

Within each etanercept trial, randomisation appeared to be successful in terms of baseline characteristics, as summarised in Table 12. Between the trials, baseline demographics and disease characteristics were broadly homogeneous. Baseline characteristics were presented for relevant treatment arms only.

Table 12: Etanercept trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Etanercept versus placebo										
Leonardi (2003)	Etan ^{1*}	162	45.4 (1.0)	67%	C: 67%	NR	19 (1)	29% (2)	18.5 (0.7)	12.7 (0.5)
	Etan ²	164	44.8 (0.8)	65%	C: 65%	NR	19 (1)	30% (2)	18.4 (0.7)	11.3 (0.5)
	Pbo	166	45.6 (1.0)	63%	C: 63%	NR	18 (1)	29% (1)	18.3 (0.6)	12.8 (0.6)
Gottlieb (2003)	Etan ^{1*}	57	48.2 (25-72)	58%	C: 89%	92 (NR)	23 (2)	30% (2)	17.8 (1.1)	NR
	Pbo	55	46.5 (18-77)	67%	C: 95%	91 (NR)	20 (2)	34% (3)	19.5 (1.3)	NR
Papp (2005)	Etan ^{1*}	196	45.4 (12.0)	65%	C: 92%	NR	22 (NR)	29% (18)	19.1 (8.2)	11.5 (7.2)
	Etan ²	194	45.2 (12.4)	67%	C: 89%	NR	20 (NR)	29% (17)	19.5 (8.8)	11.4 (6.5)
	Pbo	193	44.8 (11.3)	64%	C: 91%	NR	19 (NR)	27% (17)	18.6 (8.6)	12.2 (6.8)
van de Kerkhof (2008)	Etan ^{3*}	96	45.9 (12.8)	62%	NR	83 (16)	19 (11)	27% (15)	21.4 (9.3)	13.2 (NR)
	Pbo	46	43.6 (12.6)	54%	NR	79 (20)	17 (8)	30% (18)	21.0 (8.7)	13.6 (NR)
Tyring (2006)	Etan ²	311	45.8 (NR)	65%	C: 90%	93 (NR)	20 (NR)	27% (18)	18.3 (7.6)	12.1 (6.7)
	Pbo	307	45.5 (NR)	70%	C: 88%	91 (NR)	20 (NR)	27% (17)	18.1 (7.4)	12.5 (6.7)
OPT COMPARE	Etan ²	335	42.0 (18-74)	70%	C: 87%	82 (48-144)	18 (1-62)	25% (10-93)	19.4 (12.0-63.6)	12.0 (0-30)
	Pbo	107	46.0 (21-81)	66%	C: 84%	80 (47-130)	17 (1-57)	26% (11-79)	19.5 (12.4-54.6)	11.5 (0-30)
M10-114	Etan ²	141	43.1 (12.5)	70%	C: 90%	95 (20)	NR	24% (15)	19.4 (8.0)	NR
	Pbo	68	44.0 (13.6)	69%	C: 96%	97(27)	NR	24% (16)	18.5 (6.9)	NR
M10-315	Etan ²	139	45.2 (14.8)	61%	C: 91%	97 (25)	15 (12)	25% (14)	18.5 (6.0)	NR
	Pbo	72	45.0 (13.9)	64%	C: 93%	93 (25)	16 (12)	22% (13)	18.3 (6.4)	NR
Etanercept versus etanercept										
PRESTA	Etan ^{3*}	373	46.9 (11.4)	62%	C: 90%	NR	19 (11)	30% (22)	19.0 (9.8)	12.3 (7.5)
	Etan ²	379	46.1 (11.4)	64%	C: 88%	NR	19 (12)	31% (22)	19.8 (10.7)	12.3 (7.5)

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
PRISTINE	Etan ^{3*}	137	43.9 (12.7)	74%	C: 63% A: 24%	87 (18)	17 (11)	33% (21)	20.9 (9.4)	15.0 (8.0)
	Etan ²	136	44.0 (12.7)	65%	C: 65% A: 23%	84 (19)	18 (10)	33% (19)	21.4 (9.4)	14.1 (7.3)
Etanercept versus etanercept plus methotrexate										
Gottlieb (2012)	Etan ²	239	45.2 (12.8)	70%	C:74% H: 16%	96 (25)	17 (13)	24% (14)	18.3 (6.6)	NR
AVERAGE ACROSS ALL TRIALS^a										
N = 4,073	NR	NR	45.1	66%	C: 84%	90	19	28%	19.1	12.4

A = Asian; BSA = body surface area; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; NR = not reported; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; SE = standard error; *Italics = (SE), (range) or median (range)*; Shaded = previously considered by the PBAC

^a Arms presented above only

^{1*} Etanercept 25 mg SC twice weekly (PI recommended dose)

² Etanercept 50 mg SC twice weekly

^{3*} Etanercept 50 mg SC once weekly (PI recommended dose)

The PBS criteria for initial treatment with etanercept requires patients to have severe CPP, defined by a PASI score of greater than 15. Although when stipulated, inclusion in the identified trials required a PASI score of 10 and above or 12 and above, the mean baseline PASI score was greater than 15 in each of the identified trials, suggesting that the trial patients had severe CPP. This situation was previously accepted by the PBAC when considering etanercept. Overall, the average etanercept trial patient had a BSA affected of 28%, a baseline PASI score of 19.1 and a baseline DLQI score of 12.4. In terms of patient characteristics, the average etanercept patient was 45.1 years old, male, Caucasian, and had been suffering from CPP for 19 years.

Treatment details

Table 73, Appendix B, summarises the treatment regimens utilised in the identified etanercept trials during the placebo- or comparator-controlled periods.

The approved Product Information recommended dose of etanercept for the treatment of CPP is 50 mg weekly (either as 25 mg twice weekly or 50 mg once weekly) via subcutaneous injection. This dosing regimen was utilised in the Leonardi (2003), Gottlieb (2003), Papp (2005), van de Kerkhof (2008), PRESTA and PRISTINE trials. The remaining trials did not utilise the recommended dose, with the majority instead utilising a 50 mg twice weekly regimen. It was noted that the PBS restriction for etanercept does not include dose restrictions. However, the PBS listings limit the maximum quantity and repeats that can be prescribed to allow enough supply for the 50 mg twice weekly regimen.

A number of the RCTs were not placebo-controlled. The PRESTA and PRISTINE trials compared etanercept dosing regimens. Gottlieb (2012) compared etanercept plus methotrexate with etanercept alone.

All of the trials provided results at 12 weeks.

Efficacy

Table 13 presents a summary of the trials included in the review of etanercept, and a comparison of those previously considered by the PBAC and those that were newly identified in the systematic literature review.

The trials previously considered by the PBAC were broadly similar; all were randomised, double-blind, placebo-controlled and multi-centre. Leonardi (2003) and Papp (2005) did not describe if outcome assessors were blinded, and all were funded by a pharmaceutical company. All trials required patients to have at least 10% of their body surface area affected, but Gottlieb (2003) did not require patients to have a minimum PASI score; Leonardi (2003) and Papp (2005) required a minimum score of 10.

Of the eight trials identified in the systematic literature review, all were randomised, double-blinded and multi-centred. The PRESTA, PRISTINE and Gottlieb (2012) trials were not placebo-controlled. All had a low to unclear risk of bias, with those with an unclear risk not describing the methods of randomisation and allocation concealment or whether outcomes assessors were blinded. All trials were funded by a pharmaceutical company, which might increase the risk of bias.

Although Trying (2006), OPT COMPARE, M10-114, M10-315, and Gottlieb (2012) did not present results for one of the approved etanercept dosing regimens, they were included in this analysis as 50 mg twice weekly appears to be a commonly utilised dose and the PBS restriction does not prevent its use.

Table 13: Etanercept trials: comparison of trial characteristics

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	Outcomes	Other details
Etanercept versus placebo								
Leonardi (2003)	Yes: Mar 2006	652	R, DB, PC, MC	12 weeks (24 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 10 PASI	% PASI 75 at Week 12; Safety; QoL	-
Gottlieb (2003)	Yes: Mar 2006	122	R, DB, PC, MC	24 weeks	Low (High ^a)	≥ 10% BSA	% PASI 75 at Week 12; Safety; QoL	-
Papp (2005)	Yes: Mar 2006	611	R, DB, PC, MC	12 weeks (24 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 10 PASI	% PASI 75 at Week 12; Safety; QoL	-
van de Kerkhof (2008)	No	142	R, DB, PC, MC	12 weeks (24 weeks)	Low (High ^a)	≥ 10% BSA ≥ 10 PASI	% PASI 75 at Week 12; Safety; QoL	-

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	Outcomes	Other details
Tyring (2006)	No	618	R, DB, PC, MC	12 weeks (96 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 10 PASI	% PASI 75 at Week 12; Safety; QoL	Non-PI dose of etanercept
OPT COMPARE	No	1,106	R, DB, PC, MC	12 weeks	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 12; Safety; QoL	Non-PI dose of etanercept; versus tofacitinib
M10-114	No	347	R, DB, PC, MC	12 weeks	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 12; Safety	Non-PI dose of etanercept; versus briakinumab
M10-315	No	139	R, DB, PC, MC	12 weeks	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 12; Safety	Non-PI dose of etanercept; versus briakinumab
Etanercept versus etanercept								
PRESTA	No	752	R, DB, MC	12 weeks (24 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 3 PGA	% PASI 75 at Week 12; Safety; QoL	No placebo arm
PRISTINE	No	273	R, DB, MC	12 weeks (24 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 10 PASI	% PASI 75 at Week 12; Safety	No placebo arm
Etanercept versus etanercept plus methotrexate								
Gottlieb (2012)	No	239	R, DB, MC	12 weeks (24 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 10 PASI	% PASI 75 at Week 12; Safety	Non-PI dose of etanercept; no placebo arm

BSA = body surface area; DB = double blind; MC = multi-centre; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; PGA = Physicians Global Assessment; QoL = quality of life; R = randomised; Shaded = previously considered by the PBAC

^a Trial was funded by a pharmaceutical company

Overall, the trials previously considered by the PBAC were comparable with those identified in the systematic literature review. All trials required patients to have at least 10% of their BSA affected, and the majority required a PASI score of 10 or 12 at entry. All trials were double-blinded for at least 12 weeks, and all reported efficacy and safety outcomes at this time.

Table 14 presents the key efficacy outcomes from the etanercept trials – the proportion of patients achieving a PASI 75 response and the mean change in DLQI scores. It also allows for a comparison of results from trials previously considered by the PBAC with results from trials newly identified in the systematic literature review. Overall, the efficacy of etanercept in the newly identified trials was consistent with that considered previously.

The Leonardi (2003), Gottlieb (2003) and Papp (2005) trials were considered by the PBAC in March 2006. These three trials included a comparison of the recommended dosage regimen, etanercept 25 mg twice weekly, with placebo at 12 weeks. Leonardi (2003) and

Papp (2005) also included a comparison with the commonly used dosage regimen, etanercept 50 mg twice weekly.

Of the newly identified evidence, van de Kerkhof (2008), PRESTA and PRISTINE considered the efficacy of the recommended dose, etanercept 50 mg once weekly, at 12 weeks.

At the recommended doses of etanercept, the newly identified evidence supported that previously considered by the PBAC. Efficacy results were very similar in terms of the proportion of patients achieving a PASI 75 response, regardless of whether patients received 25 mg twice weekly (Gottlieb 2003: 30%; Leonardi 2003 and Papp 2005: 34%) or 50 mg once weekly (van de Kerkhof 2008: 38%; PRESTA: 36%; and PRISTINE: 37%).

Both Leonardi (2003) and Papp (2005) reported that when given at 50 mg twice weekly, 49% of etanercept patients achieved a PASI 75 response at 12 weeks. This improved response, at the higher dose, was supported by the evidence identified in the systematic literature review.

DRAFT

Table 14: Etanercept trials: efficacy results – proportion of patients achieving a PASI 75 response and mean change in DLQI scores

Trial	Time horizon	PASI 75; n/N (%)				Δ DLQI; mean (SD)			
		Etan ¹	Etan ²	Etan ³	Pbo	Etan ¹	Etan ²	Etan ³	Pbo
Leonardi (2003)	12 weeks	55/162 (34%)	NR	81/164 (49%)	6/166 (4%)	NR6.5 (NR)	NR	-6.9 (NR)	-1.4 (NR)
Gottlieb (2003)	12 weeks	17/57 (30%)	NR	NR	1/55 (2%)	-64% (NR)	NR	NR	-7% (NR)
Papp (2005)	12 weeks	67/196 (34%)	NR	96/194 (49%)	6/193 (3%)	NR	NR	NR	NR
van de Kerkhof (2008)	12 weeks	NR	36/96 (38%)	NR	1/46 (2%)	NR	-7.4 (NR)	NR	-1.2 (NR)
Tyring (2006)	12 weeks	NR	NR	147/311 (47%)	15/307 (5%)	NR	NR	-8.4 (NR)	-2.8 (NR)
OPT COMPARE	12 weeks	NR	NR	197/335 (59%)	6/107 (6%)	NR	NR	-8.9 (NR)	-2.0 (NR)
M10-114	12 weeks	NR	NR	NR/141 (56%)	NR/68 (7%)	NR	NR	NR	NR
M10-315	12 weeks	NR	NR	NR/139 (40%)	NR/72 (7%)	NR	NR	NR	NR
Etanercept versus etanercept									
PRESTA	12 weeks	NR	NR/373 (36%)	NR/379 (55%)	NR	NR	-6.8 (NR)	-7.9 (NR)	NR
PRISTINE	12 weeks	NR	NR/137 (37%)	NR/136 (62%)	NR	NR	-8.1 (0.5)	-10.2 (0.5)	NR
Etanercept versus etanercept plus methotrexate									
Gottlieb (2012)	12 weeks	NR	NR	NR/239 (54%)	NR	NR	NR	NR	NR

DLQI = Dermatology Life Quality Index; Etan = etanercept; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SD = standard deviation; SE = standard error; *Italics = (SE)*; Shaded = previously considered by the PBAC

¹ Etanercept 25 mg SC twice weekly (PI recommended dose)

² Etanercept 50 mg SC once weekly (PI recommended dose)

³ Etanercept 50 mg SC twice weekly

In terms of quality of life, the evidence identified in the systematic literature review supported that previously considered by the PBAC. Etanercept, when given at the recommended dose, resulted in an improvement in mean DLQI scores of 6.5 to 8.1. When given at the higher dose of 50 mg twice weekly, the mean improvement in DLQI scores ranged from 6.5 (Leonardi 2003) to 10.2 (PRISTINE).

Table 74 in Appendix B compares the efficacy results across all of the etanercept trials in terms of the proportions of patients achieving PASI 50, 75, 90 and 100 responses.

PASI 50, 75 and 90 response rates following etanercept treatment for 12 weeks at the recommended Product Information dosages were very similar – on average, approximately

65% of patients achieved a PASI 50 response, 35% achieved a PASI 75 response and 12% a PASI 90 response.

When using the non-Product Information recommended dosing regimen of 50 mg twice weekly the proportion of patients achieving a PASI 75 and 90 response was improved to approximately 49% and 24% respectively.

Safety

A summary of the adverse events reported across the etanercept trials is presented in Table 15.

The identified trials reported adverse events at either 12 or 24 weeks. At 12 weeks an average of 50% to 60% of all etanercept and placebo had experienced an adverse event. Similar rates were reported at 24 weeks. The proportion patients who experienced a serious adverse event did not exceed 7% and no deaths were reported in any of the trials. The incidence of adverse events resulting in discontinuation from the trials was consistently low.

DRAFT

Table 15: Etanercept trials: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Etanercept versus placebo							
van de Kerkhof (2008)	12 weeks	Etan ^{1*}	96	NR	2 (2%)	0	NR
		Pbo	46	NR	6 (7%)	0	NR
Tyring (2006)	12 weeks	Etan ²	312	153 (49%)	6 (2%)	0	4 (1%)
		Pbo	306	137 (45%)	3 (1%)	0	5 (2%)
OPT COMPARE ^a	12 weeks	Etan ²	335	192 (57%)	7 (2%)	0	11 (3%)
		Pbo	107	55 (51%)	2 (2%)	0	4 (4%)
M10-114	12 weeks	Etan ²	141	76 (54%)	1 (< 1%)	0	4 (3%)
		Pbo	68	31 (46%)	1 (2%)	0	0
M10-315	12 weeks	Etan ²	139	69 (50%)	1 (< 1%)	0	4 (3%)
		Pbo	72	32 (44%)	2 (3%)	0	2 (3%)
Gottlieb (2003)	24 weeks	Etan ^{3*}	57	NR	2 (4%)	NR	2 (4%)
		Pbo	55	NR	3 (5%)	NR	6 (11%)
Etanercept versus etanercept							
PRESTA	24 weeks	Etan ^{1*}	373	190 (51%)	11 (3%)	0	NR
		Etan ²	379	213 (56%)	15 (4%)	0	NR
PRISTINE	24 weeks	Etan ^{1*}	137	88 (64%)	4 (3%)	0	3 (2%)
		Etan ²	136	94 (69%)	3 (2%)	0	6 (4%)
Etanercept versus etanercept plus methotrexate							
Gottlieb (2012)	24 weeks	Etan ²	239	143 (60%)	3 (1%)	0	NR

AE = adverse event; Etan = etanercept; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SAE = serious adverse event; SC = subcutaneous; Shaded = previously considered by the PBAC

^{1*} Etanercept 50 mg SC once weekly (PI recommended dose)

² Etanercept 50 mg SC twice weekly

^{3*} Etanercept 25 mg SC twice weekly (PI recommended dose)

The PRESTA and PRISTINE trials compared etanercept 50 mg once weekly with 50 mg twice weekly – the incidence of any adverse events and serious adverse events were highly comparable in both arms of both of these trials.

2.3.4 Infliximab

Infliximab is a chimeric human-murine monoclonal antibody that binds to human tumour necrosis factor-alpha. It was recommended by the PBAC in July 2006 and listed on the PBS in December 2007 for the treatment of severe CPP. The submission presented an indirect comparison with efalizumab, with placebo as the common comparator, for the proportion of patients achieving a PASI 75 response.

Publication details

For the treatment of CPP, eight infliximab trials, with 11 related publications were identified. The citation details, a brief description of the publication, the outcomes, and whether the trial has been previously considered by the PBAC are presented below in Table 16.

Table 16: Infliximab trials: publication details

Trial	Citation	Description	Seen by PBAC?
Infliximab versus placebo			
Chaudhari (2001) (37)	Chaudhari U, Romano P, Mulcahy LD, et al. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. <i>Lancet</i> . 2001; 357(9271): 1842-1847.	RCT: efficacy, safety	Yes
EXPRESS (38, 39)	Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a Phase III, multicentre, double-blind trial. <i>Lancet</i> . 2005; 366(9494): 1367-1374.	RCT: efficacy, safety; OL extension: longer-term efficacy	Yes
	Reich K, Nestle FO, Papp K, et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. <i>British Journal of Dermatology</i> . 2006; 154(6): 1161-1168.	RCT: QoL	No
Gottlieb (2004) (40, 41)	Gottlieb AB, Evans R, Li S, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. <i>Journal of the American Academy of Dermatology</i> . 2004; 51(4): 534-542.	RCT: efficacy, safety	No
	Feldman S, Gordon K, Bala M, et al. Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. <i>The British Journal of Dermatology</i> . 2005; 152(5): 954-960.	RCT: QoL	Yes
Menter (2007) (42)	Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. <i>Journal of the American Academy of Dermatology</i> . 2007; 56(1): 31.e1-15.	RCT: efficacy, safety, QoL; OL extension: longer-term efficacy	No
Torii (2010) (43)	Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. <i>Journal of Dermatological Science</i> . 2010; 59(1): 40-49.	RCT: efficacy, safety, QoL; OL extension: longer-term efficacy, safety	No
Yang (2012) (44)	Yang HZ, Wang K, Jin HZ, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. <i>Chinese Medical Journal</i> . 2012; 125(11): 1845-1851.	RCT: efficacy, safety	No
Infliximab versus methotrexate			

Trial	Citation	Description	Seen by PBAC?
RESTORE (45, 46)	Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. Methotrexate in patients with moderate-to-severe plaque psoriasis: Results of an open-label, active-controlled, randomized trial (RESTORE 1). <i>British Journal of Dermatology</i> . 2011; 165(5): 1109-1117.	RCT: efficacy, safety, QoL	No
	Reich K, Wozel G, Zheng H, et al. Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: Results of a randomized, long-term extension trial (RESTORE 2). <i>British Journal of Dermatology</i> . 2013; 168(6): 1325-1334.	OL extension: longer-term efficacy, safety	No
Infliximab versus etanercept			
PIECE (47)	Vries A, Thio H, Kort W, et al. A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. <i>British Journal of Dermatology</i> . 2017; 176(3): 624-633.	RCT: efficacy, safety	No

OL = open label; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial; Shaded = previously considered by the PBAC

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the infliximab trials are presented in Table 76, Appendix B.

The inclusion criteria for the identified infliximab trials were very similar in terms of including adults who had moderate-to-severe plaque psoriasis for at least six months. The Gottlieb (2004), Menter (2007), EXPRESS, Torii (2010), Yang (2012) and RESTORE trials all required patients to have a BSA affected of 10% or greater, and a baseline PASI score of 12 or above. PIECE required a BSA affected of 10% or greater and a baseline PASI score of 10 or above, and Chaudhari (2001) only required patients to have a BSA affected of 5% or greater.

In terms of prior therapies, the criteria differed between trials. Menter (2007), EXPRESS and RESTORE required that patients be candidates for systemic or phototherapy; Gottlieb (2004) Yang (2012) and PIECE required patients to be unresponsive to systemic therapy; Chaudhari (2001) required patients to have failed corticosteroids; and Torii (2010) did not specify. In general, prior exposure to an anti-tumour necrosis factor or a biologic resulted in exclusion from the trial. The exclusion criteria varied between the trials; however, patients were most often excluded if they were suffering from latent tuberculosis, had a history of serious infection or were immunocompromised.

Baseline characteristics

Table 17 presents the baseline demographic and disease characteristics for patients in the infliximab trials. Only arms that received the approved Product Information dose of infliximab or placebo and/or etanercept are presented.

The within trial randomisation appeared successful, with the exception of Chaudhari (2001); however, Chaudhari (2001) was a very small trial (N = 33).

Between the trials, the baseline demographic and disease characteristics were broadly homogeneous, with the exception of Torii (2010) and, to a lesser degree, Yang (2012). The populations of these trials consisted of only Asian patients who had a lower body weight, a shorter duration of CPP, and more severe disease with a higher BSA affected and higher baseline PASI scores.

Table 17: Infliximab trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Infliximab versus placebo										
Chaudhari (2001)	Inf ¹	11	51 (14)	64%	NR	87 (20)	NR	22% (12)	NR	NR
	Pbo	11	45 (12)	73%	NR	85 (19)	NR	20% (6)	NR	NR
EXPRESS	Inf ¹	301	42.6 (11.7)	69%	NR	86 (20)	19 (11)	34% (19)	22.9 (9.3)	12.7 (7.0)
	Pbo	77	43.8 (12.6)	79%	NR	89 (19)	17 (11)	34% (18)	22.8 (8.7)	11.8 (7.5)
Gottlieb (2004)	Inf ¹	99	44 (34-53)	74%	NR	NR	16 (10-25)	25% (20-40)	20 (14-28)	13.2 (7.0)
	Pbo	51	45 (30-52)	61%	NR	NR	16 (6-22)	26% (19-51)	18 (15-27)	13.8 (6.6)
Menter (2007)	Inf ¹	314	44.5 (13.0)	65%	C: 93%	92 (23)	19 (12)	29% (16)	20.4 (7.5)	13.1 (7.0)
	Pbo	208	44.4 (12.5)	69%	C: 91%	91 (23)	18 (11)	28% (18)	19.8 (7.7)	13.4 (7.3)
Torii (2010)	Inf ¹	35	46.9 (13.0)	63%	A: 100%	69 (13)	14 (9)	46% (21)	31.9 (12.8)	12.7 (6.8)
	Pbo	19	43.3 (12.3)	74%	A: 100%	70 (9)	11 (7)	50% (27)	33.1 (15.6)	10.5 (6.8)
Yang (2012)	Inf ¹	84	39.4 (12.3)	71%	A: 100%	68 (9)	16 (11)	NR	23.9 (10.7)	14.4 (6.2)
	Pbo	45	40.1 (11.1)	78%	A: 100%	67 (10)	16 (9)	NR	25.3 (12.7)	14.4 (6.3)
Infliximab versus methotrexate										
RESTORE	Inf ¹	653	44.1 (18-78)	67%	C: 97%	85 (19)	19 (12)	32% (17)	21.4 (8.0)	13.5 (7.2)
Infliximab versus etanercept										
PIECE	Inf ¹	25	45.9 (13.7)	72%	NR	NR	22 (13)	28% (22)	17.8 (9.7)	NR
	Etan ²	23	42.4 (13.2)	56%	NR	NR	18 (11)	21% (13)	15.9 (5.1)	NR
AVERAGE ACROSS ALL TRIALS^a										
N = 1,956	-	-	43.9	68%	C: 82%	86	18	31%	21.6	13.2

A = Asian; BSA = body surface area; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; Inf = infliximab; IQR = interquartile range; IV = intravenous; NR = not reported; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SD = standard deviation; *Italics = (range) or median (IQR)*; Shaded = previously considered by the PBAC

^a Arms presented above only

¹ Infliximab 5 mg/kg IV at Weeks 0, 2, 6; and then every 8 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

The PBS criteria for initial treatment with infliximab required patients to have severe CPP (i.e. a PASI score of greater than 15). Although inclusion in the identified trials required a baseline PASI score of greater than 12 (when stipulated) patients in the infliximab trials appeared to have severe CPP, with the average baseline PASI score in each of the identified

trials greater than 15. This situation was previously accepted by the PBAC in the consideration of infliximab for the treatment of severe CPP. Overall, the infliximab trial patients had, on average, 31% of their BSA affected, a baseline PASI score of 21.6 and a baseline DLQI score of 13.2. Patients were 43.9 years old, male, Caucasian and had had psoriasis for approximately 18 years.

Treatment details

Table 77, Appendix B presents a summary of the treatment details for the infliximab trials for the placebo- or comparator-controlled period.

Each of the trials utilised the recommended dosing regimen for infliximab (5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks) in one arm. The five placebo-controlled trials, reported efficacy results at 10 weeks. The RESTORE trial was methotrexate-controlled and had a time horizon of 16 weeks. The PIECE trial used etanercept as a comparator and reported efficacy results at 12 and 24 weeks (for further comparisons of trials which were etanercept-controlled, refer to section 2.3.8).

Infliximab is the only PBS-listed biologic for the treatment of severe CPP which is administered intravenously. The other biologics are given via subcutaneous injections.

Efficacy

Table 18 presents a summary of the trials included in the review of infliximab, and provides a comparison of those previously considered by the PBAC and those that were identified in the systematic literature review.

The EXPRESS and Gottlieb (2004) trials, which have been considered by the PBAC previously, were broadly similar. Both were randomised, double-blind, placebo-controlled and multi-centred, required patients to have a BSA affected of at least 10% and a baseline PASI score of at least 12, and an unclear risk of bias due to no description of whether outcome assessors were blinded. Chaudhari (2001) differed as it was not multi-centred and required patients to have a BSA affected of 5% at baseline.

Of the trials identified in the systematic literature review, the RESTORE and PIECE trials were not double-blinded; this resulted in a high risk of bias. The risk of bias was unclear in Menter (2007) and Torii (2010) as the blinding of outcome assessors was not described. Yang (2012) had an unclear risk of bias as the methods of randomisation and allocation concealment were not described. All trials were funded by a pharmaceutical company. At baseline all trials required a BSA affected of at least 10% and all, except PIECE, required a PASI score of 12 and over.

Table 18: Infliximab trials: comparison of trial characteristics

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	Outcomes	Other details
Infliximab versus placebo								
Chaudhari (2001)	Yes: Jul 2006	33	R, DB, PC	10 weeks	Unclear (High ^a)	≥ 5% BSA	% PASI 75 at Week 10; Safety	-
EXPRESS	Yes: Jul 2006	378	R, DB, PC, MC	24 weeks (46 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety; QoL	-
Gottlieb (2004)	Yes: Jul 2006, QoL data	249	R, DB, PC, MC	10 weeks (30 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety; QoL	-
Menter (2007)	No	835	R, DB, PC, MC	10 weeks (50 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety; QoL	-
Torii (2010)	No	54	R, DB, PC, MC	14 weeks (78 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety; QoL	Japanese patients only; more severe disease (BSA > 45%; PASI > 31)
Yang (2012)	No	129	R, DB, PC, MC	10 weeks (26 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety	Chinese patients only
Infliximab versus methotrexate								
RESTORE	No	868	R, OL, MC	16 weeks (26 weeks)	High (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 16; Safety; QoL	OL; outcomes at 16 weeks
Infliximab versus etanercept								
PIECE	No	50	R, SB, MC	24 weeks (48 weeks)	High (High ^a)	≥ 10% BSA ≥ 10 PASI	% PASI 75 at Week 12; Safety	Outcome assessors were blinded; outcomes at 12 weeks

BSA = body surface area; DB = double blind; MC = multi-centre; OL = open label; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; QoL = quality of life; R = randomised; SB = single blind; Shaded = previously considered by the PBAC

^a Trial was funded by a pharmaceutical company

The trials EXPRESS and Gottlieb (2004) trials previously considered by the PBAC were, in general, comparable to the majority of the newly identified trials, particularly in terms of the design, patient population and outcomes. It should be noted that Torii (2010) and Yang (2012) only considered Asian patients and the RESTORE and PIECE trials were not double-blinded.

Table 19 presents the key efficacy outcomes from the infliximab trials – the proportion of patients achieving a PASI 75 response and the mean change in DLQI scores. The table also provides a comparison of results between trials already considered by the PBAC and trials

which were newly identified in the systematic literature review. Overall, the efficacy of infliximab in the newly identified trials was consistent with that considered previously.

The PBAC had considered efficacy evidence provided by the very small Chaudhari (2001) trial and the larger EXPRESS trial in July 2006. These trials reported approximately 80% of patients, who received the recommended dose of infliximab, achieved a PASI 75 response at 10 weeks. The evidence identified in the systematic literature review demonstrated a similar efficacy (response rates ranged from 75% (Menter 2007 and PIECE) to 88% (Gottlieb 2004)). The exception was Torii (2010); this small trial reported 69% of infliximab patients achieved a PASI 75 response compared to 0% of placebo patients.

Table 19: Infliximab trials: efficacy results – proportion of patients achieving a PASI 75 response and mean change in DLQI scores

Trial	Time horizon	PASI 75; n/N (%)		Δ DLQI; mean (SD)	
		Infliximab ¹	Placebo	Infliximab ¹	Placebo
Infliximab versus placebo					
Chaudhari (2001)	10 weeks	9/11 (82%)	2/11 (18%)	NR	NR
EXPRESS	10 weeks	242/301 (80%)	2/77 (3%)	-10.3 (7.1)	-0.4 (5.7)
Gottlieb (2004)	10 weeks	87/99 (88%)	3/51 (6%)	-10.3 (7.3)	-2.6 (5.7)
Menter (2007)	10 weeks	NR/314 (76%)	NR/208 (2%)	-9.0 (NR)	0 (NR)
Torii (2010)	10 weeks	NR/35 (69%)	0/19	-9.9 (7.1)	-0.4 (6.2)
Yang (2012)	10 weeks	68/84 (81%)	1/45 (2%)	-7.9 (NR)	-1.3 (NR)
Infliximab versus methotrexate					
RESTORE	16 weeks	508/653 (78%)	NR	-11.6 (NR)	NR
Infliximab versus etanercept			Etanercept²		Etanercept²
PIECE	12 weeks	19/25 (76%)	5/23 (22%)	NR	NR

DLQI = Dermatology Life Quality Index; IV = intravenous; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SD = standard deviation; *Italics = median*; Shaded = previously considered by the PBAC

¹ Infliximab 5 mg/kg IV at Weeks 0, 2, 6, and then every 8 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

In terms of quality of life, the previously considered EXPRESS and Gottlieb (2004) trials reported a significant improvement in DLQI scores (10.3 points) at 10 weeks. Menter (2007), Torii (2010), Yang (2012) and RESTORE, which were identified in the systematic literature review reported similar results (-7.9 to -11.6).

The efficacy results from the infliximab trials are compared in terms of the proportion of patients achieving a PASI 50, 75, 90 and 100 response in Table 78, Appendix B.

The proportion of infliximab treated patients who received the recommended dosing regimen and achieved a PASI 50, 75 and 90 response at 10 weeks in the three largest trials (Menter 2007, EXPRESS and RESTORE, n ≥ 250 in the relevant arm) were very similar and approximately (weighted average) 88%, 78% and 53% respectively. In the Menter (2007) and EXPRESS trials the respective proportion of placebo patients achieving PASI 50, 75 and

90 response were 8% (EXPRESS only), 2% and 1%. Infliximab and placebo PASI responses were similar in the smaller placebo-controlled trials.

Safety

Table 20 presents a summary of the adverse events reported in each of the infliximab trials.

The placebo-controlled infliximab trials reported adverse events at 10 to 30 weeks. At the Product Information recommended dose, the incidence of any adverse event increased from 43% at 10 weeks in Yang (2012) to approximately 80% at 24 to 30 weeks in the EXPRESS and Gottlieb (2004) trials. The incidence of serious adverse events was consistently low ($\leq 8\%$) across all arms when reported. No trials reported any deaths; Menter (2007) and EXPRESS reported a low proportion of infliximab patients who discontinued due to adverse events ($\leq 9\%$).

Table 20: Infliximab trials: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Infliximab versus placebo							
Yang (2012)	10 weeks	Inf ¹	84	36 (43%)	1 (1%)	NR	NR
		Pbo	45	17 (38%)	0	NR	NR
Menter (2007)	14 weeks	Inf ¹	314	216 (69%)	NR	NR	16 (5%)
		Pbo	208	116 (56%)	NR	NR	5 (2%)
EXPRESS	24 weeks	Inf ^{1*}	298	245 (82%)	17 (6%)	NR	27 (9%)
		Pbo	76	55 (71%)	2 (3%)	NR	5 (7%)
Gottlieb (2004)	30 weeks	Inf ¹	99	78 (79%)	8 (8%)	NR	NR
		Pbo	51	32 (63%)	0	NR	NR
Infliximab versus methotrexate							
RESTORE	16 weeks	Inf ¹	653	418 (64%)	39 (6%)	NR	NR

AE = adverse event; Inf = infliximab; IV = intravenous; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SAE serious adverse event; Shaded = previously considered by the PBAC

¹ Infliximab 5 mg/kg IV at Weeks 0, 2, 6; and then every 8 weeks (PI recommended dose)

Table 79 in Appendix B provides a summary of specific adverse events of interest including infection, serious infection, malignancy, skin cancer, cardiovascular disease, upper respiratory tract infection, liver enzyme changes, headache, pruritus and administration site disorders.

Results are presented at 10 to 30 weeks. Infection, upper respiratory tract infection, headache and administration site disorders were most commonly reported. When reported, the incidence of serious infection, malignancy and skin cancers associated with infliximab at 24 and 30 weeks did not exceed 1%. Cardiovascular disease was not reported in any of the trials.

2.3.5 Ixekizumab

Ixekizumab targets the interleukin cytokine pathway (IL-17). It is the most recently listed PBS biologic – it was considered by the PBAC in July 2016 and was listed on the PBS in February

2017. The submission presented an indirect comparison of ixekizumab with ustekinumab (primary comparator), secukinumab and adalimumab using placebo and/or etanercept as the common comparator.

Publication details

For the treatment of CPP, three ixekizumab RCTs, with two related publications, were identified. The citation details, a brief description of the publication and the outcomes and whether the trial has been previously considered by the PBAC are presented below in Table 21.

Table 21: Ixekizumab trials: publication details

Trial	Citation	Description	Seen by PBAC?
Ixekizumab versus placebo			
UNCOVER 1 (50)	Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. <i>New England Journal of Medicine</i> . 2016; 375(4): 345-356.	RCT: efficacy, safety	Yes
Ixekizumab versus etanercept versus placebo			
UNCOVER 2, 3 (51)	Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two Phase 3 randomised trials. <i>Lancet</i> . 2015; 386(9993): 541-551.	RCT: efficacy, safety, QoL	Yes

OL = open label; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial; Shaded = previously considered by the PBAC

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the ixekizumab trials are presented in Table 80, Appendix B.

The identified ixekizumab trials included adult patients who had plaque psoriasis for at least six months. The three trials required patients to have a BSA affected of 10% or greater, a baseline PASI score of 12 or above and a static PGA score of three or higher.

Patients were excluded from the UNCOVER 1, 2 and 3 trials if they had received a biologic or topical treatment within two weeks. Patients were also excluded if they had non-plaque psoriasis or a recent infection.

Baseline characteristics

Table 22 summarises the baseline demographic and disease characteristics for trial patients receiving the recommended dose of ixekizumab and the relevant comparators.

Randomisation was successful within all three trials and patients across the three trials were very homogeneous.

Table 22: Ixekizumab trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Ixekizumab versus placebo										
UNCOVER 1	Ixe ¹	433	45 (12)	67%	C: 93%	92 (23)	20 (12)	28% (18)	20 (8)	NR
	Pbo	431	46 (13)	70%	C: 93%	92 (25)	20 (12)	27% (18)	20 (9)	NR
Ixekizumab versus etanercept versus placebo										
UNCOVER 2	Ixe ¹	351	45 (13)	63%	C: 94%	89 (22)	18 (12)	25% (16)	19 (7)	12 (7)
	Etan ²	358	45 (13)	66%	C: 94%	93 (22)	19 (12)	25% (16)	19 (7)	13 (7)
	Pbo	168	45 (12)	71%	C: 89%	92 (22)	19 (13)	27% (18)	21 (8)	13 (7)
UNCOVER 3	Ixe ¹	385	46 (13)	66%	C: 94%	90 (23)	18 (12)	28% (17)	21 (8)	12 (7)
	Etan ²	382	46 (14)	70%	C: 92%	92 (24)	18 (12)	28% (17)	21 (8)	12 (7)
	Pbo	193	46 (12)	71%	C: 91%	91 (21)	18 (13)	29% (17)	21 (8)	13 (7)
AVERAGE ACROSS ALL TRIALS^a										
N = 2,701	NR	NR	45.5	68%	C: 93%	91	19	27%	20.2	12.4

BSA = body surface area; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; Ixe = ixekizumab; NR = not reported; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Shaded = previously considered by the PBAC

^a Arms presented above only

¹ Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

² Etanercept 50 mg SC twice weekly

The PBS criteria for initial treatment with ixekizumab requires patients to have a PASI score of greater than 15 (i.e. severe CPP). Although inclusion in the identified trials required a PASI score of greater than 12, patients treated in the ixekizumab trials appeared to have severe CPP, with the average baseline PASI score in each of the identified trials greater than 15. This situation was previously accepted by the PBAC in consideration of ixekizumab for the treatment of severe CPP. Overall, patients in the ixekizumab trials had an average BSA affected of 27% and a baseline PASI score of 20.2. Patients were, on average, 45.5 years old, male, Caucasian and had had psoriasis for 19 years.

Treatment details

Table 81 in Appendix B presents a summary of the treatment details in the ixekizumab trials for the placebo- and/or comparator-controlled periods.

The Australian approved Product Information recommended dose of ixekizumab is 160 mg at Week 0, 80 mg at Weeks 2, 4, 6, 8, 10 and 12 and then 80 mg every four weeks. This regimen was used by the three UNCOVER trials.

UNCOVER 1 was a placebo-controlled trial. UNCOVER 2 and 3 compared ixekizumab with etanercept and placebo (see Section 2.3.8 for further details). All three of the ixekizumab trials were placebo-controlled for 12 weeks.

Efficacy

Table 23 presents the key efficacy outcomes from the ixekizumab trials – the proportion of patients achieving a PASI 75 response and the mean change in DLQI scores. Overall, the efficacy of ixekizumab in Leonardi (2012) was consistent with that considered by the PBAC previously.

Data from the three UNCOVER trials were considered by the PBAC in July 2016. At the recommended dosing regimen, approximately 89% of patients achieved a PASI 75 response at 12 weeks.

Table 23: Ixekizumab trials: efficacy results – proportion of patients achieving PASI 75 response and mean change in DLQI scores

Trial	Seen by PBAC?	Time horizon	PASI 75; n/N (%)			Δ DLQI; mean (SD)		
			Ixekizumab ¹	Etanercept ²	Placebo	Ixe ¹	Etan ²	Placebo
Ixekizumab versus placebo								
UNCOVER 1	Yes	12 weeks	NR/433 (89%)	-	NR/431 (4%)	NR	NR	NR
Ixekizumab versus etanercept versus placebo								
UNCOVER 2	Yes	12 weeks	315/351 (90%)	149/358 (42%)	4/168 (2%)	-10.4 (0.3)	-7.7 (0.3)	-2.0 (0.4)
UNCOVER 3	Yes	12 weeks	336/385 (87%)	204/382 (53%)	14/193 (7%)	-10.2 (0.2)	-8.0 (0.2)	-1.7 (0.3)

DLQI = Dermatology Life Quality Index; Etan = etanercept; Ixe = ixekizumab; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; *Italics* = (standard error); Shaded = previously considered by the PBAC

¹ Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

² Etanercept 50 mg SC twice weekly

In terms of quality of life, ixekizumab treatment resulted in a mean improvement of DLQI scores of up to 10.4 points at 12 weeks.

Table 82, Appendix B, compares the proportions of patients achieving PASI 75, 90 and 100 responses at 12 weeks. Ixekizumab, when utilised at the recommended Product Information dose, resulted in approximately 70% of patients achieving a PASI 90 response and 38% achieving a PASI 100 response. The proportion of placebo patients achieving the same responses were minimal (< 7%).

Safety

The adverse events reported in the ixekizumab trials are summarised in Table 24.

Adverse event rates were combined for the UNCOVER 2 and 3 trials. In the UNCOVER trials, the proportion of patients experiencing an adverse event when receiving the recommended dose of ixekizumab was approximately 59%, compared to 47% for placebo patients. The incidence of serious adverse events was consistently low in the three UNCOVER trials (≤ 3%) and no deaths were reported.

Table 24: Ixekizumab trials: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Ixekizumab versus placebo							
UNCOVER 1	12 weeks	Ixe ¹	433	257 (59%)	6 (1%)	0	NR
		Pbo	431	210 (49%)	5 (1%)	0	NR
Ixekizumab versus etanercept versus placebo							
UNCOVER 2, 3	12 weeks	Ixe ¹	734	424 (58%)	14 (2%)	0	NR
		Etan ²	739	399 (54%)	14 (2%)	0	NR
		Pbo	360	160 (44%)	7 (2%)	0	NR

AE = adverse event; Etan = etanercept; Ixe = ixekizumab; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SAE = serious adverse event; SC = subcutaneous; Shaded = previously considered by the PBAC

¹ Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

² Etanercept 50 mg SC twice weekly

Table 83 in Appendix B provides a summary of specific adverse events of interest including infection, serious infection, malignancy, skin cancer, cardiovascular disease, upper respiratory tract infection, liver enzyme changes, headache, pruritus and administration site disorders.

In the UNCOVER trials, 20% to 30% of patients experienced an infection at 12 weeks. The next most common adverse events were nasopharyngitis and administration site disorders. Less than 1% of patients experienced cardiovascular disease. The rates of serious infection, malignancy, skin cancers and liver enzyme changes were not reported.

2.3.6 Secukinumab

Secukinumab is a fully human IgG1 antibody that selectively binds to and neutralises the pro-inflammatory cytokine interleukin 17A. Secukinumab was listed on the PBS in September 2015. The submission presented indirect comparisons with ustekinumab, adalimumab and infliximab with placebo as the common comparator and a direct comparison with etanercept.

Publication details

For the treatment of CPP, six secukinumab trials, with five related publications, were identified. The citation details, a brief description of the publication and the outcomes and whether the trial has been previously considered by the PBAC are presented below in Table 25.

Table 25: Secukinumab trials: publication details

Trial	Citation	Description	Seen by PBAC?
Secukinumab versus placebo			
FEATURE (53)	Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). <i>British Journal of Dermatology</i> . 2015; 172(2): 484-493.	RCT: efficacy, safety	Yes
JUNCTURE (54)	Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). <i>Journal of the European Academy of Dermatology and Venereology</i> . 2015; 29(6): 1082-1090.	RCT: efficacy, safety	Yes
Secukinumab versus secukinumab			
SCULPTURE (60)	Mrowietz U, Leonardi CL, Girolomoni G, et al. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). <i>Journal of the American Academy of Dermatology</i> . 2015; 73(1): 27-36.e1.	RCT: efficacy, safety	No
Secukinumab versus etanercept versus placebo			
FIXTURE/ERASURE (58)	Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis-results of two Phase 3 trials. <i>New England Journal of Medicine</i> . 2014; 371(4): 326-338.	RCT: efficacy, safety, QoL OL extension: longer-term efficacy	Yes
Secukinumab versus ustekinumab			
CLEAR (59)	Thaci D, Blauvelt A, Reich K, T et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. <i>Journal of the American Academy of Dermatology</i> . 2015; 73(3): 400-409.	RCT: efficacy, safety	No

OL = open label; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial; Shaded = previously considered by the PBAC

The CLEAR trial is also included in the analysis of ustekinumab (see Section 2.3.7).

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the identified trials are presented in Table 84.

The identified secukinumab trials were very similar in terms of including adults who had moderate-to-severe plaque psoriasis for at least six months. All trials required patients to have a BSA affected of 10% or more, a baseline PASI score of 12 or above and an Investigator's/PGA score of 3 or above.

In addition, all trials required patients to be either poorly controlled or unresponsive to topical, systemic or phototherapies. Previous use of a biologic targeting interleukin 17A was not permitted in most of the trials.

The exclusion criteria varied between the trials; however, the key exclusion criteria were other forms of psoriasis and if patients were immunocompromised.

Baseline characteristics

Table 26 presents a summary of the baseline characteristics of patients in the secukinumab trials. Only arms receiving the approved Product Information dose of secukinumab and the relevant comparator are presented.

Within each trial randomisation was highly successful. Between the trials, the patient demographics (age, sex, race, weight) were broadly consistent. In terms of disease characteristics at baseline, patients from the JUNCTURE trial had a slightly lower average BSA affected. Baseline DLQI scores were not reported in any of the trials that used dosage regimen in the Australian PI.

Table 26: Secukinumab trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Secukinumab versus placebo										
ERASURE	Sec ¹	245	44.9 (13.5)	69%	C: 70% A: 21%	89 (24)	17 (11)	33% (19)	22.5 (9.2)	NR
	Pbo	248	45.4 (12.6)	69%	C: 71% A: 19%	90 (25)	17 (12)	30% (16)	21.4 (9.1)	NR
FEATURE	Sec ¹	59	45.1 (12.6)	64%	C: 92%	93 (26)	18 (12)	33% (18)	20.7 (8.0)	NR
	Pbo	59	46.5 (14.1)	66%	C: 97%	88 (22)	20 (14)	32% (17)	21.1 (8.5)	NR
JUNCTURE	Sec ¹	60	46.6 (14.2)	77%	C: 93%	91 (23)	21 (14)	26% (13)	18.9 (6.4)	NR
	Pbo	61	43.7 (12.7)	62%	C: 97%	90 (21)	20 (12)	26% (15)	19.4 (6.7)	NR
Secukinumab versus secukinumab										
SCULPTURE	Sec ¹	484	46.7 (12.8)	69%	C: 71% A: 25%	85 (23)	17 (13)	34% (20)	23.3 (9.6)	NR
Secukinumab versus etanercept versus placebo										
FIXTURE	Sec ¹	327	44.5 (13.2)	69%	C: 69% A: 22%	83 (22)	16 (12)	34% (19)	23.9 (9.9)	NR
	Etan ²	326	43.8 (13.0)	71%	C: 67% A: 23%	85 (21)	16 (12)	34% (18)	23.2 (9.8)	NR
	Pbo	326	44.1 (12.6)	73%	C: 67% A: 22%	82 (20)	17 (12)	35% (19)	24.1 (10.5)	NR
Secukinumab versus ustekinumab										
CLEAR	Sec ¹	337	45.2 (14.0)	68%	C: 89%	87 (20)	20 (13)	33% (18)	21.7 (8.5)	NR
	Ust ³	339	44.6 (13.7)	74%	C: 85%	87 (22)	16 (11)	32% (17)	21.5 (8.1)	NR
AVERAGE ACROSS ALL TRIALS^a										
N = 2,871	NR	NR	45.0	70%	C: 76%	86	17	33%	22.5	NR

A = Asian; BSA = body surface area; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; NR = not reported; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; SE = standard error; Sec = Secukinumab; Ust = ustekinumab; Shaded = previously considered by the PBAC

^a Arms presented above only

¹ Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

³ Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

The PBS criteria for initial treatment with secukinumab requires patients to have a PASI score of greater than 15 (i.e. severe CPP). Although inclusion in the identified trials required a baseline PASI score of 12 or above, patients in the secukinumab trials appeared to have severe CPP, with the average PASI score in each of the trials greater than 15. This situation was previously accepted by the PBAC in the consideration of secukinumab for the treatment of severe CPP. Overall, the average secukinumab trial patient had a BSA affected of 33% and a baseline PASI of 22.5. Patients were 45.0 years old, male, Caucasian and had had psoriasis for 17 years.

Treatment details

The treatment details for the secukinumab trials are presented in Table 85, Appendix B for the placebo- and/or comparator-controlled periods.

The dosing regimen for secukinumab recommended in the Product Information is 300 mg, delivered subcutaneously at Weeks 0, 1, 2, 3 and 4, and then every four weeks.

Seven of the trials were placebo-controlled; the CLEAR trial was ustekinumab-controlled and the SCULPTURE trial compared doses of secukinumab. All trials reported outcomes at 12 weeks, with the exception of CLEAR, which reported outcomes at 16 weeks.

Efficacy

Table 27 presents a summary of the trials included in the review of secukinumab, and provides a comparison of those previously considered by the PBAC and those that were identified in the systematic literature review.

The four trials previously considered by the PBAC, ERASURE, FEATURE, JUNCTURE and FIXTURE, were similar – all were randomised, double-blind, placebo-controlled and multi-centred, had a trial duration of 12 weeks, a low risk of bias (although all were funded by a pharmaceutical company) and all had similar patient populations.

The SCULPTURE and CLEAR trials were identified in the systematic literature review. Both were not placebo-controlled. SCULPTURE compared two doses of secukinumab and had an unclear risk of bias due to not providing details on the methods of randomisation and allocation concealment or on whether the outcome assessors were blinded. The CLEAR trial presented results at 16 weeks and compared secukinumab with ustekinumab.

Table 27: Secukinumab trials: comparison of trial characteristics

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	Outcomes	Other details
Secukinumab versus placebo								
ERASURE	Yes: Mar 2015	738	R, DB, PC, MC	12 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	-
FEATURE	Yes: Mar 2015	177	R, DB, PC, MC	12 weeks (208 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	-
JUNCTURE	Yes: Mar 2015	182	R, DB, PC, MC	12 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	-
Secukinumab versus secukinumab								
SCULPTURE	No	966	R, DB, MC	12 weeks (52 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	No placebo arm
Secukinumab versus etanercept versus placebo								
FIXTURE	Yes: Mar 2015	737	R, DB, PC, MC	12 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety; QoL	-
Secukinumab versus ustekinumab								
CLEAR	No	676	R, DB, MC	16 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	No placebo arm; outcomes at 16 weeks

BSA = body surface area; DB = double blind; MC = multi-centre; OL = open label; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; QoL = quality of life; R = randomised; SB = single blind; Shaded = previously considered by the PBAC

The trials previously seen by the PBAC were comparable with those identified in the systematic literature review in terms of the patient populations included. In addition, all were randomised, double-blinded and multi-centred.

Table 28 the key efficacy outcomes from the secukinumab trials – the proportion of patients achieving a PASI 75 response and the mean change in DLQI scores. It also compares the results of the trials previously considered by the PBAC with the results of the trials, which were newly identified in the systematic literature review. Overall, the efficacy of secukinumab at the recommended dose in the trials identified in the systematic review was consistent with that considered previously.

The PBAC had considered evidence from the ERASURE, FEATURE, JUNCTURE and FIXTURE trials in March 2015. These trials compared the recommended dose of secukinumab with a lower dosing regimen and with placebo. At the recommended dose, the proportion of patients achieving a PASI 75 response at 12 weeks ranged from 76% in FEATURE to 87% in

JUNCTURE. The SCULPTURE trial, which was identified in the systematic literature review, reported 90% of patients achieving a PASI 75 response at 12 weeks for the recommended dose and the CLEAR trial, which reported results at 16 weeks, had a response rate of 93%.

Table 28: Secukinumab trials: efficacy results – proportion of patients achieving PASI 75 response and mean change in DLQI scores

Trial	Time horizon	PASI 75; n/N (%)		Δ DLQI; mean (SD)			
		Secukinumab ¹	Placebo	Secukinumab ¹	Placebo		
Secukinumab versus placebo							
ERASURE	12 weeks	NR/245 (82%)	NR/248 (5%)	-10.1 (NR)	-1.1 (NR)		
FEATURE	12 weeks	NR/59 (76%)	NR/59 (0%)	NR	NR		
JUNCTURE	12 weeks	NR/60 (87%)	NR/61 (3%)	NR	NR		
Secukinumab versus secukinumab							
SCULPTURE	12 weeks	NR/484 (90%)	NR	NR	NR		
Secukinumab versus etanercept versus placebo			Etan²	Placebo	Etan²	Placebo	
FIXTURE	12 weeks	NR/327 (77%)	NR/326 (44%)	NR/326 (5%)	-10.4 (NR)	-7.9 (NR)	-1.9 (NR)
Secukinumab versus ustekinumab			Ustekinumab³		Ustekinumab³		
CLEAR	16 weeks	311/334 (93%)	277/335 (83%)	NR	NR		

DLQI = Dermatology Life Quality Index; Etan = etanercept; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Sec = secukinumab; Shaded = previously considered by the PBAC

¹ Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

³ Ustekinumab 45 mg SC for patients ≤ 100 kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose) Only two trials reported mean change in DLQI scores, ERASURE and FIXTURE. These trials had been previously considered by the PBAC. Secukinumab appeared to result in an improved quality of life compared to placebo.

Table 86, Appendix B, compares the proportion of patients achieving a PASI 50, 75, 90 and 100 responses.

In the larger trials which utilised the recommended dose regimen for secukinumab (ERASURE, FIXTURE and SCULPTURE) the proportion of patients achieving a PASI 90 response ranged from 54% to 59% and the proportions achieving a PASI 100 response ranged from 28% to 29% at 12 weeks. Results from the CLEAR trial suggest that these responses increase with a longer duration of treatment, as at 16 weeks the proportions of patients achieving PASI 75, 90 and 100 responses were 93%, 79% and 44% respectively.

Safety

Table 29 summarises the adverse events reported in the secukinumab trials.

In the large ERASURE, FIXTURE and SCULPTURE trials 51% to 56% of patients who received the recommended dose of secukinumab reported an adverse event and 1% to 2% of patients reported a serious adverse event. The proportion of patients experiencing an

adverse event resulting in discontinuation from the trial was consistently low across all arms of all trials.

One death was reported in the secukinumab arm of the SCULPTURE trial. The SCULPTURE trial death was the result of a cerebral haemorrhagic stroke that the investigators did not consider related to secukinumab treatment.

Table 29: Secukinumab trials: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Secukinumab versus placebo							
ERASURE	12 weeks	Sec ¹	245	135 (55%)	6 (2%)	0	3 (1%)
		Pbo	248	116 (47%)	4 (2%)	0	4 (2%)
FEATURE	12 weeks	Sec ¹	59	30 (51%)	3 (5%)	0	1 (2%)
		Pbo	59	28 (48%)	1 (2%)	0	1 (2%)
JUNCTURE	12 weeks	Sec ¹	60	42 (70%)	1 (2%)	0	0
		Pbo	61	33 (54%)	1 (2%)	0	1 (2%)
Secukinumab versus secukinumab							
SCULPTURE	12 weeks	Sec ¹	483	248 (51%)	9 (2%)	0	9 (2%)
Secukinumab versus etanercept versus placebo							
FIXTURE	12 weeks	Sec ¹	326	181 (56%)	4 (1%)	0	4 (1%)
		Etan ²	323	186 (58%)	3 (1%)	0	6 (2%)
		Pbo	327	163 (50%)	6 (2%)	0	3 (1%)
Secukinumab versus ustekinumab							
CLEAR	16 weeks	Sec ¹	335	215 (64%)	10 (3%)	0	3 (1%)
		Ust ³	336	196 (58%)	10 (3%)	0	4 (1%)

AE = adverse event; Etan = etanercept; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SAE = serious adverse event; SC = subcutaneous; Sec = Secukinumab; Ust = ustekinumab; Shaded = previously considered by the PBAC

¹ Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

³ Ustekinumab 45 mg SC for patients ≤ 100 kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

Table 87 in Appendix B provides a summary of specific adverse events of interest including infection, serious infection, malignancy, skin cancer, cardiovascular disease, upper respiratory tract infection, liver enzyme changes, headache, pruritus and administration site disorders.

Nasopharyngitis, headache and pruritus were the most commonly reported adverse events in the secukinumab trials. Approximately 28% of patients receiving the recommended dosing regimen of secukinumab in the ERASURE, FIXTURE and CLEAR trials reported an infection at 12 or 16 weeks; serious infections were rarely reported.

2.3.7 Ustekinumab

Ustekinumab is a human IgG1 monoclonal antibody that specifically binds to the shared p40 protein subunit of the cytokines interleukin-12 and -23. It was listed on the PBS in March 2010 for the treatment of severe CPP on the basis of indirect comparisons with adalimumab, etanercept and infliximab (placebo was the common comparator).

Publication details

For the treatment of CPP, ten ustekinumab trials (including the CLEAR trial which was also identified for secukinumab), with 11 related publications, were identified. The citation details, a brief description of the publication and the outcomes and whether the trial has been previously considered by the PBAC are presented below in Table 30.

Table 30: Ustekinumab trials: publication details

Trial	Citation	Description	Seen by PBAC?
Ustekinumab versus placebo			
PHOENIX 1 (61-64)	Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial. <i>Lancet</i> . 2008; 371(9625): 1665-1674.	RCT: efficacy, safety,	Yes
	Lebwohl M, Papp K, Han C, et al. Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. <i>British Journal of Dermatology</i> . 2010; 162(1): 137-146.	RCT: QoL	No
	Kimball AB, Gordon KB, Fakhrazadeh S, et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial through up to 3 years. <i>British Journal of Dermatology</i> . 2012; 166(4): 861-872.	OL extension: longer-term efficacy, safety	No
	Kimball AB, Papp KA, Wasfi Y, et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. <i>Journal of the European Academy of Dermatology and Venereology</i> . 2013; 27(12): 1535-1545.	OL extension: longer-term efficacy, safety	No
PHOENIX 2 (65, 66)	Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). <i>Lancet</i> . 2008; 371(9625): 1675-1684.	RCT: efficacy, safety	Yes
	Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled Phase III trial. <i>Journal of the American Academy of Dermatology</i> . 2010; 63(3): 457-465.	RCT: QoL	No
PEARL (68)	Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a Phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). <i>Journal of Dermatological Science</i> . 2011; 63(3): 154-163.	RCT: efficacy, safety, QoL	No

Trial	Citation	Description	Seen by PBAC?
LOTUS (70)	Zhu X, Zheng M, Song M, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a Phase 3 clinical trial (LOTUS). <i>Journal of Drugs in Dermatology</i> . 2013; 12(2): 166-174.	RCT: efficacy, safety, QoL	No
Ustekinumab versus brodalumab versus placebo			
AMAGINE 2, 3 (71)	Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. <i>New England Journal of Medicine</i> . 2015; 373(14): 1318-1328.	RCT: efficacy, safety	No
Ustekinumab versus etanercept			
ACCEPT (72)	Griffiths CEM, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. <i>New England Journal of Medicine</i> . 2010; 362 (2): 118-128.	RCT: efficacy, safety	Yes
Ustekinumab versus secukinumab			
CLEAR (59)	Thaci D, Blauvelt A, Reich K, T et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. <i>Journal of the American Academy of Dermatology</i> . 2015; 73(3): 400-409.	RCT: efficacy, safety	No

OL = open label; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial; Shaded = previously considered by the PBAC

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the identified trials are presented in Table 88, Appendix B.

The inclusion criteria for the identified ustekinumab trials were very similar in terms of including adults who had moderate-to-severe plaque psoriasis for at least six months. All trials required patients to have a BSA affected of 10% or greater, a baseline PASI score of 12 or above. AMAGINE 2 and 3, ACCEPT, and CLEAR required patients to have a PGA score of three or above.

The PHOENIX 1 and 2 trials required patients to be candidates for systemic or phototherapy. The ACCEPT and CLEAR trials required patients to be unresponsive to systemic agents. Previous treatment with an agents targeting interleukin-12 or interleukin-23 was not allowed.

The exclusion criteria varied between the trials; however, patients were commonly excluded if they were suffering from non-plaque psoriasis, had a history of latent tuberculosis or a recent serious infection.

Baseline characteristics

Baseline characteristics for patients in the ustekinumab trials who received the approved Product Information doses or similar or the relevant comparators are presented in Table 31.

The within trial randomisation was highly successful in the trials.

Between trials the baseline populations were broadly homogenous. The exceptions were the PEARL and LOTUS trials which recruited Asian patients only. Patients in these three trials

had a lower baseline weight, and slightly more severe disease, with a higher average BSA affected and a higher PASI score at baseline.

Table 31: Ustekinumab trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Ustekinumab versus placebo										
PHOENIX 1	Ust ^{1*}	255	44.8 (12.5)	69%	NR	94 (24)	20 (12)	27% (18)	20.5 (8.6)	11.1 (7.1)
	Ust ²	256	46.2 (11.3)	68%	NR	94 (24)	20 (11)	25% (15)	19.7 (7.6)	11.6 (6.9)
	Pbo	255	44.8 (11.3)	72%	NR	94 (24)	20 (12)	28% (17)	20.4 (8.6)	11.8 (7.4)
PHOENIX 2	Ust ^{1*}	409	45.1 (12.1)	69%	C: 91%	90 (21)	20 (12)	26% (16)	19.4 (6.8)	12.2 (7.1)
	Ust ²	411	46.6 (12.1)	67%	C: 91%	92 (21)	20 (11)	27% (17)	20.1 (7.5)	12.6 (7.3)
	Pbo	410	47.0 (12.5)	69%	C: 93%	91 (22)	20 (12)	26% (17)	19 (7.5)	12.3 (6.9)
PEARL	Ust ^{1*}	61	40.9 (12.7)	82%	A: 100%	73 (13)	12 (8)	42% (24)	25.2 (11.9)	16.1 (6.1)
	Pbo	60	40.4 (10.1)	88%	A: 100%	75 (13)	14 (7)	36% (21)	22.9 (8.6)	15.2 (7.0)
LOTUS	Ust ^{1*}	160	40.1 (12.4)	78%	A: 100%	70 (12)	15 (9)	35% (19)	23.2 (9.5)	13.7 (7.6)
	Pbo	162	39.2 (12.2)	76%	A: 100%	70 (13)	14 (9)	35% (20)	22.7 (9.5)	13.1 (7.5)
AMAGINE 2	Ust ^{1*}	300	45 (13)	68%	C: 90%	91 (24)	19 (13)	27% (19)	20.0 (8.4)	NR
	Pbo	309	44 (13)	71%	C: 88%	92 (23)	18 (12)	28% (17)	20.4 (8.2)	NR
AMAGINE 3	Ust ^{1*}	313	45 (13)	68%	C: 90%	90 (22)	18 (12)	28% (18)	20.1 (8.4)	NR
	Pbo	315	44 (13)	66%	C: 93%	89 (22)	18 (12)	28% (17)	20.1 (8.7)	NR
Ustekinumab versus etanercept										
ACCEPT	Ust ^{1*}	209	45.1 (12.6)	64%	C: 92%	90 (21)	19 (12)	27% (18)	20.5 (9.2)	NR
	Ust ²	347	44.8 (12.3)	67%	C: 89%	91 (23)	19 (12)	26% (18)	19.9 (8.4)	NR
	Etan ³	347	45.7 (13.4)	71%	C: 91%	91 (21)	19 (12)	24% (14)	18.6 (6.2)	NR
Ustekinumab versus secukinumab										
CLEAR	Ust ^{4*}	339	44.6 (13.7)	74%	C: 85%	87 (22)	16 (11)	32% (17)	21.5 (8.1)	NR
	Sec ⁵	337	45.2 (14.0)	68%	C: 89%	87 (20)	20 (13)	33% (18)	21.7 (8.5)	NR
AVERAGE ACROSS ALL TRIALS^a										
N = 5,255	NR	NR	44.8	70%	81%	89	19	28%	20.3	12.4

A = Asian; BSA = body surface area; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; NR = not reported; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Sec = secukinumab; Ust = ustekinumab; *Italics = median*; Shaded = previously considered by the PBAC

^a Arms presented above only

¹ Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

² Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks

³ Etanercept 50 mg SC twice weekly

^{4*} Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

⁵ Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

The PBS criteria for initial treatment with ustekinumab requires patients to have a PASI score of greater than 15 (i.e. severe CPP). Although inclusion in the identified trials required a baseline PASI greater than 12, it appeared that patients treated in the ustekinumab trials had severe CPP, with the average baseline PASI score exceeding 15 in each of the trials. This situation was previously accepted by the PBAC in the consideration of ustekinumab for the treatment of severe CPP. Overall, the average ustekinumab patient had an average BSA affected of 28% and a baseline PASI score of 20.3. The average patient was 44.8 years old, male, Caucasian, had suffered from psoriasis for 19 years and had a baseline DLQI score of 12.4.

Treatment details

Table 89 in Appendix B presents the treatment details for the ustekinumab trials.

The Product Information recommended dose of ustekinumab is 45 mg at Weeks 0 and 4 and then 45 mg every 12 weeks. Doses of 90 mg may be considered for patients over 100 kg. The recommended 45 mg dose was utilised in at least one arm of the PHEONIX 1 and 2, PEARL, LOTUS, AMAGINE 2 and 3, ACCEPT and CLEAR trials.

All trials were placebo-controlled, with the exception of ACCEPT, which used etanercept as a comparator, and CLEAR which compared ustekinumab with secukinumab (see Section 2.3.8). Each of the trials reported outcomes at 12 weeks, with the exception of CLEAR, which reported outcomes at 16 weeks.

Efficacy

Table 32 presents a summary of the trials included in the review of ustekinumab, and provides a comparison of those previously considered by the PBAC and those that were identified in the systematic literature review.

The PHOENIX 1 and 2 and ACCEPT trials have been considered by the PBAC previously. All three trials were randomised, double-blind and multi-centred, presented results at 12 weeks, and had similar patient populations. The PHOENIX trials had a low risk of bias (although both were funded by a pharmaceutical company); the ACCEPT trial had a high risk as the outcome assessors were not blinded.

Of the five ustekinumab trials identified in the systematic literature review, only CLEAR was not placebo-controlled. All of the trials were randomised, double-blind and multi-centred. PEARL and LOTUS had an unclear risk of bias – PEARL as the blinding of outcome assessors was not described and LOTUS as the methods of randomisation and allocation concealment and the blinding of outcome assessors was not described. The five trials had similar patient populations.

Table 32: Ustekinumab trials: comparison of trial characteristics

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	Outcomes	Other details
Ustekinumab versus placebo								

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	Outcomes	Other details
PHOENIX 1	Yes: Nov 09, Efficacy and safety	766	R, DB, PC, MC	12 weeks (76 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety; QoL	-
PHOENIX 2	Yes: Nov 09, Efficacy and safety	1,230	R, DB, PC, MC	12 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety; QoL	-
PEARL	No	121	R, DB, PC, MC	12 weeks (36 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety; QoL	Taiwanese and Korean patients; BSA > 35%
LOTUS	No	322	R, DB, PC, MC	12 weeks (36 weeks)	Unclear (High ^a)	≥ 10% BSA ≥ 12 PASI	% PASI 75 at Week 10; Safety; QoL	Chinese patients; BSA = 35%
AMAGINE 2	No	1,831	R, DB, PC, MC	12 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	-
AMAGINE 3	No	1,881	R, DB, PC, MC	12 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	-
Ustekinumab versus etanercept								
ACCEPT	Yes: Nov 09	903	R, DB, MC	12 weeks (44 weeks)	High (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	No placebo arm
Ustekinumab versus secukinumab								
CLEAR	No	676	R, DB, MC	16 weeks (52 weeks)	Low (High ^a)	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	% PASI 75 at Week 10; Safety	No placebo arm; outcomes at 16 weeks

BSA = body surface area; DB = double blind; MC = multi-centre; OL = open label; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; QoL = quality of life; R = randomised; SB = single blind; Shaded = previously considered by the PBAC

Overall, the trials previously considered by the PBAC were similar to those identified in the systematic literature review. It should be noted that the PEARL and LOTUS trials included only Asian patients.

Table 33 presents the key efficacy outcomes from the ustekinumab trials – the proportion of patients achieving a PASI 75 response and the mean change in DLQI scores. This allows a comparison of results between trials previously considered by the PBAC with trials newly identified in the systematic literature review. Overall, the efficacy of ustekinumab at the

recommended dose in the new trials was consistent with that considered by the PBAC previously.

The PBAC had considered evidence from the PHOENIX 1 and 2 trials and the ACCEPT trial in November 2009. These studies reported that approximately 67% of patients achieved a PASI 75 response at 12 weeks when treated with the recommended dose of ustekinumab (i.e. 45 mg). The PEARL, LOTUS and AMAGINE 2 and 3 reported very similar results with rates of response ranging from 67% to 70%. The CLEAR trial reported slightly higher rates (up to 83%) - this trial used the Product Information recommended doses for patients less than and greater than 100 kg.

Table 33: Ustekinumab trials: efficacy results – proportion of patients achieving PASI 75 response and mean change in DLQI scores

Trial	Time horizon	PASI 75; n/N (%)				Δ DLQI; mean (SD)		
		Ust ¹	Ust ²	Ust ³	Pbo	Ust ¹	Ust ²	Pbo
Ustekinumab versus placebo								
PHOENIX 1	12 weeks	171/255 (67%)	170/256 (66%)	NR	8/255 (3%)	-8.0 (6.9)	-8.7 (6.5)	-0.6 (6.0)
PHOENIX 2	12 weeks	273/409 (67%)	311/411 (76%)	NR	15/410 (4%)	-9.3 (7.1)	-10.0 (6.7)	-0.5 (5.7)
PEARL	12 weeks	41/61 (67%)	NR	NR	3/60 (5%)	-11.2 (7.1)	NR	-0.5 (6.5)
LOTUS	12 weeks	132/160 (83%)	NR	NR	18/162 (11%)	-9.3 (7.2)	NR	-1.9 (6.6)
AMAGINE 2	12 weeks	210/300 (70%)	NR	NR	25/309 (8%)	NR	NR	NR
AMAGINE 3	12 weeks	217/313 (69%)	NR	NR	19/315 (6%)	NR	NR	NR
Ustekinumab versus etanercept					Etan⁴			
ACCEPT	12 weeks	141/209 (68%)	256/347 (74%)	NR	197/347 (57%)	NR	NR	NR
Ustekinumab versus secukinumab					Sec⁵			
CLEAR	16 weeks	NR	NR	277/335 (83%)	311/334 (93%)	NR	NR	NR

DLQI = Dermatology Life Quality Index; Etan = etanercept; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Sec = secukinumab; Ust = ustekinumab; **Shaded** = previously considered by the PBAC

¹ Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

² Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks

³ Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

⁴ Etanercept 50 mg SC twice weekly

⁵ Secukinumab 300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks

In terms of quality of life, ustekinumab resulted in large improvements in DLQI scores compared to placebo, regardless of the dosing regimen used. The results presented by the

PHOENIX trials were not considered previously by the PBAC (only efficacy and safety data was considered by the PBAC).

Table 90, Appendix B, compares the proportion of patients achieving a PASI 50, 75, 90 and 100 responses. All of the larger 12 week trials (PHOENIX 1 and 2, LOTUS, AMAGINE 2 and 3 and ACCEPT) utilised the recommended dosing regimen for ustekinumab. The proportions of patients achieving PASI 50, 75, 90 and 100 responses in these trials were broadly similar: 84% to 91% of patients achieved a PASI 50 response; 67% to 83% achieved a PASI 75; 36% to 67% achieved a PASI 90; and 13% to 24% of patients achieved a PASI 100 response.

Safety

Adverse events reported in the ustekinumab trials are summarised in Table 34.

In the larger PHOENIX 1 and 2, LOTUS, AMAGINE 2 and 3 and ACCEPT trials, the proportion of patients who received the recommended dose of ustekinumab and reported an adverse event ranged between 43% and 66%. The proportion who reported a serious adverse event or experienced an adverse event that resulted in discontinuation from the trial did not exceed 2%. One death was reported; an ustekinumab patient in the PHOENIX 2 trial who had underlying dilated cardiomyopathy suffered a non-ischaemic sudden cardiac death.

Table 34: Ustekinumab trials: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Ustekinumab versus placebo							
PHOENIX 1	12 weeks	Ust ^{1*}	255	147 (58%)	2 (1%)	0	1 (< 1%)
		Ust ²	256	131 (51%)	4 (2%)	0	4 (2%)
		Pbo	255	123 (48%)	2 (1%)	0	6 (2%)
PHOENIX 2	12 weeks	Ust ^{1*}	409	217 (53%)	8 (2%)	0	1 (< 1%)
		Ust ²	411	197 (48%)	5 (1%)	1 (< 1%)	6 (2%)
		Pbo	410	204 (50%)	8 (2%)	0	8 (2%)
PEARL	12 weeks	Ust ^{1*}	61	40 (66%)	0	0	0
		Pbo	60	42 (70%)	2 (3%)	0	3 (5%)
LOTUS	12 weeks	Ust ^{1*}	160	68 (43%)	1 (< 1%)	NR	3 (2%)
		Pbo	161	62 (39%)	1 (< 1%)	NR	2 (1%)
AMAGINE 2	12 weeks	Ust ^{1*}	300	177 (59%)	4 (1%)	0	4 (1%)
		Pbo	309	165 (53%)	8 (3%)	0	1 (< 1%)
AMAGINE 3	12 weeks	Ust ^{1*}	313	168 (54%)	2 (< 1%)	0	2 (< 1%)
		Pbo	313	152 (49%)	3 (1%)	0	3 (1%)
Ustekinumab versus etanercept							
ACCEPT	12 weeks	Ust ^{1*}	209	138 (66%)	4 (2%)	NR	4 (2%)
		Ust ²	347	240 (69%)	4 (1%)	NR	4 (1%)
		Etan ³	347	243 (70%)	4 (1%)	NR	8 (2%)
Ustekinumab versus secukinumab							
CLEAR	16 weeks	Ust ^{4*}	336	196 (58%)	10 (3%)	0	4 (1%)
		Sec ⁵	335	215 (64%)	10 (3%)	0	3 (1%)

AE = adverse event; Etan = etanercept; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SAE serious adverse event; SC = subcutaneous; Sec = secukinumab; Ust = ustekinumab; Shaded = previously considered by the PBAC

¹ Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

² Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks

³ Etanercept 50 mg SC twice weekly

^{4*} Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

⁵ Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

Table 91 in Appendix B provides a summary of specific adverse events of interest including infection, serious infection, malignancy, skin cancer, cardiovascular disease, upper respiratory tract infection, liver enzyme changes, headache, pruritus and administration site disorders.

Approximately 20% to 30% of patients in the larger trials (PHOENIX 1 and 2, LOTUS, AMAGINE 2 and 3, ACCEPT and CLEAR) had an infection. Other common adverse events associated with ustekinumab were upper respiratory tract infection, nasopharyngitis and headache.

The incidences of serious infection, malignancy, skin cancer and cardiovascular disease were less than 3% in all of the trials.

2.3.8 Direct comparisons of PBS-listed biologics

Number of trials and treatment details

A number of trials identified in the systematic literature review included two of the PBS-listed biologics, allowing for a direct comparison. Five trials included etanercept as a comparator (PIECE versus infliximab; UNCOVER 2 and 3 versus ixekizumab; FIXTURE versus secukinumab; and ACCEPT versus ustekinumab) and one trial, the CLEAR trial, directly compared secukinumab and ustekinumab. These trials and the treatment details summarised in Table 92, Appendix B.

In each of the trials, which utilised etanercept as a comparator, etanercept was dosed at 50 mg twice weekly. This regimen differed from the dosage in the approved Australian Product Information (25 mg twice weekly or 50 mg once weekly). Approved Australian dosage regimens were utilised for infliximab, ixekizumab, secukinumab and ustekinumab.

The CLEAR trial, which compared secukinumab and ustekinumab, utilised the recommended dosing regimens for both biologics.

Baseline characteristics

The baseline characteristics for patients in each trial are re-presented in Table 93, Appendix B.

The within trial randomisation was very successful in each of the trials, with the exception of the small PIECE trial (N = 48) which compared infliximab and etanercept. The populations of the UNCOVER 2 and 3 trials (ixekizumab versus etanercept versus placebo) were highly homogeneous.

Effectiveness

The efficacy results for the trials which compared PBS-listed biologics are presented in Table 35.

Based on the proportion of patients achieving a PASI 75 response in the PIECE trial, infliximab, given at the recommended dose, appeared more effective than etanercept, given at above the recommended dose, at treating CPP at both 12 (76% versus 22%) and 24 weeks (72% versus 35%). It should be noted that the population in the PIECE trial was small.

Ixekizumab given at the recommended dosing regimen is also more effective than etanercept, given at above the recommended dose. In UNCOVER 2, 90% of ixekizumab and 42% of etanercept patients achieved a PASI 75 response at 12 weeks. The results from the UNCOVER 3 trial were similar – 87% of ixekizumab patients and 53% of etanercept patients.

In the FIXTURE trial the approved dose of secukinumab resulted in 77% of patients achieving a PASI 75 response at 12 weeks compared to 44% of etanercept patients.

Ustekinumab, given at the Australian Product Information recommended dose, appeared to have the most comparable efficacy to etanercept, given at a dose higher than recommended. Sixty-eight percent of ustekinumab patients and 57% of etanercept patients achieved a PASI 75 response at 12 weeks.

In the CLEAR trial both secukinumab and ustekinumab were given at the recommended doses. The proportion of patients achieving a PASI 75 response was higher for secukinumab patients (93% versus 83%) at 12 weeks.

Table 35: Direct comparisons of PBS-listed biologics: efficacy results

Trial	Time horizon	Arm	N	PASI 75; n (%)	Δ DLQI; mean (SD)
Infliximab versus etanercept					
PIECE	12 weeks	Infliximab ^{1*}	25	19 (76%)	NR
		Etanercept ²	23	5 (22%)	NR
	24 weeks	Infliximab ^{1*}	25	18 (72%)	NR
		Etanercept ²	23	8 (35%)	NR
Ixekizumab versus etanercept versus placebo					
UNCOVER 2	12 weeks	Ixekizumab ^{3*}	351	315 (90%)	-10.4 (0.3)
		Etanercept ²	358	149 (42%)	-7.7 (0.3)
		Placebo	168	4 (2%)	-2.0 (0.4)
UNCOVER 3	12 weeks	Ixekizumab ^{3*}	385	336 (87%)	-10.2 (0.2)
		Etanercept ²	382	204 (53%)	-8.0 (0.2)
		Placebo	193	14 (7%)	-1.7 (0.3)
Secukinumab versus etanercept versus placebo					
FIXTURE	12 weeks	Secukinumab ^{4*}	327	77%	-10.4
		Etanercept ²	326	44%	-7.9
		Placebo	326	5%	-1.9
Ustekinumab versus etanercept					
ACCEPT	12 weeks	Ustekinumab ^{5*}	209	141 (68%)	NR
		Ustekinumab ⁵	347	256 (74%)	NR
		Etanercept ²	347	197 (57%)	NR
Secukinumab versus ustekinumab					
CLEAR	16 weeks	Secukinumab ^{4*}	334	311 (93%)	NR
		Ustekinumab ^{7*}	335	277 (83%)	NR

DLQI = Dermatology Life Quality Index; IV = intravenous; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; SC = subcutaneous; SE = standard error; *Italics* = (SE)

^{1*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

^{3*} Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

^{4*} Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

^{5*} Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

⁶ Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks

^{7*} Ustekinumab 45 mg SC for patients ≤ 100 kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

In terms of quality of life, ixekizumab in the UNCOVER 2 and 3 trials, resulted in a mean improvement in DLQI score of 10.2 to 10.4 points compared to a 7.7 to 8.0 point

improvement with etanercept. The improvements were very similar in the FIXTURE trial; secukinumab resulted in a 10.4-point improvement in DLQI and etanercept in a 7.9-point improvement.

Change in DLQI scores were not reported in the other trials.

Safety

Table 36 summarises the adverse events reported in the trials comparing the PBS-listed biologics. No adverse event data was provided for the comparison of infliximab with etanercept from the PIECE trial. The UNCOVER trials provided combined adverse event data.

The proportions of patients reporting any adverse event, serious adverse events and adverse events that resulted in discontinuation from the respective trial were very similar in each comparison with etanercept.

In the CLEAR trial secukinumab patients reported marginally more adverse events compared to ustekinumab. The proportion of serious adverse events and adverse events resulting in discontinuation from the trial were equal.

Table 36: Direct comparisons of PBS-listed biologics: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Ixekizumab versus etanercept versus placebo							
UNCOVER 2, 3	12 weeks	Ixe ¹	734	424 (58%)	14 (2%)	0	NR
		Etan ²	739	399 (54%)	14 (2%)	0	NR
		Pbo	360	160 (44%)	7 (2%)	0	NR
Secukinumab versus etanercept versus placebo							
FIXTURE	12 weeks	Sec ³	326	181 (56%)	4 (1%)	0	4 (1%)
		Etan ²	323	186 (58%)	3 (1%)	0	6 (2%)
		Pbo	327	163 (50%)	6 (2%)	0	3 (1%)
Ustekinumab versus etanercept							
ACCEPT	12 weeks	Ust ⁴	209	138 (66%)	4 (2%)	NR	4 (2%)
		Ust ⁵	347	240 (69%)	4 (1%)	NR	4 (1%)
		Etan ³	347	243 (70%)	4 (1%)	NR	8 (2%)
Secukinumab versus ustekinumab							
CLEAR	16 weeks	Sec ³	335	215 (64%)	10 (3%)	0	3 (1%)
		Ust ⁶	336	196 (58%)	10 (3%)	0	4 (1%)

AE = adverse event; Etan = etanercept; Ixe = ixekizumab; NR = not reported; Pbo = placebo; PI = Product Information; SC = subcutaneous; SAE = serious adverse event; Sec = secukinumab; Ust = ustekinumab

¹ Ixekizumab 160 mg SC Week 0; 80 mg Weeks 2, 4, 6, 8, 10 (PI recommended dose)

² Etanercept 50 mg SC twice weekly

³ Secukinumab 300 mg SC Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

⁴ Ustekinumab 45 mg SC Weeks 0, 4 (PI recommended dose)

⁵ Ustekinumab 90 mg SC Weeks 0, 4

⁶ Ustekinumab 45 mg SC for patients ≤ 100 kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

A summary of specific adverse events of interest including infection, serious infection, malignancy, skin cancer, cardiovascular disease, upper respiratory tract infection, liver enzyme changes, headache, pruritus and administration site disorders is provided in Table 98, Appendix B.

In the UNCOVER 2 and 3, FIXTURE and ACCEPT trials the incidence of each adverse event was very similar for the biologic being studied and etanercept. The only exception was administration site disorders in the ACCEPT trial in which approximately 4% of ustekinumab patients and 25% of etanercept patients had an event. The ACCEPT trial reported that the majority of these reactions were mild and no anaphylaxis or serum sickness-like reactions were reported.

In the CLEAR trial, the incidence of adverse events was very similar for secukinumab and ustekinumab patients.

2.4 Network meta-analysis results for the PBS-listed biologics in the treatment of severe CPP

Two outcome measures were selected for the network meta-analyses:

1. The proportion of patients achieving a PASI 75 response at 12 weeks; and
2. The incidence of any adverse event at 12 weeks.

Excel was used to consolidate and standardise the outcome measures. The data were then imported into STATA for meta-analysis and network meta-analysis.

A multiple-treatments network meta-analysis was undertaken to summarise the results of the PBS-listed biologics for each of the outcomes where common treatment arms existed (PASI 75 and adverse events) using the trial data in the clinical evidence base. The network meta-analysis was conducted using STATA network package and mvmeta (73, 74) (The STATA.do file for PASI 75 is presented in Appendix C).

The network meta-analysis allowed for heterogeneity between trials during calculation (random effects). An inconsistency model was also applied to test for disagreement between direct and indirect evidence (73). As the outcomes were dichotomous outcomes, the measurements of treatment effect calculated were odds ratios (OR) and their 95% CI. Differences between treatments were considered statistically significant if there were no overlap in 95% CI.

The network meta-analysis considered the approved Product Information doses of the PBS-listed biologics. Etanercept 25 mg twice weekly was considered separately to etanercept 50 mg once weekly and ustekinumab 90 mg, which is recommended in patients greater than 100 kg was included.

Efficacy

Figure 1 presents the number of trials and the comparisons available for assessing comparative efficacy in terms of the proportion of patients achieving a PASI 75 response at 12 weeks. Thirty-five RCTs were identified for inclusion in the analysis (N = 22,422).

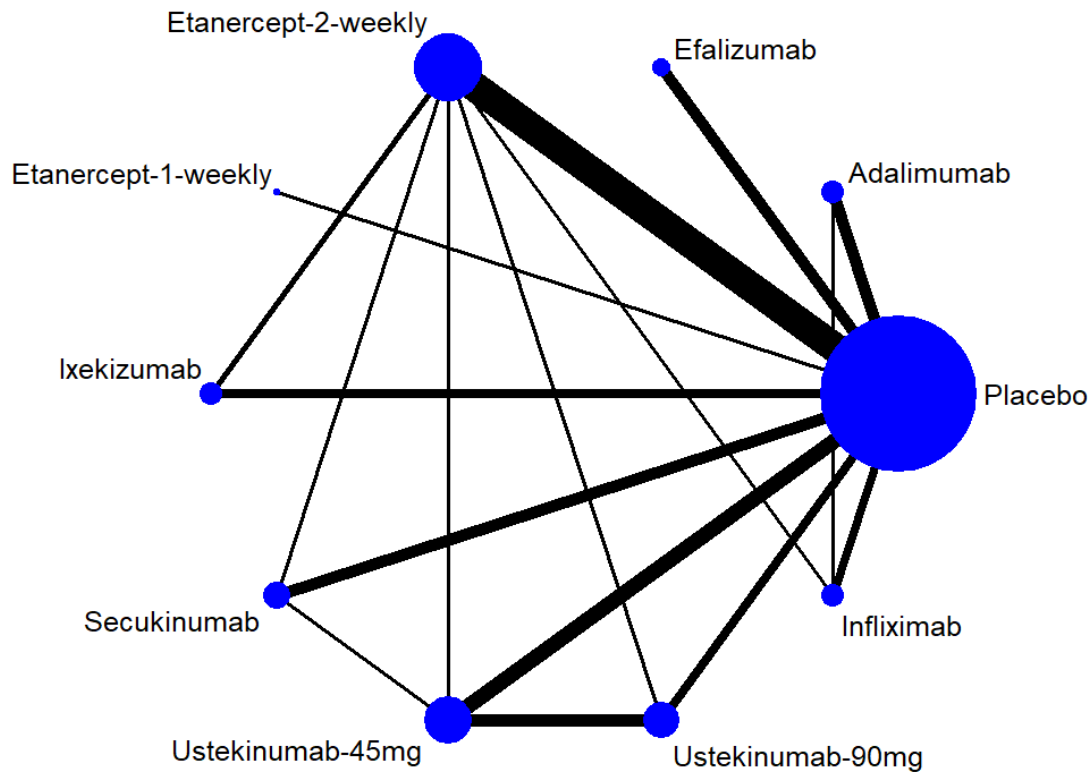


Figure 1: Network analysis of trial evidence available for the proportion of patients achieving a Psoriasis Area and Severity Index 75 response at 12 weeks

Lines identify trials, which included trials with those comparisons, and thickness of lines represent the number of patients in the trials

Figure 8, Appendix C presents the efficacy results (PASI 75 response at 12 weeks to placebo) of the individual trials and the network meta-analysis results comparing individual biologics to placebo.

Figure 2 demonstrates that all of the PBS-listed biologics provided a significantly better response when compared to placebo. Ixekizumab produced the largest pooled effect (OR = 177.98; 95% CI: 126.67, 250.08), followed by infliximab (OR = 104.65; 95% CI: 48.00, 228.19).

Efalizumab, which is no longer PBS-listed, had the lowest efficacy point estimate of the biologics. Of the PBS-listed biologics etanercept, was the next lowest compared to placebo (OR = 21.48; 95% CI: 17.19, 26.83 (25 mg twice weekly) and OR = 27.00; 95% CI: 3.47, 209.94 (50 mg once weekly)).

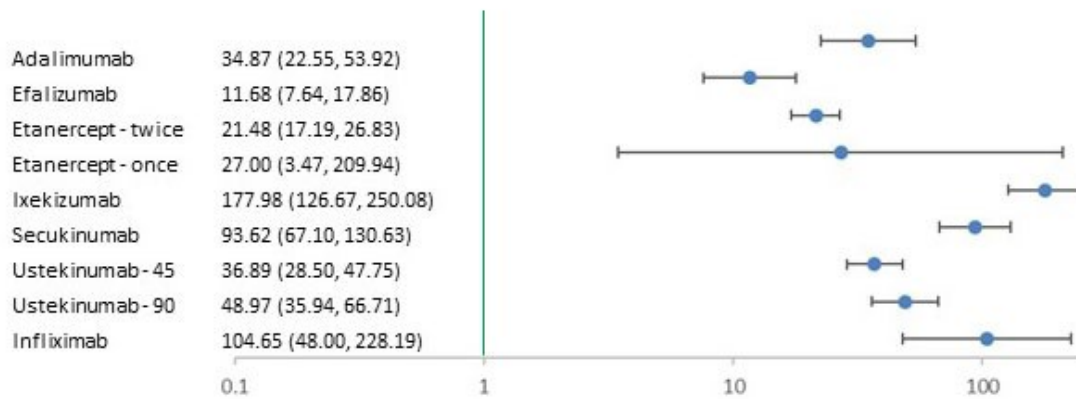


Figure 2: Forest plot of the OR (95% CI) for the proportion of patients achieving a PASI 75 response at 12 weeks – PBS-listed biologic versus placebo. Network diagram of dichotomous variable.

Figure 3 presents the results of the network meta-analysis, comparing the efficacy of the PBS-listed biologics at achieving a PASI 75 at 12 weeks against each other.

The forest plots demonstrated that ixekizumab provided a significantly better response to adalimumab (OR = 5.11; 95% CI: 2.94, 8.87), etanercept 25 mg twice weekly (OR = 8.29; 95% CI: 6.05, 11.36), secukinumab (OR = 1.90; 95% CI: 1.22, 2.96) and ustekinumab (OR = 4.82; 95% CI: 3.24, 7.18 (45 mg)). Ixekizumab did not have a significantly better response when compared to etanercept 50 mg once weekly or infliximab, due to the large uncertainty in the evidence comparing these two treatments (large confidence intervals).

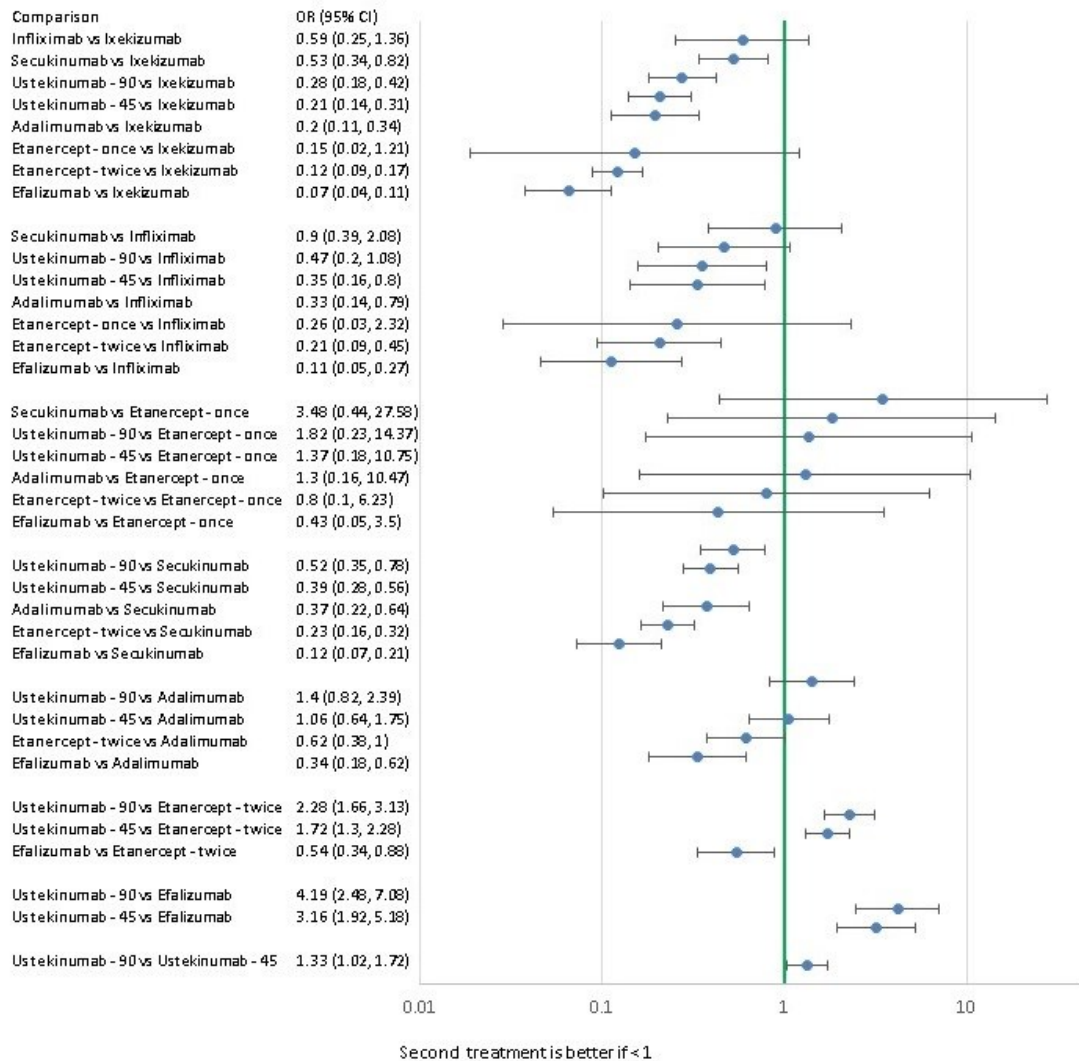


Figure 3: Forest plot of the OR (95% CI) for the proportion of patients achieving a PASI 75 response at 12 weeks – PBS-listed biologic versus PBS-listed biologic. Network diagram of dichotomous variable.

OR values less than one suggest that the first biologic in the comparison is less likely to result in a PASI 75 response compared to the second

CI = confidence interval; Etanercept – once = etanercept 50 mg once weekly; Etanercept – twice = etanercept 25 mg twice weekly; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PBS = Pharmaceutical Benefits Scheme; vs = versus

Safety

Figure 4 presents the number of trials and the comparisons available for assessing comparative safety in terms of the proportion of patients experiencing an adverse event at 12 weeks. Twenty four RCTs were identified for inclusion in the analysis (N = 7,877).

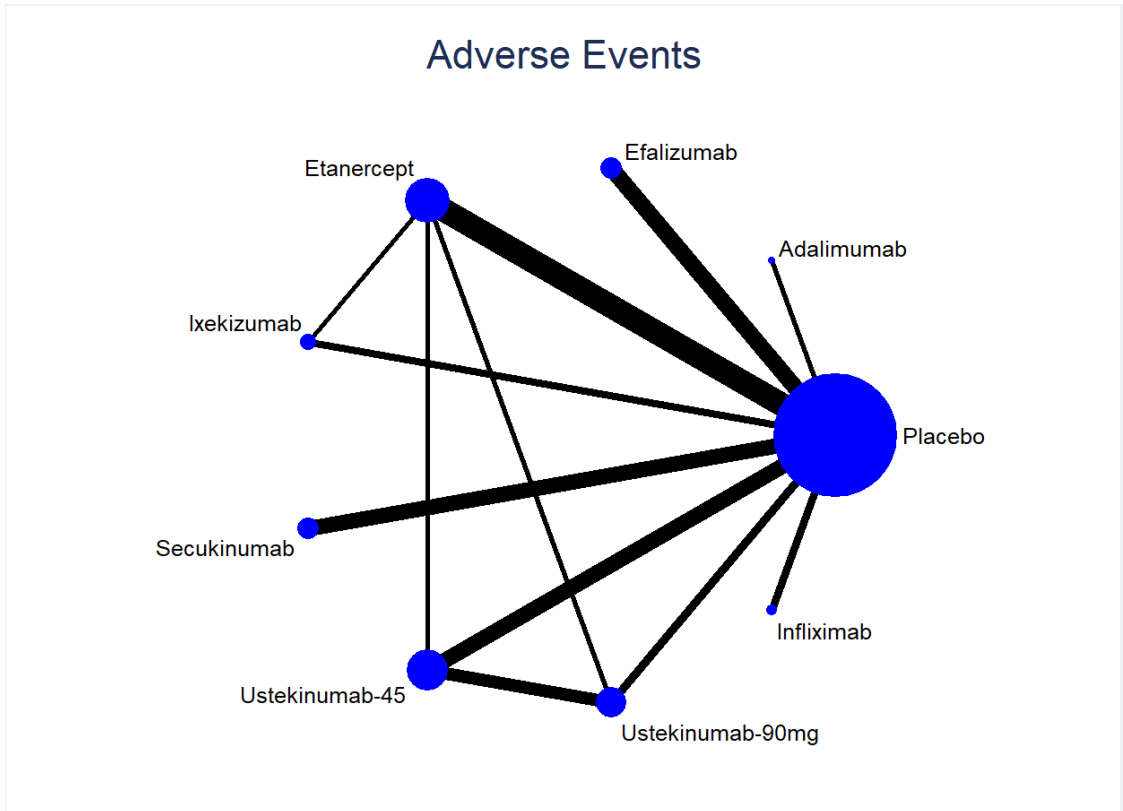


Figure 4: Network analysis of trial evidence available for the proportion of patients experiencing and adverse event at 12 weeks

Lines identify trials, which included trials with those comparisons, and thickness of lines represent the number of patients in the trials

Figure 5 presents the results of the network meta-analysis, comparing the safety of the PBS-listed biologics with placebo in terms of the proportions of patients experiencing an adverse event at 12 weeks. The forest plot demonstrated that the de-registered efalizumab was most likely, compared to placebo, to result in an adverse event at 12 weeks (OR= 1.70; 95% CI: 1.40, 2.06), followed by ixekizumab (OR = 1.56; 95% CI: 1.32, 1.84) (infliximab was higher than ixekizumab but had wide confidence intervals).

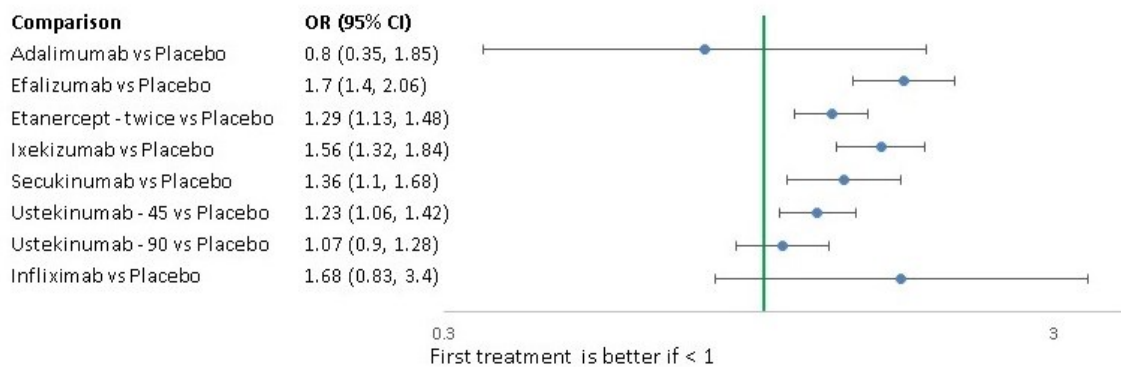


Figure 5: Forest plot of the OR (95% CI) for the proportion of patients experiencing an adverse event at 12 weeks – PBS-listed biologic versus placebo. Network diagram of dichotomous variable.

OR values less than one suggest that the first biologic in the comparison is less likely to result in an adverse event compared to the second

CI = confidence interval; Etanercept – once = etanercept 50 mg once weekly; Etanercept – twice = etanercept 25 mg twice weekly; OR = odds ratio; PBS = Pharmaceutical Benefits Scheme; vs = versus

Figure 6 presents the results of the network meta-analysis, comparing the safety of the PBS-listed biologics in terms of the proportions of patients experiencing an adverse event at 12 weeks.

in Table 37. No evidence was identified for the use of infliximab, ixekizumab or secukinumab in children with severe CPP.

Table 37: Biologics in children and adolescents: publication details

Trial	Citation	Description	Seen by PBAC?
Adalimumab versus methotrexate			
Papp (2017)	Papp K, Thaçi D, Marcoux D, et al. Efficacy and safety of adalimumab every other week versus methotrexate once weekly in children and adolescents with severe chronic plaque psoriasis: a randomised, double-blind, Phase 3 trial. <i>Lancet</i> . 2017; 390: 40-49.	RCT: efficacy, safety, QoL	No
Etanercept versus placebo			
Paller (2008)	Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. <i>New England Journal of Medicine</i> . 2008; 358(3): 241-251.	RCT: efficacy, safety	Yes
	Langley RG, Paller AS, Hebert AA, et al. Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial. <i>Journal of the American Academy of Dermatology</i> . 2010; 64(1): 64-70.	RCT: QoL	Yes
	Paller AS, Siegfried EC, Eichenfield LF, et al. Long-term etanercept in pediatric patients with plaque psoriasis. <i>Journal of the American Academy of Dermatology</i> . 2010; 63(5): 762-768.	OL extension: longer term efficacy, safety	Yes
Ustekinumab versus placebo			
CADMUS	Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized Phase 3 CADMUS study. <i>Journal of the American Academy of Dermatology</i> . 2015; 73(4): 594-603.	RCT: efficacy, safety, QoL	No

OL = open-label; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial

The risk of bias was assessed to be low in terms of allocation concealment, blinding of participants and personnel, incomplete outcome reporting and selective outcome reporting - see Table 95, Appendix D. Papp (2017) stated that assessors were blinded; however, this was unclear in Paller (2008) and CADMUS. Pharmaceutical companies sponsored all three trials, resulting in a high risk of other biases.

Inclusion and exclusion criteria

Table 96, Appendix D presents the inclusion and exclusion criteria for the three trials which considered the use biologics in children and adolescents.

The Papp (2017) and Paller (2008) trials recruited children and adolescents from 4 to 17 years of age; CADMUS recruited adolescents aged 12 to 17. All three trials required patients to have had CPP for at least six months and for it to be poorly controlled or unresponsive to topical therapy. The Paller (2008) and CADMUS trials included patients with a BSA affected of 10% or more, a baseline PASI score of 12 or more and a baseline PGA score of three or more. These characteristics differed in the Papp (2017) trial.

The exclusion criteria were not defined in the CADMUS publication. As Papp (2017) used methotrexate as a comparator, recent use or a contraindication to methotrexate excluded

patients from the trial. Patients were also excluded if they had used a biologic other than etanercept within four weeks or received recent phototherapy. Patients were excluded from Paller (2008) if they had another form of psoriasis, other skin conditions or had received previous treatment with an anti-tumour necrosis factor.

Baseline characteristics

The baseline characteristics are presented in Table 38. For children and adolescents the Children's Dermatology Life Quality Index (CDLQI) score was used to assess quality of life. This score ranges from 0 to 30, with higher scores indicating a worse quality of life.

The within trial randomisation appeared successful in the Paller (2008) etanercept trial. In terms of disease characteristics, the within trial randomisation was successful in Papp (2017) and CADMUS; however, in terms of baseline characteristics randomisation in these small trials was less successful.

Table 38: Biologics in children: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	CDLQI; mean (SD)
Adalimumab versus methotrexate										
Papp (2017)	Ada ¹	39	12.6 (4.4)	54%	W: 87%	50 (23)	5 (3)	26% (16)	16.9 (5.8)	NR
	Ada ²	38	13.0 (3.3)	45%	W: 92%	51 (20)	5 (4)	28% (20)	18.9 (10.0)	NR
Etanercept versus placebo										
Paller (2008)	Etan ^{3*}	106	14 (4-17)	52%	W: 78%	60 (18-168)	7 (0-18)	21% (10-90)	16.7 (12.0-51.6)	8.9 (6.0)
	Pbo	105	13 (4-17)	50%	W: 71%	60 (17-132)	6 (0-16)	20% (10-95)	16.4 (12.0-56.7)	10.0 (6.4)
Ustekinumab versus placebo										
CADMUS	Ust ⁴	37	15.1 (1.7)	49%	W: 81%	68 (25)	6 (4)	34% (21)	21.0 (8.5)	9.4 (6.5)
	Ust ⁵	36	14.8 (1.7)	44%	W: 94%	62 (17)	6 (4)	32% (23)	21.7 (10.4)	10.3 (6.6)
	Pbo	37	15.6 (1.5)	54%	W: 92%	65 (15)	6 (5)	27% (16)	20.8 (8.0)	9.1 (6.4)

Ada = adalimumab; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; Mtx = methotrexate; NR = not reported; PASI = Psoriasis Area and Severity Index; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Ust = ustekinumab; *Italics = median (range)*

¹ Adalimumab 0.4 mg/kg SC every other week

² Adalimumab 0.8 mg/kg SC every other week

^{3*} Etanercept 0.8 mg/kg SC once weekly (PI recommended dose)

⁴ Ustekinumab 0.375 mg/kg if ≤ 60 kg or 22.5 mg if 60-100 kg or 45 mg if > 100 kg SC at Weeks 0, 4

⁵ Ustekinumab 0.75 mg/kg if ≤ 60 kg or 45 mg if 60-100 kg or 90 mg if > 100 kg SC at Weeks 0, 4

Children and adolescents are required to have a PASI score of greater than 15 (i.e. severe CPP) to be eligible to receive etanercept. It appeared that patients in each of the identified trials had severe CPP as the average baseline PASI scores exceeded 15.

Treatment details

The treatment regimens used in each of the trials and the approved Australian Product Information recommended doses for children and adolescents are presented in Table 97, Appendix D.

For children and adolescents less than 40 kg (≥ 40 kg) the recommended dose of adalimumab for the treatment of CPP is 20 mg (40 mg) subcutaneously every other week. The Papp (2017) trial did not utilise this dose, instead examining the effect of adalimumab at either 0.4 mg/kg every other week or 0.8 mg/kg every other week compared to oral methotrexate. Papp (2017) reported outcomes at 16 weeks.

The recommended dose of etanercept for children and adolescents is 0.8 mg/kg subcutaneously weekly. This dose was compared to placebo over 12 weeks in the Paller (2008) trial.

The approved Australian Product Information for ustekinumab does not provide a recommended dose for children and adolescents. The CADMUS trial compared two dosing regimens of ustekinumab (0.375 mg/kg or 0.75 mg/kg at Weeks 0 and 4) to placebo over 12 weeks.

Efficacy

The following outcomes were used to assess the efficacy of the PBS-listed biologics in the treatment of children and adolescents with CPP:

- Proportion of patients achieving a PASI 50, 75, 90 and 100 response; and
- Mean change in CDLQI score.

Efficacy results for adalimumab, etanercept and ustekinumab are presented in Table 39.

The efficacy of adalimumab was difficult to assess, as adalimumab was not given at the recommended dose. However, adalimumab appeared more effective than methotrexate when given at 0.8 mg/kg every other week in terms of the proportions of patients achieving PASI 75, 90 and 100 responses at 16 weeks.

Etanercept, given at the recommended dose for children and adolescents in the Paller (2008) trial resulted in 75%, 57% and 27% of patients achieving a PASI 50, 75 and 90 response respectively. The proportion of placebo patients achieving the corresponding responses were 23%, 11% and 7%.

Ustekinumab was more effective than placebo in terms of the proportions of patients achieving a PASI 75 and 90 response at both dosing regimens after 12 weeks. Approximately 80% of ustekinumab patients compared to 11% of placebo patients achieved a PASI 75 response and 58% compared to 5% achieved a PASI 90 response.

Table 39: Biologics in children and adolescents: efficacy results

Trial	Time horizon	Arm	N	PASI 50; n (%)	PASI 75; n (%)	PASI 90; n (%)	PASI 100; n (%)	Δ CDLQI; mean (SD)
Adalimumab versus methotrexate								
Papp (2017)	16 weeks	Ada ¹	39	NR	17 (44%)	12 (31%)	4 (10%)	-4.9 (6.2)
		Ada ²	38	NR	22 (58%)	11 (29%)	7 (18%)	-6.6 (6.2)
Etanercept versus placebo								
Paller (2008)	12 weeks	Etan ^{3*}	106	75%	57%	27%	NR	-52%
		Pbo	105	23%	11%	7%	NR	-18%
Ustekinumab versus placebo								
CADMUS	12 weeks	Ust ⁴	37	NR	29 (78%)	20 (54%)	NR	-5.6 (6.4)
		Ust ⁵	36	NR	29 (81%)	22 (61%)	NR	-6.7 (5.6)
		Pbo	37	NR	4 (11%)	2 (5%)	NR	-1.5 (3.2)

Ada = adalimumab; CDLQI = Children's Dermatology Life Quality Index; Etan = etanercept; Mtx = methotrexate; NR = not reported; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; Pbo = placebo; SD = standard deviation; Ust = ustekinumab; *Italics = percentage change in CDLQI*

¹ Adalimumab 0.4 mg/kg SC every other week

² Adalimumab 0.8 mg/kg SC every other week

^{3*} Etanercept 0.8 mg/kg SC once weekly (PI recommended dose)

⁴ Ustekinumab 0.375 mg/kg if ≤ 60 kg or 22.5 mg if 60-100 kg or 45 mg if > 100 kg SC at Weeks 0, 4

⁵ Ustekinumab 0.75 mg/kg if ≤ 60 kg or 45 mg if 60-100 kg or 90 mg if > 100 kg SC at Weeks 0, 4

In terms of improving quality of life, adalimumab and methotrexate treatment had a similar effect. Etanercept and ustekinumab both appeared to result in an improved quality of life compared to placebo.

Safety

The adverse events reported by children and adolescents in the Papp (2017), Paller (2008) and CADMUS trials are summarised in Table 40.

Adverse events were poorly reported in all the three trials. Approximately 70% of adalimumab and methotrexate patients in Papp (2017) and 50% of ustekinumab and placebo patients in CADMUS experienced an adverse event. The total number of adverse events in Paller (2008) was significantly higher for patients who received etanercept (914) than for those who received placebo (144).

Serious adverse events were rarely reported.

Table 40: Biologics in children: summary of adverse events; number of patients affected (%)

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Adalimumab versus methotrexate							
Papp (2017)	16 weeks	Ada ¹	39	30 (77%)	3 (8%)	NR	NR
		Ada ²	38	26 (68%)	0	NR	NR
Etanercept versus placebo							
Paller (2008)	12 weeks	Etan ^{3*}	210	<i>914</i>	0	0	NR
		Pbo	105	<i>144</i>	0	0	NR
Ustekinumab versus placebo							
CADMUS	12 weeks	Ust ⁴	37	19 (51%)	1 (3%)	NR	0
		Ust ⁵	36	16 (44%)	0	NR	0
		Pbo	37	21 (57%)	0	NR	0

Ada = adalimumab; AE = adverse event; Etan = etanercept; Mtx = methotrexate; NR = not reported; Pbo = placebo; PI = Product Information; SAE = serious adverse event; SC = subcutaneous; Ust = ustekinumab; *Italics = number of events*

¹ Adalimumab 0.4 mg/kg SC every other week

² Adalimumab 0.8 mg/kg SC every other week

^{3*} Etanercept 0.8 mg/kg SC once weekly (PI recommended dose)

⁴ Ustekinumab 0.375 mg/kg if ≤ 60 kg or 22.5 mg if 60-100 kg or 45 mg if > 100 kg SC at Weeks 0, 4

⁵ Ustekinumab 0.75 mg/kg if ≤ 60 kg or 45 mg if 60-100 kg or 90 mg if > 100 kg SC at Weeks 0, 4

A summary of specific adverse events of interest including infection, serious infection, malignancy, skin cancer, cardiovascular disease, upper respiratory tract infection, liver enzyme changes, headache, pruritus and administration site disorders is presented in Table 98, Appendix D.

2.6 Longer-term safety of the PBS-listed biologics in the treatment of severe CPP

A number of the RCT's identified in the systematic literature review allowed patients to enter open-label extension studies following the blinded and/or comparator-controlled periods. The longer-term safety data (i.e. ≥ 1 year/50 weeks) for the PBS-listed biologics in the treatment of CPP presented below are from these open-label extension studies and four large observational studies (N > 200) relating to the longer-term use of etanercept identified in the systematic review.

Adverse event data from the Therapeutic Goods Administration (TGA) included information on adverse events reported from 2000 to 2017. Reports for adalimumab (2004 to 2017), etanercept (2000-2017), infliximab (2000-2017), ixekizumab (2017), secukinumab (2015-2017) and ustekinumab (2010-2017) were obtained. Various adverse events were reported and were mainly associated with gastrointestinal disorders, immune system disorders and infections. However, given the varying time frames for data collection, the biases associated with reporting of adverse events, and that it is not possible to identify what indication the medications were being used for when the event occurred, it is not possible to interpret comparative safety between the medications using this data. This data has not been included in the outcomes below.

The publication details, inclusion and exclusion criteria, baseline characteristics and treatment details for each of the open-label extension studies are presented above in the relevant section for each biologic. The publication details, inclusion and exclusion criteria, baseline characteristics and treatment details of the four observational studies are presented in Table 99 to Table 102 Appendix E.

Safety

Table 41 presents the longer-term safety data for adalimumab, etanercept, infliximab, ixekizumab and ustekinumab in the treatment of CPP. No longer-term safety data were identified for secukinumab.

The differing time horizons and dosing regimens utilised made it difficult to compare the longer-term safety of the PBS-listed biologics. In the longer-term extension studies, the proportions of patients experiencing any adverse event was relatively unchanged compared to the comparator-controlled period for the respective adalimumab, etanercept, infliximab and ixekizumab trials. The three-year adverse event rate for ustekinumab in PHOENIX 1 was higher than that reported in the 12 week trial.

The incidence of serious adverse events increased in the longer-term for all of the PBS-listed biologics; however remained relatively low. The exception was the Asahina (2015) adalimumab study; at 220 weeks (approximately four years) the proportion of patients experiencing a serious adverse event was 25%.

The long-term incidences of death, serious infection, malignancy, skin cancer and cardiovascular disease were very low for each of the biologics. Asahina (2015) was the only study to report liver disease as a long term effect; however, it should be noted that liver disease in this study included any value for hepatic-related laboratory tests which exceeded the upper limit of normal (ULN).

Table 41: Longer-term safety of biologics in the treatment of CPP (% of patients affected)

Trial	Time horizon	Arm	N	AEs	SAEs	Death	Infection	Serious infection	Malignancy	CVD	Liver disease
Adalimumab											
Gordon (2015)	52 weeks	Ada ^{1*}	38	61%	3%	NR	37%	3%	0	0	NR
Gordon (2006)	60 weeks	Ada ^{1*}	92	78%	2%	0	NR	0	1%	0	NR
		Ada ²	50	78%	14%	2%	NR	0	6%	8%	NR
REVEAL	Year 1	Ada ³	1,159	3,174	5%	0	NR	2%	< 1%	< 1%	NR
	Year 2		621	978	6%	0	NR	< 1%	1%	< 1%	NR
	Year 3		443	857	11%	0	NR	2%	1%	1%	NR
Asahina (2015)	220 weeks	Ada ³	163	2,851	25%	0	NR	4%	2%	3%	59%
Etanercept											
CRYSTAL	54 weeks	Etan ^{4*}	357	79%	6%	0	NR	1%	1%	NR	NR
		Etan ⁵	363	75%	9%	1%	NR	1%	2%	NR	NR
Elewski (2007)	72 weeks	Etan ⁶	912	NR	8%	< 1%	NR	2%	7%	NR	NR
Tyring (2006)	84 weeks	Etan ⁷	618	NR	NR	< 1%	NR	2%	2%	NR	NR

Trial	Time horizon	Arm	N	AEs	SAEs	Death	Infection	Serious infection	Malignancy	CVD	Liver disease
Luger (2016)	3 years	Etan ⁸	926	30%	6%	< 1%	9%	< 1%	1%	NR	NR
OBSERVE-5	3 years	Etan ⁸	2,511	NR	12%	1%	NR	3%	3%	1%	NR
Infliximab											
Torii (2010)	72 weeks	Inf ^{9*}	50	100%	12%	0	86%	2%	NR	NR	NR
RESTORE	124 weeks	Inf ^{9*}	222	73%	11%	0	-	5%	1%	0	-
		Inf ¹⁰	219	71%	11%	1%	-	1%	< 1%	< 1%	-
Ixekizumab											
Leonardi (2012)	52 weeks	Ixe ¹¹	120	67%	8%	-	-	2%	1%	3%	-
Ustekinumab											
PHOENIX 1	3 years	Ust ^{12*}	378	92%	8%	0	76%	1%	4%	1%	-
		Ust ¹³	375	91%	10%	1%	77%	3%	1%	< 1%	-
	5 years	Ust ^{12*}	289	-	-	< 1%	-	5%	3%	3%	-
		Ust ¹³	254	-	-	2%	-	7%	2%	1%	-

Ada = adalimumab; AE = adverse event; CVD = cardiovascular disease; Inf = infliximab; IV = intravenous; NR = not reported; PI = Product Information; SAE = serious adverse event; SC = subcutaneous; Ust = ustekinumab; *Italics = number of events*

^{1*} Adalimumab 80 mg SC Week 0; then 40 mg every other week (PI recommended dose)

² Adalimumab 80 mg SC Week 0; then 40 mg every week

³ Adalimumab – all patients who had received a dose

^{4*} Etanercept 25 mg SC twice weekly (PI recommended dose)

⁵ Etanercept 50 mg SC twice weekly until response; pause until relapse; 25 mg twice weekly until response; pause until relapse

⁶ Etanercept 50 mg SC once or twice weekly

⁷ Etanercept 50 mg SC twice weekly

⁸ Etanercept SC – dose determined by study investigator

^{9*} Infliximab 5 mg/kg IV every 8 weeks (PI recommended dose)

¹⁰ Infliximab 5 mg/kg IV when required

¹¹ Ixekizumab 120 mg SC every 4 weeks

^{12*} Ustekinumab 45 mg SC every 12 weeks (PI recommended dose)

¹³ Ustekinumab 90 mg SC every 12 weeks

Efficacy

Although the ToR2 focussed on the longer-term safety of the PBS-listed biologics, some longer-term efficacy data was identified in the systematic literature review. These data are presented in Table 103, Appendix E.

Again, the differing time horizons and dosing regimens utilised made it difficult to compare the longer-term efficacy of each PBS-listed biologic. However, in terms of the proportions of patients continuing to achieve a PASI 75 response, it appeared that the biologics continued to have an efficacious effect beyond one year. Ustekinumab appeared to retain its efficacy for up to five years.

Quality of life improvements also appeared to be maintained in the longer-term.

2.7 Efficacy and safety of biologics in the treatment of mild-to-moderate CPP

An aim of ToR 2 and the systematic literature review was to compare evidence on the efficacy and safety of the PBS-listed biologics in the treatment of mild-to-moderate CPP compared to severe CPP. Severe CPP is defined in the PBS restrictions as a PASI score of greater than 15.

The majority of the RCTs identified in the literature review (including those that were considered by the PBAC previously) required patients to have moderate-to-severe CPP which, when described, was defined as:

- a baseline PASI score of either 10 and above or 12 and above; and
- a BSA affected of 10% or more.

Previously, when considering the biologics for the treatment of severe CPP, the PBAC had accepted the trial data as the average baseline PASI scores exceeded 15.

None of the identified trials were designed to compare outcomes based on baseline PASI scores or provided relevant subgroup analyses. Therefore, it was not possible to compare the efficacy and safety of the biologics in mild-to-moderate CPP to their efficacy and safety in severe CPP.

Although none of the identified trials claimed to assess the use of the PBS-listed biologics in patients with mild-to-moderate CPP, one etanercept study was identified in the systematic literature review in which patients had an average baseline PASI score that did not exceed 15. This small trial, Gisondi (2008), is discussed below.

Publication details

The publication details of the identified RCT, Gisondi (2008), are presented in Table 42.

Table 42: Mild-to-moderate CPP: publication details

Trial	Citation	Description	Seen by PBAC?
Gisondi (2008)	Gisondi P, Del Giglio M, Cotena C and Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. <i>British Journal of Dermatology</i> . 2008; 158: 1345-1349.	RCT: efficacy	No

CPP = chronic plaque psoriasis; PBAC = Pharmaceutical Benefits Advisory Committee; RCT = randomised controlled trial

Gisondi (2008) had a low risk of bias (see Table 104, Appendix F) in terms of random sequence generation, allocation concealment, blinding of assessors, incomplete reporting and selective outcome reporting, and a high risk of bias in terms of blinding of participants. The trial was funded by a pharmaceutical company.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the Gisondi (2008) trial are presented in Table 105, Appendix F. Patients were included if they were adult and had active, but stable, plaque psoriasis. There was no minimum PASI score or BSA affected defined in the trial. Patients

were excluded if they had another type of psoriasis, psoriatic arthritis, or if they had previously received biologics

Baseline characteristics

Baseline characteristics for patients in the small Gisondi (2008) trial are presented in Table 43. Randomisation appeared successful in terms of age, weight, baseline BSA affected and PASI scores. Randomisation was less successful in terms of gender and duration of disease.

Table 43: Mild-to-moderate CPP: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Etanercept versus etanercept plus acitretin versus acitretin										
Gisondi (2008)	Etan ^{1*}	22	55.3 (10.9)	55%	NR	80 (9)	24 (11)	13% (6)	11.0 (4.6)	NR
	Etan ^{1*} + Aci	18	53.4 (12.3)	50%	NR	78 (11)	19 (16)	13% (8)	11.9 (6.5)	NR
	Aci	20	55.0 (11.3)	60%	NR	78 (10)	19 (17)	11% (7)	10.4 (5.3)	NR
AVERAGE FOR TRIAL										
N = 60	NR	NR	54.6	55%	NR	79	21	12%	11.1	NR

Aci = acitretin; BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; NR = not reported; PASI = Psoriasis Area and Severity Index; PI = Product Information; SC = subcutaneous; SD = standard deviation

^{1*} Etanercept 25 mg SC twice weekly (PI recommended dose)

Overall, the average Gisondi (2008) trial patient had 12% BSA affected and a baseline PASI score of 11.1. Patients were 54.6 years old, male, approximately 79 kg and had been suffering from CPP for approximately 21 years. Baseline DLQI scores were not reported.

Treatment details

Table 106, Appendix F, summarises the treatment regimens used in the Gisondi (2008) trial. Etanercept was given at the recommended dose (25 mg twice weekly) for 24 weeks and compared to etanercept plus acitretin and acitretin alone.

Efficacy

Gisondi (2008) reported the proportions of patients achieving a PASI 50 and PASI 75 response. These results are presented in Table 44 for the etanercept arm only, and compared with the results from Gottlieb (2003). Gottlieb (2003) used the same dosing regimen and time horizon, but included patients with a mean baseline PASI score of 17.8.

Table 44: Mild-to-moderate CPP efficacy results, plus a comparison with severe CPP results

Trial	Time horizon	Arm	N	PASI 50, n (%)	PASI 75, n (%)
Gisondi (2008)	24 weeks	Etanercept 25 mg SC twice weekly	22	15 (68%)	10 (45%)
Gottlieb (2003)	24 weeks	Etanercept 25 mg SC twice weekly	57	NR (77%)	32 (56%)

CPP = chronic plaque psoriasis; NR = not reported; PASI 50, 75 = reduction in Psoriasis Area and Severity Index score of 50% or 75%; PI = Product Information; SC = subcutaneous

Although both trials were small, the naïve indirect comparison (there was no common placebo comparator) suggested that etanercept might be marginally more effective in patients with a baseline PASI greater than 15 than in those with less severe disease.

Safety

Gisondi (2008) did not report any relevant safety outcomes.

Adalimumab subgroup analysis

[Redacted text]

[Redacted text]

[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

[Redacted text]

[Redacted text]

2.8 Efficacy of the PBS-listed biologics in patients with severe CPP and concomitant PsA

PsA is a chronic inflammatory arthritis that occurs in up to 39% of individuals who suffer from psoriasis. (76) PsA is a serious disease which results an increasing number of joints affected and an increasing severity of the joints affected over time. (77) At present, all of the biologics listed on the PBS for the treatment of severe CPP are also listed for the treatment of PsA, with the exception of ixekizumab.

Although PsA appears to be more prevalent in patients with psoriasis of low severity, (76) as part of the ToR 2, the effectiveness of the PBS-listed biologics in patients with severe CPP and concomitant PsA was considered.

Publication details

The systemic literature review identified four trials (with 6 associated publications) which considered the effectiveness etanercept, infliximab and secukinumab in patients with severe CPP and PsA. These are listed in Table 46. (To enable an analysis, severe CPP was considered to be a baseline PASI score of greater than or equal to 10.)

Table 46: Severe CPP and PsA trials: publication details

Trial ID	Citation	Description
Etanercept		
Mease (2000)	Mease P, Goffe B, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. <i>Lancet</i> . 2000; 356(9227): 385-390.	RCT: efficacy, safety
PRESTA	Sterry W, Ortonne JP, Kirkham B, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. <i>BMJ</i> . 2010; 340: c147.	RCT: Efficacy, safety
	Gniadecki R, Robertson D, Molta CT, et al. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. <i>Journal of the European Academy of Dermatology and Venereology</i> . 2010; 26(11): 1436-1443.	RCT: QoL
Infliximab		
IMPACT 2	Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. <i>Annals of the Rheumatic Diseases</i> . 2005; 64(8): 1150-1157.	RCT: efficacy, safety
	Kavanaugh A, Krueger GG, Beutler A, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. <i>Annals of the Rheumatic Diseases</i> . 2007; 66(4): 498-505.	OL extension: longer-term efficacy, safety
Secukinumab		
FUTURE 2	McInnes IB, Mease PJ, Kirkman B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, Phase 3 trials. <i>Lancet</i> . 2015; 386: 1137-1146.	RCT: efficacy, safety

CPP = chronic plaque psoriasis; PsA = psoriatic arthritis; QoL = quality of life; RCT = randomised controlled trial

No trials for the use of adalimumab, ixekizumab or ustekinumab in the treatment of severe CPP and PsA were identified in the systematic literature review.

The risk of bias was assessed in Table 107, Appendix G. All trials were double blinded in terms of participants and personnel, and had a low risk of incomplete outcome and selective outcome reporting. The manner of random sequence generation was not described in the PRESTA trial and allocation concealment was unclear PRESTA and the IMPACT 2 trials. However, all four trials were sponsored by a pharmaceutical company, which resulted in a high risk of other biases.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the identified trials relating to the treatment of severe CPP with concomitant PsA are presented in Table 108, Appendix G.

The inclusion criteria for the identified trials were very similar in terms of including adults who had plaque psoriasis and active PsA. PsA was defined as two or more swollen and two or more tender or painful joints in the PRESTA trial, three or more joints in the Mease (2000) and FUTURE 2 trials and five or more joints in the IMPACT 2 trial.

Three of the trials - Mease (2000), IMPACT 2, and FUTURE 2 - required patients to be unresponsive to non-steroidal anti-inflammatory drugs and a candidate for immunomodulatory therapy.

The exclusion criteria varied between the trials; however, patients were commonly excluded if they were suffering from other skin conditions or had a recent serious infection.

Baseline characteristics

The baseline characteristics for the patients in the identified trials are presented in Table 47.

The disease characteristics presented are:

- PASI score;
- number of tender joints and number of swollen joints –
 - 76- or 78-joint count of tender and swollen joints, including 66 or 68 routinely evaluated in a rheumatology count, plus 10 additional joints often involved in PsA (the first carpometacarpal and the distal interphalangeal joint of the toes);
- the Health Assessment Questionnaire Disability Index (HAQ DI) –
 - this is a questionnaire designed for the assessment of disability due to rheumatoid arthritis;
 - scores range from 0 to 3, with higher scores indicating more severe disease.

Trials with an average baseline PASI score of ten or greater were included in the analysis. Only arms receiving approved Product Information doses, commonly utilised doses or placebo are presented.

The within trial randomisation was broadly successful, especially in the larger trials. In Mease (2000), which had small patient numbers (N = 60), randomisation in terms of weight and baseline PASI score was less successful.

The populations of the two etanercept trials were heterogeneous in terms of gender, HAQ DI score and PASI score at baseline.

Table 47: Severe CPP and PsA trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race, %	Weight, kg; mean (SD)	DoD, years; mean (SD)	Tender joints; mean (SD)	Swollen joints; mean (SD)	HAQ DI; mean (SD)	PASI; mean (SD)
Etanercept											
Mease (2000)	Etan ^{1*}	30	46 (30-70)	53%	W: 90%	91 (58-141)	9 (1-31)	23 (11-32)	14.0 (8-23)	1.3 (0.9-1.6)	10.1 (2.3-30.0)
	Pbo	30	44 (24-63)	60%	W: 83%	81 (60-132)	10 (1-30)	19 (10-39)	14.7 (7-24)	1.2 (0.8-1.6)	6.0 (1.5-17.7)
PRESTA	Etan ^{2*}	373	47 (11)	62%	W: 90%	NR	7 (7)	19.3 (17.7)	12.9 (15.2)	0.9 (0.7)	19.0 (9.8)
	Etan ³	379	46 (11)	64%	W: 88%	NR	7 (7)	19.2 (17.9)	12.0 (14.9)	0.9 (0.7)	19.8 (10.7)
Infliximab											
IMPACT 2	Inf ^{4*}	100	47 (13)	71%	NR	NR	8 (7)	24.6 (14.1)	13.9 (7.9)	1.1 (0.6)	11.4 (12.7)
	Pbo	100	47 (11)	51%	NR	NR	8 (8)	25.1 (13.3)	14.4 (8.9)	1.1 (0.6)	10.2 (9.0)
Secukinumab											
FUTURE 2	Sec ^{5*}	100	47 (12)	44%	W: 90%	91 (20)	NR	24.1 (19.4)	11.9 (10.1)	1.2 (0.6)	16.2 (14.3)
	Sec ^{6*}	100	47 (13)	51%	W: 96%	85 (18)	NR	20.2 (13.3)	11.2 (7.8)	1.3 (0.6)	11.9 (8.4)
	Pbo	98	50 (13)	40%	W: 96%	86 (20)	NR	23.4 (19.0)	12.1 (10.7)	1.2 (0.7)	11.6 (8.3)

CPP = chronic plaque psoriasis; DoD = duration of disease; Etan = etanercept; HAQ DI = Health Assessment Questionnaire disability index; Inf = infliximab; IV = intravenous; NR = not reported; PASI = Psoriasis Area and Severity Index; Pbo = placebo; PsA = psoriatic arthritis; SC = subcutaneous; SD = standard deviation; Sec = secukinumab; *Italics = median (range)*

^{1*} Etanercept 25 mg SC twice weekly (PI recommended dose)

^{2*} Etanercept 50 mg SC once weekly (PI recommended dose)

³ Etanercept 50 mg SC twice weekly

^{4*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

^{5*} Secukinumab 150 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose, PsA)

^{6*} Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose, CPP)

Mean baseline PASI scores were lower than in the CPP trials identified and analysed in the relevant sections above (with the exception of PRESTA).

Treatment details

Treatment details for the trials which included patients with severe CPP and concomitant PsA are summarised in Table 109, Appendix G.

The recommended doses for the treatment of PsA are the same as for the treatment of CPP for etanercept and infliximab. For secukinumab, the recommended dose for PsA is halved to 150 mg at Weeks 0, 1, 2, 3, 4 and then 150 mg every four weeks. Each of the included trials include the recommended dosing regimen for the relevant biologic in at least one treatment arm. The secukinumab trial, FUTURE 2, included the recommended dosing regimen for severe CPP and for PsA.

All of the trials were placebo-controlled except PRESTA which compared two dosing regimens of etanercept.

Efficacy

The following efficacy outcomes were presented for patients with PsA:

- Proportion of patients achieving a PASI 75 response;
- Mean change in DLQI score;
- Proportion of patients achieving a reduction in American College of Rheumatology (ACR) score of 20 (ARC 20) –
 - an ARC 20 response is considered to be a clinically important outcome;
 - the ARC score is based on count of tender and swollen joints;
- Proportion of patients who met the Psoriatic Arthritis Response Criteria (PsARC) –
 - to meet the criteria patients must demonstrate improvement in two of four PsARC criteria, with no criteria worsening;
- Mean change in Health Assessment Questionnaire Disability Index (HAQ DI) –
 - an assessment of physical function;
 - scores range from 0 to 3, with higher scores indicating a higher degree of disability.

Table 48 provides a comparison of the efficacy results for etanercept, infliximab and secukinumab in the treatment of severe CPP and PsA.

Efficacy in the treatment of PsA was assessed in terms of the proportion of patients achieving an ACR 20 response:

- At 24 weeks in the larger etanercept trial, PRESTA, 72% of etanercept patients who received the recommended dose had achieved an ACR 20 response;
- At 24 weeks 54% of infliximab patients in the IMPACT 2 trial achieved an ACR 20 response compared to 16% of placebo patients; and
- At 16 weeks 51% of secukinumab patients in the FUTURE 2 trial who received the recommended dose for PsA achieved an ACR 20 response compared to 15% of placebo patients. When patients received the recommended dose for severe CPP, the proportion achieving an ACR 20 was marginally higher, at 54%.

In terms of treatment of CPP, the proportions of patients achieving PASI 75 responses were marginally lower than in the analyses of severe CPP for the relevant biologics. However, the relevance of the comparisons were difficult to assess as the baseline PASI scores were lower in the trials presented in Table 48.

Table 48: Severe CPP and PsA trials: efficacy results

Trial	Time horizon	Arm	N	ACR 20, %	PsARC, %	PASI 75, %	Δ HAQ DI, mean (SD)	Δ DLQI, mean (SD)
Etanercept								
Mease (2000)	12 weeks	Etan ^{1*}	30	73%	87%	26%	-1.2	NR
		Pbo	30	13%	23%	0	-0.1	NR
PRESTA	12 weeks	Etan ^{2*}	373	61%	76%	36%	NR	-6.8
		Etan ³	379	66%	77%	55%	NR	-7.9
	24 weeks	Etan ^{2*}	373	72%	80%	62%	NR	-8.0
		Etan ³	379	69%	82%	70%	NR	-8.3
Infliximab								
IMPACT 2	16 weeks	Inf ^{4*}	100	58%	77%	64%	NR	NR
		Pbo	100	11%	27%	2%	NR	NR
	24 weeks	Inf ^{4*}	100	54%	70%	60%	NR	NR
		Pbo	100	16%	32%	1%	NR	NR
Secukinumab								
FUTURE 2	16 weeks	Sec ^{6*}	100	51%	NR	48%	-0.5 (0.1)	NR
		Sec ^{7*}	100	54%	NR	63%	-0.6 (0.1)	NR
		Pbo	98	15%	NR	16%	-0.3 (0.1)	NR

ARC 20 = reduction in American College of Rheumatology score of 20%; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; Etan = etanercept; HAQ DI = Health Assessment Questionnaire Disability Index; Inf = infliximab; IV = intravenous; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PI = Product Information; Pbo = placebo; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; SC = subcutaneous; SD = standard deviation; Sec = secukinumab

^{1*} Etanercept 25 mg SC twice weekly (PI recommended dose)

^{2*} Etanercept 50 mg SC once weekly (PI recommended dose)

³ Etanercept 50 mg SC twice weekly

^{4*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

^{5*} Secukinumab 150 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose, PsA)

^{6*} Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose, CPP)

Safety

Although the ToR2 focussed on the effectiveness of the PBS-listed biologics on PsA, some safety data was identified in the systematic literature review. These data are presented in Table 110 and Table 111 Appendix G. Overall, the safety results from these trials were similar to those in Section 2.3.

2.9 Efficacy of the PBS-listed biologics in hands, feet, face, and/or genital involvement

All of the biologics which are PBS-listed for the treatment of severe CPP are also PBS-listed for the treatment of CPP with hands, face and/or feet involvement.

Publication details

Three trials (and four related publications), which analysed the PBS-listed biologics in patients with CPP that involvement the hands and/or feet, were identified in the systematic literature review. These trials related to the use of adalimumab, infliximab and secukinumab and they are presented in Table 49. The trials and subgroup analysis that were identified included palmoplantar and finger nail involvement, no trials were identified which considered the effect of the PBS-listed biologics on CPP specifically focused on face or genital involvement.

Table 49: CPP with hands and/or feet involvement trials: publication details

Trial ID	Citation
Adalimumab	
REACH	Leonardi C, Langley RG, Papp K, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. <i>Archives of Dermatology</i> . 2011; 147(4): 429-436.
	Poulin Y, Crowley JJ, Langley RG, et al. Efficacy of adalimumab across subgroups of patients with moderate-to-severe chronic plaque psoriasis of the hands and/or feet: post hoc analysis of REACH. <i>Journal of the European Academy of Dermatology and Venereology</i> . 2014; 28(12): 882-890.
Infliximab	
Bissonnette (2011)	Bissonnette R, Poulin Y, Guenther L, et al. Treatment of palmoplantar psoriasis with infliximab: a randomized, double-blind placebo-controlled study. <i>Journal of the European Academy of Dermatology and Venereology</i> . 2011; 25(12): 1402-1408.
Secukinumab	
GESTURE	Gottlieb A, Sullivan J, van Doorn M, et al. Secukinumab shows significant efficacy in palmoplantar psoriasis: results from GESTURE, a randomized controlled trial. <i>Journal of the American Academy of Dermatology</i> . 2017; 76(1): 70-80.

CPP = chronic plaque psoriasis

The risk of bias in the three RCTs was assessed in Table 112, Appendix H. All trials included in the analysis had a low risk of bias in terms of random sequence generation, allocation concealment blinding of participants and personnel and incomplete outcome reporting. Blinding of outcome assessment was not described, and therefore unclear, in Bissonnette (2011) and GESTURE. All of the trials were funded by a pharmaceutical company.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the identified trials are presented in Table 113, Appendix H.

The inclusion and exclusion criteria for the identified trials were difficult to compare, as they were quite different. Broadly, adult patients were included if they had a hands and/or feet PGA (hf PGA) score of either two and above or three and above.

Baseline characteristics

The baseline disease characteristics presented are:

- hf PGA score –
 - this is a five score scale ranging from Clear (0) to Severe (4);

- modified-Palmoplantar Psoriasis Area and Severity (m-PPASI) Index –
 - evaluates erythema, infiltration and desquamation as well as the area affected with psoriasis on each palm and sole;
 - scores range from 0 to 72, with higher scores indicating more severe disease.

The baseline characteristics for patients with CPP and hands and/or feet involvement are presented in Table 50.

The within trial randomisation did not appear to be overly successful, with differences in baseline age and gender within the arms of the REACH and Bissonnette (2011) trials, differences in terms of duration of disease in the REACH and GESTURE trials and differences in disease severity in the REACH, Bissonnette (2011) and GESTURE trials. This was likely due to the small trial numbers.

When they could be compared, the between trial populations were highly heterogeneous.

Table 50: CPP with hands and/or feet involvement trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	DoD, years; mean (SD)	hf PGA mod; %	hf PGA severe; %	m-PPASI; mean (SD)	PASI; mean (SD)
Adalimumab										
REACH	Ada ^{1*}	49	49.0 (11.4)	43%	C: 92%	10.0 (12.4)	76%	25%	NR	8.8 (8.2)
	Pbo	23	54.8 (11.4)	35%	C: 87%	7.2 (6.7)	74%	26%	NR	5.7 (4.5)
Infliximab										
Bissonnette (2011)	Inf ^{2*}	12	57.8 (12.4)	43%	C: 100%	NR	58%	33%	24.1 (11.4)	6.5 (3.0)
	Pbo	12	49.9 (14.7)	33%	C: 100%	NR	25%	66%	26.7 (12.4)	7.1 (3.3)
Secukinumab										
GESTURE	Sec ³	68	52.4 (12.6)	59%	C: 93%	7.5 (8.8)	57%	43%	24.1 (15.8)	8.7 (10.4)
	Sec ^{4*}	69	48.8 (14.2)	55%	C: 97%	7.9 (8.2)	73%	28%	23.9 (13.2)	8.0 (9.6)
	Pbo	68	50.9 (13.0)	50%	C: 96%	11.8 (10.4)	68%	32%	24.1 (14.4)	7.7 (7.3)

Ada = adalimumab; C = Caucasian; CPP = chronic plaque psoriasis; DoD = duration of disease; hf PGA = hands and/or feet Physician's Global Assessment; Inf = infliximab; IV = intravenous; mod = moderate; m-PPASI = modified Palmoplantar Psoriasis Area and Severity Index; NR = not reported; PASI = Psoriasis Area and Severity Index; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Sec = secukinumab

^{1*} Adalimumab 80 mg SC Week 0; then 40 mg every other week from Week 1 (PI recommended dose)

^{2*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6 (PI recommended dose)

³ Secukinumab 150 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks

^{4*} Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks

Based on mean baseline PASI scores, patients in all three trials did not have severe CPP.

Treatment details

Table 114, Appendix H presents the treatment details for patients with CPP and hands and/or feet involvement. The recommended doses for adalimumab, infliximab and secukinumab in the treatment of hands and/or face psoriasis are the same as for CPP. The REACH (adalimumab), Bissonnette (2011) (infliximab) and GESTURE (secukinumab) trials all utilised the recommended dose.

All trials were placebo-controlled and reported results at 12 to 16 weeks.

Efficacy

The efficacy outcomes assessed for the treatment of CPP with hand and/or feet involvement were the proportions of patients achieving:

- a PASI 75 response;
- a reduction in m-PPPASI score of 50% and 75% (m-PPPASI 50, 75); and
- a hf PGA score of Clear (0) or Almost Clear (1).

Table 51 provides a comparison of the efficacy results, when reported, for the treatment of psoriasis of the hands and/or feet.

The proportion of patients achieving a hf PGA score of Clear (0) or Almost Clear (1) was reported for all trials. At the recommended doses adalimumab, infliximab and secukinumab treatment resulted in 31%, 25% and 33% respectively of patients achieving a hf PGA score of 0 or 1. The proportions of placebo patients in the respective trials achieving the same response were 4%, 8% and 2%.

The results suggested that all three biologics might have some effect in treating psoriasis of the hands and/or feet; however it should be noted that patient numbers in each of the trials were small.

Table 51: CPP with hands and/or feet involvement trials: efficacy results

Trial	Time horizon	Arm	N	m-PPPASI 50, %	m-PPPASI 75, %	hf PGA of 0 or 1, %	PASI 75, %
Adalimumab							
REACH	16 weeks	Ada ^{1*}	49	NR	NR	31%	NR
		Pbo	23	NR	NR	4%	NR
Infliximab							
Bissonnette (2011)	14 weeks	Inf ^{2*}	12	67%	33%	25%	NR
		Pbo	12	8%	8%	8%	NR
Secukinumab							
GESTURE	16 weeks	Sec ³	68	NR	NR	22%	NR
		Sec ^{4*}	69	NR	NR	33%	NR
		Pbo	68	NR	NR	2%	NR

Ada = adalimumab; CPP = chronic plaque psoriasis; hf PGA = hands and/or feet Physician's Global Assessment; Inf = infliximab; IV = intravenous; m-PPPASI 50, 75 = reduction in modified-Palmoplantar Psoriasis Area and Severity Index score of 50% or 75%; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PI = Product Information; SC = subcutaneous; Sec = secukinumab

^{1*} Adalimumab 80 mg SC Week 0; then 40 mg every other week from Week 1 (PI recommended dose)

^{2*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6 (PI recommended dose)

³ Secukinumab 150 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks

^{4*} Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks

Safety

Although the ToR 2 focussed on the effectiveness of the PBS-listed biologics in CPP with hands and/or feet involvement, some safety data was identified in the systematic literature review. These data are presented in Table 115 and Table 116, Appendix H.

2.10 Discussion

A systematic literature review, *PBS-listed biologics used in the treatment of severe CPP*, was conducted to identify recent clinical evidence. The main aims of this review were to:

- evaluate the efficacy and safety of the PBS-listed biologics; and
- compare new evidence to that previously considered by the PBAC.

This was done through the quantitative analysis of clinical evidence identified for each PBS-listed biologic and network meta-analyses, which allowed comparison of the agents in terms of efficacy and safety. In addition, the effectiveness of the PBS-listed biologics in the treatment of patients with severe CPP and concomitant PsA and in patients with CPP and hands, face and/or feet involvement was considered.

The systematic literature review identified 98 publications, which related to 69 RCTs and four large observational studies ($N \geq 200$) and over 31,000 patients.

The quality of each RCT was assessed in terms of the risk of bias. For most trials the risk of bias was low in terms of the manner in which random sequence was generated, allocation concealment, the blinding of participants and personnel incomplete outcome reporting and selective outcome reporting. The blinding of outcome assessors was not described in a number of the studies, making this the area of most uncertainty. The other issue in terms of bias, was that all trials, with the exception of one infliximab trial, was funded by a pharmaceutical company.

Inclusion and exclusion criteria, baseline characteristics and treatment details were compared for each of the trials.

Most trials identified a baseline BSA affected of 10% as a key inclusion criteria; however, the baseline PASI score varied. Although the review was to assess the PBS-listed biologics in the treatment of severe CPP, which is defined in the PBS restrictions as a PASI score of greater than 15, the majority of trials assessed the biologics in moderate-to-severe CPP required a minimum baseline PASI score of 10 or 12. The PBAC had previously accepted trials with a lower entry PASI score if the mean or median baseline scores were greater than 15. The same reasoning was applied in this review, all trials in the analysis had an average baseline PASI score that exceeded 15.

The baseline disease characteristics for the identified trials included patients with an average BSA affected of approximately 30% and an average baseline PASI score of 20. The patients treated with each biologic were broadly homogeneous (means) in terms of age (45 years), gender (68% male), weight (89 kg), duration of disease (18 years) and baseline DLQI score (12.3).

The majority of the identified trials assessed the Australian approved Product Information recommended dose of the relevant biologic. The time horizons of the RCTs ranged from ten to 24 weeks, with 12 weeks the most common point at which outcomes were reported.

Each PBS-listed biologic was assessed in terms of efficacy, quality of life and safety. The network meta-analyses assessed the two outcomes, the proportion of patients achieving a

PASI 75 response at 12 weeks and the proportion of patients experiencing any adverse event at 12 weeks.

In terms of efficacy, the network meta-analysis demonstrated that all of the PBS-listed biologics were similar and provided a significantly better response when compared to placebo, with ixekizumab producing the largest pooled effect, followed by infliximab, with etanercept (50 mg once weekly) having the lowest pooled estimate. Ixekizumab provided a statistically significant better response to adalimumab, etanercept (25 mg twice weekly), secukinumab and ustekinumab.

In terms of safety, the meta-analysis demonstrated that efalizumab, which was de-registered and removed from the PBS due to safety concerns in 2009, was the most likely to result in any adverse event at 12 weeks. Of the currently PBS-listed biologics, while having similar pooled results, ixekizumab was the most likely to result in an adverse event when compared to placebo. When compared to each other, infliximab was most likely to result in an adverse event; ustekinumab and etanercept demonstrated the lowest point estimates.

The data used to populate the network meta-analyses was derived from each of the identified RCTs. A quantitative analysis of each PBS-listed biologic was performed. Also, any new evidence identified in the systematic literature review was compared to that previously considered by the PBAC. For each of the biologics, the new evidence provided very similar results to those already seen and, thus supported the PBACs decisions in terms of:

- efficacy and the proportion of patients achieving a PASI 75 response; and
- quality of life and mean change in DLQI scores.

Etanercept is the only biologic listed on the PBS for the treatment of CPP in children and adolescents. Although trials were identified considering the use of adalimumab and ustekinumab in this population, their small size made it difficult to assess the efficacy and safety of these biologics.

Longer-term safety (i.e. after 1 year of treatment) of the PBS-listed biologics in the treatment of severe CPP was assessed by considering the results from open-label extension studies of the identified RCTs and four large observational studies. A number of studies were identified for each of the PBS-listed biologics, with the exception of secukinumab. Most of the open-label extension studies had adverse event rates which were comparable with the short-term comparator-controlled RCTs. For the majority of the biologics, the incidence of serious adverse events remained low in the longer-term. The exception might be adalimumab, which, in one study had a serious adverse event rate of 25% after four years.

The longer-term incidence of serious infection, malignancy, skin cancers and cardiovascular disease were low, and comparable to the comparator-controlled RCTs.

All of the biologics listed on the PBS for the treatment of severe CPP are also listed on the PBS for the treatment of the PsA, with the exception of ixekizumab. PsA occurs in approximately 40% of CPP patients, and appears to be more prevalent in patients with less severe disease. An aim of ToR 2 was to assess the effectiveness of the PBS-listed biologics in patients who had severe CPP with concomitant PsA. To enable an analysis, a lower cut off PASI score was used as studies were limited. Four trials were identified (two relating to

etanercept, one to infliximab and one to secukinumab). Over 50% of patients in each of the trials achieved a reduction in ACR score of 20%, which is considered to be a clinically important outcome. It appeared that the biologics were marginally less effective in terms of the proportion of patients achieving a PASI 75 response in patients with concomitant PsA than in patients without.

All of the PBS-listed biologics for the treatment of severe CPP are also listed for the treatment of CPP with hands, face and/or feet involvement. Five small trials (including two subgroup analyses) were identified for the use of adalimumab, infliximab and secukinumab in this population. The results suggested that the biologics have some effect in this treating CPP of the hands and/or feet.

The assessment of the efficacy and safety of the PBS-listed biologics in the treatment of mild-to-moderate CPP was not possible as none of the identified trials were designed to compare outcomes based on baseline PASI scores or provided relevant subgroup analyses. One etanercept trial was identified in which patients had a mean baseline PASI score which did not exceed 15. Although it was not possible to directly compare efficacy results, it appeared that etanercept might be marginally more effective in patients with more severe disease. The trials in patients with CPP plus PsA also corroborated this result as these patients had lower PASI at baseline and the response rates were lower than seen in the trials with higher PASI baseline in CPP patients.

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82. Janssen Cilag Pty Ltd. Remicade (infliximab) - Product Information. Macquarie Park: Janssen Cilag; 2017.
83. Eli Lilly Australia Pty Ltd. Taltz (ixekinumab) - Product Information. West Ryde: Eli Lilly; 2017.
84. Novartis Pharmaceuticals Australia Pty Ltd. Cosentyx (secukinumab) - Product Information. Macquarie Park: Novartis; 2017.
85. Janssen Cilag Pty Ltd. Stelara (ustekinumab) - Product Information. Macquarie Park: Janssen Cilag; 2017.

Appendix A – ToR2: Methods

Summary of the systematic literature review process

The focus of the systematic literature review was to evaluate recent clinical evidence of the efficacy and safety of the biologics used in the treatment of severe CPP and compare the recent evidence to that considered previously by the PBAC. It was performed in three stages:

- 1) Identifying the most relevant systematic literature reviews on the efficacy and safety of biologic medications for the treatment of severe CPP;
- 2) Updating the literature search using the relevant systematic literature reviews as identified in Step 1 as a starting point; and
- 3) Identifying the relevant RCTs and large observational studies from Step 2.

The systematic literature search

The search strategy was developed by first identifying relevant systematic literature review protocols. The Cochrane protocols “Biologics for chronic plaque psoriasis” published in 2009, and “Systemic pharmacological treatments for chronic plaque psoriasis” published in 2015 were identified as relevant systematic literature reviews on the efficacy and safety of biologics used in the treatment of CPP. (78, 79) The key search terms from these protocols were reviewed and updated to include all trials and studies published since 2003 that related to the PBS listed biologics for the treatment of severe CPP.

The PBS-listed biologics included in the literature search were: adalimumab, efalizumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab. Although efalizumab was removed from the PBS in May 2009 due to safety concerns, it was included in the search as it formed the basis of a number of PBAC submission’s cost-minimisations analyses. Table 52 presents a summary of the PBS listed biologics.

Table 52: PBS-listed biologics and the date(s) of PBAC consideration

Biologic	Date(s) of PBAC consideration
Etanercept	March 2006; March 2009
Infliximab	March 2006; July 2007
Adalimumab	March 2009
Ustekinumab	November 2009
Secukinumab	March 2015
Ixekizumab	July 2016
Efalizumab ^a	November 2005

PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme

^a Efalizumab was removed from the PBS in May 2009 due to safety concerns

The following sources were used to identify relevant publications:

- Ovid MEDLINE;
- EMBASE;
- The Cochrane Library Database;
- Clinical trial registries; and
- Bibliography review of publications.

The searches were conducted on 23 May 2017. Each bibliographic database was systematically searched using the search terms provided in Table 53.

Table 53: Search strategy to locate psoriasis (OVID MEDLINE)

#	Searches
1	psoriasis.mp. or exp Psoriasis/
2	biologics.mp. or exp Biological Products/
3	alefacept.mp.
4	efalizumab.mp.
5	etanercept.mp. or exp Etanercept/
6	infliximab.mp. or exp Infliximab/
7	adalimumab.mp. or exp Adalimumab/
8	fusion protein.mp.
9	T cell inhibitor.mp.
10	TNF alpha.mp. or Tumor Necrosis Factor-alpha/
11	monoclonal antibody.mp. or exp Antibodies, Monoclonal/
12	ustekinumab.mp. or exp Ustekinumab/
13	secukinumab.mp.
14	ixekizumab.mp.
15	briakinumab.mp.
16	tildrakizumab.mp.
17	guselkumab.mp.
18	brodalumab.mp.
19	IL-12.mp. or exp Interleukin-12/
20	IL-17.mp. or exp Interleukin-17/
21	IL-23.mp. or exp Interleukin-23/

22	tofacitinib.mp.
23	sotrastaurin.mp.
24	certolizumab.mp.
25	rituximab.mp. or exp Rituximab/
26	anakinra.mp. or exp Interleukin 1 Receptor Antagonist Protein/
27	omalizumab.mp. or exp Omalizumab/
28	abatacept.mp. or exp Abatacept/
29	dupilumab.mp.
30	exp Randomized Controlled Trials as Topic/ or exp Clinical Trials as Topic/ or RCT.mp.
31	exp Prospective Studies/ or exp Cohort Studies/ or cohort.mp.
32	control trial.mp.
33	exp Double-Blind Method/ or double blind.mp.
34	exp Single-Blind Method/ or single blind.mp.
35	randomised.mp.
36	observational study/
37	exp Cross-Sectional Studies/
38	exp Case-Control Studies/ or case-control.mp.
39	exp Longitudinal Studies/ or longitudinal.mp.
40	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
41	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
42	1 and 40 and 41

Inclusion and exclusion criteria

Articles remaining were checked independently by two staff members and included in the final analysis if they met all of the following criteria:

- English language
- Patients with severe CPP
- Published since 2003
- Randomised trials or large observational studies (i.e. > 200 patients)
- Included at least one of the PBS-listed biologics
- Provided efficacy, quality of life or safety outcomes
- Utilised recommended doses.

Table 54: Number of publications identified in the systematic literature review and reasons for exclusion

	Number of publications
Ovid MEDLINE	776
EMBASE	285
Cochrane Library Database	556
Clinical trials registries	0
From bibliography searches	4
Total references	1,621
Excluded after title/abstract review	1,237
Duplicates	139
Wrong intervention (did not contain a PBS-listed biologic)	527
No relevant outcome measures	257
Wrong patient group	49
Wrong study design	211
Other reason (e.g. protocol, guidelines)	23
Review	170
Publication prior to 2003	0
Total references remaining	245
Excluded after full publication review	159
Abstract only of published study	25
No relevant outcome measures	12
Wrong intervention (did not contain a PBS-listed biologic)	3
Wrong patient group	4
Wrong study design	32
Other reason (e.g. protocol, guidelines, dose)	8
Subgroup analysis only of existing study	12
No new data	30
Review	30
Observational study with n < 200	3
Total references included in review	86

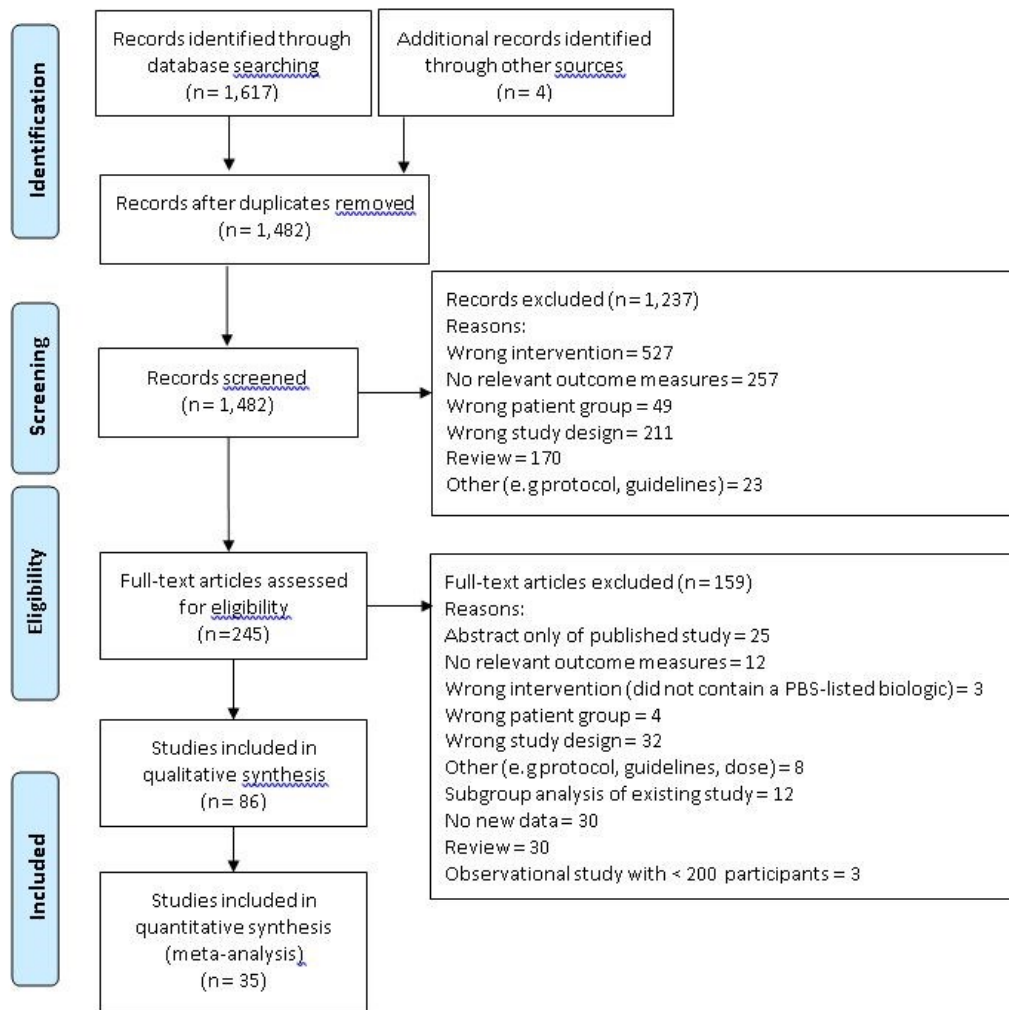


Figure 7: PRISMA flow diagram

Appendix B – ToR2: Efficacy and safety of the PBS-listed biologics in the treatment of severe CPP

Risk of bias

Table 55: Adalimumab trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
REVEAL	Low	Low	Low	Unclear	Low	Low	High
Asahina (2010)	Unclear	Unclear	Low	Unclear	Low	Low	High
Gordon (2006)	Low	Low	Low	Unclear	Low	Low	High
CHAMPION	Low	Low	Low	Low	Low	Low	High
Cai (2017)	Unclear	Unclear	Low	Unclear	Low	Low	High
Gordon (2015)	Unclear	Unclear	High	Low	Low	Low	High
Papp (2016)	Low	Low	Low	Low	Low	Low	High

Shaded = previously considered by the Pharmaceutical Benefits Advisory Committee

Table 56: Efalizumab trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
CLEAR	Low	Low	Low	Low	Low	Low	High
Gordon (2003)	Low	Low	Low	Low	Low	Low	High
Lebwohl (2003)	Low	Low	Low	Low	Low	Low	High
Leonardi (2005)	Low	Low	Low	Unclear	Low	Low	High
Papp (2006)	Low	Low	Low	Unclear	Low	Low	High
Gottlieb (2004)	Unclear	Unclear	Low	Unclear	Low	Low	High

Shaded = previously considered by the Pharmaceutical Benefits Advisory Committee

Table 57: Etanercept trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
Leonardi (2003)	Low	Low	Low	Unclear	Low	Low	High
Gottlieb (2003)	Low	Low	Low	Low	Low	Low	High
Papp (2005)	Low	Low	Low	Unclear	Low	Low	High
van de Kerkhof (2008)	Low	Low	Low	Low	Low	Low	High
Trying (2006)	Low	Low	Low	Unclear	Low	Low	High
OPT COMPARE	Low	Low	Low	Low	Low	Low	High
M10-114	Unclear	Unclear	Low	Unclear	Low	Low	High
M10-315	Unclear	Unclear	Low	Unclear	Low	Low	High
PRESTA	Unclear	Unclear	Low	Unclear	Low	Low	High
PRISTINE	Unclear	Unclear	Low	Unclear	Low	Low	High
Gottlieb (2012)	Unclear	Unclear	Low	Low	Low	Low	High

Shaded = previously considered by the Pharmaceutical Benefits Advisory Committee

Table 58: Infliximab trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
Chaudhari (2001)	Low	Low	Low	Unclear	Low	Low	High
EXPRESS	Low	Low	Low	Unclear	Low	Low	High
Gottlieb (2004)	Low	Low	Low	Unclear	Low	Low	High
Menter (2007)	Low	Low	Low	Unclear	Low	Low	High
Torii (2010)	Low	Low	Low	Unclear	Low	Low	Unclear
Yang (2012)	Unclear	Unclear	Low	Unclear	Low	Low	High
RESTORE	Low	Low	High	High	Low	Low	High
PIECE	Low	Low	High	Low	Low	Low	High

Shaded = previously considered by the Pharmaceutical Benefits Advisory Committee

Table 59: Ixekizumab trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
UNCOVER 1	Low	Low	Low	Low	Low	Low	High
UNCOVER 2	Low	Low	Low	Low	Low	Low	High
UNCOVER 3	Low	Low	Low	Low	Low	Low	High

Shaded = previously considered by the Pharmaceutical Benefits Advisory Committee

Table 60: Secukinumab trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
ERASURE	Low	Low	Low	Low	Low	Low	High
FEATURE	Low	Low	Low	Low	Low	Low	High
JUNCTURE	Low	Low	Low	Low	Low	Low	High
SCULPTURE	Unclear	Unclear	Low	Unclear	Low	Low	High
FIXTURE	Low	Low	Low	Low	Low	Low	High
CLEAR	Low	Low	Low	Low	Low	Low	High

Shaded = previously considered by the Pharmaceutical Benefits Advisory Committee

Table 61: Ustekinumab trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
PHOENIX 1	Low	Low	Low	Low	Low	Low	High
PHOENIX 2	Low	Low	Low	Low	Low	Low	High
PEARL	Low	Low	Low	Unclear	Low	Low	High
LOTUS	Unclear	Unclear	Low	Unclear	Low	Low	High

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
AMAGINE 2	Low	Low	Low	Low	Low	Low	High
AMAGINE 3	Low	Low	Low	Low	Low	Low	High
ACCEPT	Low	Low	Low	High	Low	Low	High
CLEAR	Low	Low	Low	Low	Low	Low	High

Shaded = previously considered by the Pharmaceutical Benefits Advisory Committee Results

Adalimumab

Inclusion and exclusion criteria

Table 62: Adalimumab trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Adalimumab versus placebo		
REVEAL	<ul style="list-style-type: none"> - ≥ 18 years; - clinical diagnosis of mod-to-severe CPP for ≥ 6 months; - stable for ≥ 2 months; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3 	<ul style="list-style-type: none"> - history of CNS demyelinating disease, cancer or lymphoproliferative disease (except non-melanoma skin cancer or cervical cancer); - non-latent TB
Asahina (2010)	<ul style="list-style-type: none"> - ≥ 20 years; - clinical diagnosis of mod-to-severe CPP for ≥ 6 months; - stable for ≥ 2 months; - BSA ≥ 10%, PASI ≥ 12 	<ul style="list-style-type: none"> - previous anti-TNF therapy; - active skin disease or infections, systemic lupus erythematosus, scleroderma or rheumatoid arthritis; - CNS demyelinating disease, cancer, lymphoma, leukaemia, TB, or lymphoproliferative disease; - HIV, Hep B/C, active infectious disease, immunosuppressive disease, abnormal liver or renal values; - pregnancy
Gordon (2006)	<ul style="list-style-type: none"> - ≥ 18 years; - plaque psoriasis for ≥ 1 year; - BSA ≥ 5%; - naive to TNF treatment 	<ul style="list-style-type: none"> - neurologic symptoms suggestive of CNS demyelinating disease, cancer or lymphoproliferative disease
Cai (2017)	<ul style="list-style-type: none"> - ≥ 18 years; - diagnosis of mod-to-severe psoriasis for ≥ 6 months; - stable for ≥ 2 months; - unresponsive/intolerant to systemic therapy 	<ul style="list-style-type: none"> - previous biologic treatment; - systemic treatment within 28 days
Adalimumab versus methotrexate versus placebo		

Trial	Inclusion criteria	Exclusion criteria
CHAMPION	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe psoriasis; - plaque psoriasis for ≥ 1 year, stable for ≥ 2 months; - BSA ≥ 10%, PASI ≥ 10; - candidates for systemic or phototherapy; - active psoriasis despite topical agents 	<ul style="list-style-type: none"> - concomitant therapies; - active TB; - clinically significant haematological, renal or liver disease; - demyelinating disease, cancer or lymphoproliferative disease; - immunocompromised patients
Adalimumab versus guselkumab versus placebo		
Gordon (2015)	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3 	<ul style="list-style-type: none"> - previous adalimumab or guselkumab
Biosimilar trial		
Papp (2016)	<ul style="list-style-type: none"> - 18-75 years; - stable mod-to-severe plaque psoriasis for ≥ 6 months; - candidates for phototherapy or systemic therapy and who had inadequately responded to/intolerant to ≥ 1 conventional systemic therapy; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3 	<ul style="list-style-type: none"> - evidence of TB; - non-plaque psoriasis, drug-induced psoriasis or any other skin condition; - use of adalimumab or a adalimumab biosimilar; - ≥ 2 biologics

BSA = body surface area; CNS = central nervous system; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; DMARD = disease modifying anti-rheumatic drug; Hep = hepatitis; HIV = human immunodeficiency virus; mod = moderate; NSAID = non-steroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; TB = tuberculosis; TNF = tumour necrosis factor; UV = ultraviolet; Shaded = previously considered by the PBAC

Treatment details

Table 63: Adalimumab trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 80 mg Week 0; 40 mg every other week from Week 1 (80)				
Adalimumab versus placebo				
REVEAL	16 weeks	Adalimumab	SC	80 mg Week 0; 40 mg every other week from Week 1*
		Placebo	SC	Matched placebo injections
Asahina (2010)	16 weeks/ 24 weeks	Adalimumab	SC	40 mg every other week
		Adalimumab	SC	80 mg Week 0; 40 mg every other week from Week 2*
		Adalimumab	SC	80 mg every other week
		Placebo	SC	Matched placebo injections
Gordon (2006)	12 weeks	Adalimumab	SC	80 mg Week 0; 40 mg every other week from Week 1 (plus matched placebo injections)*
		Adalimumab	SC	80 mg Weeks 0 and 1; 40 mg every week from Week 2

Trial	Time horizon	Treatment	Delivery	Dose
		Placebo	SC	Matched placebo injections
Cai (2017)	12 weeks	Adalimumab	SC	80 mg Week 0; 40 every other week*
		Placebo	SC	Matched placebo injections
Adalimumab versus methotrexate versus placebo				
CHAMPION	16 weeks	Adalimumab	SC (oral)	80 mg Week 0; 40 mg every other week from Week 1 (plus matched placebo capsules weekly)*
		Methotrexate	Oral (SC)	7.5 mg Weeks 0 and 1; 10 mg Weeks 2 and 3; 15 mg from Week 4; increasing by 5 mg every 4 weeks if no response (plus matched placebo injections)
		Placebo	SC/Oral	Matched placebo injections and oral capsules
Adalimumab versus guselkumab versus placebo				
Gordon (2015)	16 weeks	Adalimumab	SC	80 mg Week 0; 40 mg every other week from Week 1 (unblinded)*
		Guselkumab	SC	5 mg Weeks 0 and 4 and then every 12 weeks
		Guselkumab	SC	15 mg every 8 weeks
		Guselkumab	SC	50 mg Weeks 0 and 4 and then every 12 weeks
		Guselkumab	SC	100 mg every 8 weeks
		Guselkumab	SC	200 mg Weeks 0 and 4 and then every 12 weeks
		Placebo	SC	Matched placebo injections to guselkumab
		Adalimumab	SC (top)	80 mg Week 0; 40 mg every other week from Week 1 (plus matched placebo cream)*
Biosimilar trial				
Papp (2016)	16 weeks	Adalimumab	SC	80 mg Week 0; 40 mg every other week from Week 2*
		ABP 501	SC	80 mg Week 0; 40 mg every other week from Week 2*

DB = double-blind; PBAC = Pharmaceutical Benefits Advisory Committee; PI = Product Information; SC = subcutaneous; top = topical; Shaded = previously considered by the PBAC

* PI recommended dose

Efficacy

Table 64: Adalimumab trials: efficacy results – proportion of patients achieving PASI 50, 75, 90 or 100 response

Trial	Time horizon	Arm	N	PASI 50; n (%)	PASI 75; n (%)	PASI 90; n (%)	PASI 100; n (%)
Adalimumab versus placebo							
REVEAL	16 weeks	Ada ¹	814	-	71%	45%	20%
		Pbo	398	-	7%	2%	1%
Asahina (2010)	16 weeks	Ada ¹	43	35 (81%)	27 (63%)	17 (40%)	-
		Pbo	46	9 (20%)	2 (4%)	0	-
	24 weeks	Ada ¹	43	33 (77%)	30 (70%)	19 (44%)	-
		Pbo	46	9 (20%)	6 (13%)	2 (4%)	-
Gordon (2006)	12 weeks	Ada ¹	45	76%	53%	24%	11%
		Pbo	52	NR	4%	NR	0
CHAMPION	16 weeks	Ada ¹	108	88%	80%	51%	17%
		Pbo	53	30%	19%	11%	2%
Cai (2017)	12 weeks	Ada ¹	338	NR	78%	56%	13%
		Pbo	87	NR	12%	3%	1%
Gordon (2015)	16 weeks	Ada ¹	43	NR	30 (70%)	19 (44%)	11 (26%)
		Pbo	42	NR	2 (5%)	1 (2%)	0
Biosimilar trial							
Papp (2016)	16 weeks	Ada ¹	175	94%	83%	47%	20%
		ABP 501 ¹	175	92%	74%	47%	17%

ABP 501 = adalimumab biosimilar; Ada = adalimumab; NR = not reported; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Shaded = previously considered by the PBAC

¹ Adalimumab 80 mg SC Week 0; 40 mg every other week from Week 1 or 2 (PI recommended dose)

Safety

Table 65: Adalimumab trials: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Adalimumab versus placebo														
REVEAL	16 weeks	Ada ^{1*}	814	29%	< 1%	< 1%	1%	< 1%	7%	5%	NR	5%	NR	8%
		Pbo	398	22%	1%	< 1%	< 1%	0	4%	7%	NR	4%	NR	7%
Asahina (2010)	24 weeks	Ada ²	38	55%	NR	0	NR	NR	NR	NR	NR	NR	NR	16%
		Ada ^{1*}	43	42%	NR	0	NR	NR	NR	NR	NR	NR	NR	19%
		Ada ³	42	50%	NR	0	NR	NR	NR	NR	NR	NR	NR	14%

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
		Pbo	46	50%	NR	0	NR	NR	NR	NR	NR	NR	NR	7%
Gordon (2006)	12 weeks	Ada ^{1*}	45	0	NR	NR	NR	NR	NR	NR	9%	NR	NR	6%
		Ada ⁴	50	2%	NR	NR	NR	NR	NR	NR	4%	NR	NR	1%
		Pbo	52	0	NR	NR	NR	NR	NR	NR	4%	NR	NR	1%
CHAMPION	16 weeks	Ada ^{1*}	108	48%	0	NR	NR	NR	NR	28%	2%	13%	4%	NR
		Pbo	53	43%	0	NR	NR	NR	NR	21%	8%	9%	11%	NR
Cai (2017)	12 weeks	Ada ^{1*}	338	18%	0	0	NR	NR	NR	NR	NR	NR	NR	NR
		Pbo	87	16%	0	0	NR	NR	NR	NR	NR	NR	NR	NR
Gordon (2015)	16 weeks	Ada ^{1*}	43	12%	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Pbo	42	14%	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Biosimilar trial														
Papp (2016)	16 weeks	Ada ^{1*}	175	34%	< 1%	1%	NR	NR	5%	16%	1%	10%	NR	5%
		ABP 501 ^{1*}	175	34%	1%	1%	NR	NR	5%	14%	2%	8%	NR	2%

ABP 501 = adalimumab biosimilar; Ada = adalimumab; CVD = cardiovascular disease; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; URTI = upper respiratory tract infection; Shaded = previously considered by the PBAC

^{1*} Adalimumab 80 mg SC Week 0; 40 mg every other week from Week 1 or 2 (PI recommended dose)

² Adalimumab 40 mg SC every other week

³ Adalimumab 80 mg SC every other week

⁴ Adalimumab 80 mg SC Weeks 0 and 1; 40 mg every week from Week 2

Efalizumab

Publication details

Table 66: Efalizumab trials: publication details

Trial	Citation	Description	Seen by PBAC?
Efalizumab versus placebo			
CLEAR	Dubertret L, Sterry W, Bos JD, et al. Clinical Experience Acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a Phase III international randomized, placebo-controlled trial. <i>British Journal of Dermatology</i> . 2006; 155(1): 170-181.	RCT: efficacy, safety	Yes
	Ortonne J, Shear N, Shumack S, Henninger E. Impact of efalizumab on patient-reported outcomes in high-need psoriasis patients: results of the international, randomized, placebo-controlled Phase III Clinical Experience Acquired with Raptiva trial. <i>BMC Dermatology</i> . 2005; 5(1): 13.	RCT: QoL	No
Gordon (2003)	Gordon KB, Papp KA, Hamilton TK, et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. <i>Journal of the American Medical Association</i> . 2003; 290 (23): 3073-3080.	RCT: efficacy, safety, QoL	Yes
Lebwohl (2003)	Lebwohl M, Tying SK, Hamilton TK, et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. <i>New England Journal of Medicine</i> . 2003; 349(21): 2004-2013.	RCT: efficacy, safety	Yes
Leonardi (2005)	Leonardi CL, Papp KA, Gordon KB, et al. Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized Phase III trial. <i>Journal of the American Academy of Dermatology</i> . 2005; 52(3 Pt 1): 425-433.	RCT: efficacy, safety	Yes
Papp (2006)	Papp KA, Bressinck R, Fretzin S, et al. Safety of efalizumab in adults with chronic moderate to severe plaque psoriasis: a Phase IIIb, randomized, controlled trial. <i>International Journal of Dermatology</i> . 2006; 45(5): 605-614.	RCT: efficacy, safety	Yes

PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; RCT = randomised controlled trial; Shaded = previously considered by the PBAC

Inclusion and exclusion criteria

Table 67: Efalizumab trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Efalizumab versus placebo		
CLEAR	<ul style="list-style-type: none"> - 18-75 years; - ≥ 6 month history of plaque psoriasis; - BSA ≥ 10%, PASI ≥ 12; - candidate for systemic treatment (changed after a protocol amendment to patients of high-need i.e. unsuitability of ≥ 2 systemic treatments due to lack of efficacy/intolerance/contraindicated) 	<ul style="list-style-type: none"> - clinically significant disease flares; - major concomitant illnesses, immune disorders or organ dysfunction
Gordon (2003)	<ul style="list-style-type: none"> - 18-75 years; - plaque psoriasis for ≥ 6 months; - BSA ≥ 10%; PASI ≥ 12; - candidate for systemic therapy 	-
Lebwohl (2003)	<ul style="list-style-type: none"> - 18-70 years; - plaque psoriasis stable for ≥ 3 months and mod-to-severe for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12 	<ul style="list-style-type: none"> - history of or ongoing uncontrolled infection; - cancer or a history of cancer; - hepatic/renal dysfunction; - WBC < 4000/mm³ or > 14,000/mm³; - previous efalizumab
Leonardi (2005)	<ul style="list-style-type: none"> - 18-70 years; - mod-to-severe plaque psoriasis for ≥ 6 months; - stable for ≥ 3 months; - BSA ≥ 10%, PASI ≥ 12; - candidate for systemic therapy 	-
Papp (2006)	<ul style="list-style-type: none"> - 18-75 years; - required systemic therapy; - diagnosis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12; - body weight ≤ 140 kg 	<ul style="list-style-type: none"> - guttate, erythrodermic or pustular psoriasis; - previous efalizumab; - uncontrolled bacterial, viral, fungal or atypical mycobacterial infections, opportunistic infections, TB, malignancy, substance abuse, clinically unstable psoriasis, HIV, Hep B/C, pregnant or breast-feeding; - WBC < 4000/mm³ or > 14000/mm³

BSA = body surface area; CPP = chronic plaque psoriasis; CV = cerebrovascular; Hep = hepatitis; HIV = human immunodeficiency virus; mod = moderate; PASI = Psoriasis Area and Severity Index; TB = tuberculosis; WBC = white blood cell; Shaded = previously considered by the PBAC

Baseline characteristics

Table 68: Efalizumab trials: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Efalizumab versus placebo										
CLEAR	Efa ¹	529	44 (12)	67%	NR	82 (16)	19 (10)	37% (20)	23.6 (9.7)	NR
	Pbo	264	45 (12)	67%	NR	82 (16)	21 (12)	26% (21)	23.0 (9.6)	NR
Gordon (2003)	Efa ¹	369	45.3 (18-75)	68%	C: 90%	NR	19 (1-62)	28% (10-95)	19.4 (10.1-58.7)	12 (0-30)
	Pbo	187	44.9 (20-75)	71%	C: 89%	NR	19 (1-53)	27% (10-90)	19.4 (11.4-50.3)	12 (0-30)
Lebwohl (2003)	Efa ¹	232	46	65	NR	NR	19	NR	20	NR
	Pbo	122								
Leonardi (2005)	Efa ¹	162	45.2 (18-75)	73%	NR	NR	19 (1-58)	30% (10-72)	18.6 (11.9-50.1)	NR
	Pbo	170	41.7 (18-68)	73%	NR	NR	19 (1-56)	29% (10-85)	19.0 (9.6-57.6)	NR
Papp (2006)	Efa ¹	450	45.6 (12.5)	67%	C: 92%	NR	18 (12)	28% (16)	19.1 (7.5)	NR
	Pbo	236	46.4 (12.1)	59%	C: 91%	NR	18 (11)	27% (15)	18.7 (7.0)	NR
AVERAGE OF ALL TRIALS^a										
N = 2,721	NR	NR	45.1	67%	91%	82	19	30%	20.4	12.0

BSA = body surface area; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Efa = efalizumab; NR = not reported; PASI = Psoriasis Area and Severity Index; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; *Italics = (range)*; Shaded = previously considered by the PBAC

^a Arms presented above only

¹ Efalizumab 0.7 mg/kg SC Week 0; 1 mg/kg every week from Week 1 (PI recommended dose, prior to deregistration)

Treatment details

Table 69: Efalizumab trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 0.7 mg/kg Week 0; then 1 mg/kg weekly from Week 1				
Efalizumab versus placebo				
CLEAR	12 weeks	Efalizumab	SC	0.7 mg/kg Week 0; then 1 mg/kg weekly from Week 1*
		Placebo	SC	Matched placebo injections
Gordon (2003)	12 weeks	Efalizumab	SC	0.7 mg/kg Week 0; then 1 mg/kg weekly from Week 1*
		Placebo	SC	Matched placebo injections
Lebwohl (2003)	12 weeks	Efalizumab	SC	0.7 mg/kg Week 0; then 1 mg/kg weekly from Week 1*
		Efalizumab	SC	0.7 mg/kg Week 0; then 2 mg/kg weekly from Week 1
		Placebo	SC	Matched placebo injections
Leonardi (2005)	12 weeks	Efalizumab	SC	0.7 mg/kg Week 0; then 1 mg/kg weekly from Week 1*
		Efalizumab	SC	0.7 mg/kg Week 0; then 2 mg/kg weekly from Week 1
		Placebo	SC	Matched placebo injections
Papp (2006)	12 weeks	Efalizumab	SC	0.7 mg/kg Week 0; then 1 mg/kg weekly from Week 1*
		Placebo	SC	Matched placebo injections

PBAC = Pharmaceutical Benefits Advisory Committee;

PI = Product Information; SC = subcutaneous; top = topical; Shaded = previously considered by the PBAC

Efficacy

Table 70: Efalizumab trials: efficacy results

Trial	Seen by PBAC?	Time horizon	Arm	N	PASI 75; n (%)	Δ DLQI; mean (SD)
Efalizumab versus placebo						
CLEAR	Yes	12 weeks	Efa ¹	529	31%	NR
			Pbo	264	4%	NR
Gordon (2003)	Yes	12 weeks	Efa ¹	369	27%	-5.6
			Pbo	187	4%	-1.6
Lebwohl (2003)	Yes	12 weeks	Efa ¹	232	55 (22%)	NR
			Pbo	122	6 (5%)	NR
Leonardi (2005)	Yes	12 weeks	Efa ¹	162	63 (39%)	NR
			Pbo	170	4 (2%)	NR
Papp (2006)	Yes	12 weeks	Efa ¹	450	24%	NR
			Pbo	236	3%	NR

DLQI = Dermatology Life Quality Index; Efa = efalizumab; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Shaded = previously considered by the PBAC

¹ Efalizumab 0.7 mg/kg SC Week 0; 1 mg/kg every week from Week 1 (PI recommended dose, prior to de-registration)

Safety

Table 71: Efalizumab trials: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Efalizumab versus placebo							
CLEAR	12 weeks	Efa ^{1*}	529	72%	6%	0	6%
		Pbo	264	60%	3%	0	3%
Gordon (2003)	12 weeks	Efa ^{1*}	369	296 (80%)	NR	0	12 (3%)
		Pbo	187	133 (71%)	NR	0	2 (1%)
Lebwohl (2003)	12 weeks	Efa ^{1*}	232	199 (86%)	4 (2%)	NR	9 (4%)
		Efa ²	243	207 (85%)	7 (3%)	NR	7 (3%)
		Pbo	122	91 (75%)	1 (1%)	NR	2 (2%)
Leonardi (2005)	12 weeks	Efa ^{1*}	162	135 (83%)	3 (2%)	NR	6 (4%)
		Efa ²	166	148 (89%)	5 (3%)	NR	8 (5%)
		Pbo	170	130 (77%)	2 (1%)	NR	6 (4%)
Papp (2006)	12 weeks	Efa ^{1*}	450	369 (82%)	8 (2%)	0	8 (2%)
		Pbo	236	172 (73%)	8 (3%)	2 (1%)	4 (2%)

AE = adverse event; Efa = efalizumab; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SAE = serious adverse event; SC = subcutaneous; Shaded = previously considered by the PBAC

^{1*} Efalizumab 0.7 mg/kg SC Week 0; 1 mg/kg every week from Week 1 (PI recommended dose, prior to de-registration)

² Efalizumab 0.7 mg/kg SC Week 0; 2 mg/kg every week from Week 1

Etanercept

Inclusion and exclusion criteria

Table 72: Etanercept trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Etanercept versus placebo		
Leonardi (2003)	<ul style="list-style-type: none"> - ≥ 18 years; - active but stable plaque psoriasis; - BSA ≥ 10%, PASI ≥ 10; - previous phototherapy or systemic therapy 	<ul style="list-style-type: none"> - guttate, erythrodermic or pustular psoriasis; - active skin conditions; - previous etanercept or TNF antibody; - anti-CD4 antibodies or IL-2-diphtheria toxin fusion protein within 6 months
Gottlieb (2003)	<ul style="list-style-type: none"> - ≥ 18 years; - active, stable plaque psoriasis; - BSA ≥ 10%; - previous systemic or phototherapy 	<ul style="list-style-type: none"> - guttate, erythrodermic or pustular psoriasis; - other skin conditions; - other significant medical conditions

Trial	Inclusion criteria	Exclusion criteria
Papp (2005)	<ul style="list-style-type: none"> - ≥ 18 years; - active, clinically stable plaque psoriasis; - BSA ≥ 10%, PASI ≥ 10; - received or were candidate for prior systemic or phototherapy; - adequate haematological, renal and hepatic function 	<ul style="list-style-type: none"> - active guttate, erythrodermic or pustular psoriasis; - other skin conditions; - antibiotics within 1 week; - active severe infection within 4 weeks;
van de Kerkhof (2008)	<ul style="list-style-type: none"> - ≥ 18 years; - clinically stable plaque psoriasis; - BSA ≥ 10%; PASI ≥ 10; - failed to respond/were intolerant/were contraindicated to systemic or phototherapy 	<ul style="list-style-type: none"> - guttate, erythrodermic or pustular psoriasis; - other active skin conditions; - serious infection within one month; - BMI > 38 kg/m²; - previous etanercept
Tyring (2006)	<ul style="list-style-type: none"> - ≥ 18 years; - active, clinically stable plaque psoriasis; - BSA ≥ 10%; PASI ≥ 10; - received/been a candidate for systemic or phototherapy; - adequate haematological, renal and hepatic function 	<ul style="list-style-type: none"> - guttate, erythrodermic or pustular psoriasis; - other skin conditions; - history of psychiatric disease
Etanercept versus tofacitinib versus placebo		
OPT COMPARE	<ul style="list-style-type: none"> - ≥ 18 years; - chronic stable plaque psoriasis for ≥ 12 months; - BSA ≥ 10%, PASI ≥ 12; PGA ≥ 3; - candidate for systemic or phototherapy; - failed to respond/ contraindicated/ intolerant to systemic treatment 	<ul style="list-style-type: none"> - non-plaque or drug-induced psoriasis; - unable to discontinue systemic therapies; - previously unresponsive to TNF inhibitors; - active infection; - previous oral tofacitinib
Etanercept versus briakinumab versus placebo		
M10-114	<ul style="list-style-type: none"> - ≥ 18 years; - clinical diagnosis of CPP for ≥ 6 months; - stable for ≥ 2 months; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3 	<ul style="list-style-type: none"> - previous IL-12/23p40, including briakinumab, or etanercept; - unable to discontinue topical, systemic or phototherapies
M10-315	<ul style="list-style-type: none"> - ≥ 18 years; - CPP for ≥ 6 months; - stable plaque psoriasis for ≥ 2 months; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3 	<ul style="list-style-type: none"> - previous IL-12/23p40, including briakinumab, or etanercept; - unable to discontinue topical, systemic or phototherapies

Trial	Inclusion criteria	Exclusion criteria
Etanercept versus etanercept		
PRESTA	<ul style="list-style-type: none"> - ≥ 18 years; - active, stable plaque psoriasis; - BSA ≥ 10%; PGA > 2; - active PsA defined by ≥ 2 swollen joints, ≥ 2 tender or painful joints, or joint pain for > 3 months; - negative serum rheumatoid factor within 6 months 	<ul style="list-style-type: none"> - other skin conditions; - a tender, swollen joint not assessed by a rheumatologist as psoriatic arthritis; - severe comorbidities; - recent serious infection, TB
PRISTINE	<ul style="list-style-type: none"> - ≥ 18 years; - active, clinically stable CPP; - BSA ≥ 10%; PASI ≥ 10; - failed/intolerant/contraindicated/not a candidate for methotrexate, cyclosporine, PUVA 	<ul style="list-style-type: none"> - other skin conditions; - rheumatologic disease; - severe comorbidities; - recent serious infection, TB
Etanercept versus etanercept plus methotrexate		
Gottlieb (2012)	<ul style="list-style-type: none"> - ≥ 18 years; - stable mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 10; - candidate for systemic or phototherapy; - adequate/normal blood levels 	<ul style="list-style-type: none"> - guttate, erythrodermic or pustular psoriasis; - other skin conditions; - concurrent significant medical conditions

BSA = body surface area; CD4 = cluster of differentiation 4; CPP = chronic plaque psoriasis; IL = interleukin; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; PUVA = photochemotherapy; TB = tuberculosis; TNF = tumour necrosis factor; Shaded = previously considered by the PBAC

Treatment details

Table 73: Etanercept trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 50 mg once weekly or 25 mg twice weekly (81)				
Etanercept versus placebo				
Leonardi (2003)	12 weeks	Etanercept	SC	25 mg once weekly (plus matched placebo)
		Etanercept	SC	25 mg twice weekly*
		Etanercept	SC	50mg twice weekly
		Placebo	SC	Matched placebo injections
Gottlieb (2003)	12 weeks/ 24 weeks	Etanercept	SC	25 mg twice weekly*
		Placebo	SC	Matched placebo injections
Papp (2005)	12 weeks	Etanercept	SC	25 mg twice weekly*
		Etanercept	SC	50 mg twice weekly
		Placebo	SC	Matched placebo injections

Trial	Time horizon	Treatment	Delivery	Dose
van de Kerkhof (2008)	12 weeks	Etanercept	SC	50 mg once weekly*
		Placebo	SC	Matched placebo injections
Tyring (2006)	12 weeks	Etanercept	SC	50 mg twice weekly
		Placebo	SC	Matched placebo injections
Etanercept versus tofacitinib versus placebo				
OPT COMPARE	12 weeks	Etanercept	SC	50 mg twice weekly (plus matched placebo tablets)
		Tofacitinib	Oral	5 mg twice daily (plus matched placebo injections)
		Tofacitinib	Oral	10 mg twice daily (plus matched placebo injections)
		Placebo	SC + oral	Matched placebo injections and tablets
Etanercept versus briakinumab versus placebo				
M10-114	12 weeks	Etanercept	SC	50 mg twice weekly (plus matched placebo injections)
		Briakinumab	SC	200 mg at Weeks 0, 4; 100 mg at Week 8 (plus matched placebo injections)
		Placebo	SC	Matched placebo injections
M10-315	12 weeks	Etanercept	SC	50 mg twice weekly (plus matched placebo injections)
		Briakinumab	SC	200 mg at Weeks 0, 4; 100 mg at Week 8 (plus matched placebo injections)
		Placebo	SC	Matched placebo injections
Etanercept versus etanercept				
PRESTA	12 weeks	Etanercept	SC	50 mg once weekly*
		Etanercept	SC	50 mg twice weekly
PRISTINE	12 weeks	Etanercept	SC	50 mg once weekly*
		Etanercept	SC	50 mg twice weekly
Etanercept versus etanercept plus methotrexate				
Gottlieb (2012)	12 weeks/ 24 weeks	Etanercept + methotrexate	SC + oral	Etanercept: 50 mg twice weekly for 12 weeks; 50 mg once weekly for 12 weeks Methotrexate: 7.5 mg Weeks 1 and 2, 10 mg weeks 3 and 4, up to 15 mg for weeks 5-24.
		Etanercept	SC (+ oral)	50 mg twice weekly for 12 weeks; 50 mg once weekly for 12 weeks (plus matched placebo tablets)

DB = double-blind; PBAC = Pharmaceutical Benefits Advisory Committee; PI = Product Information; SC = subcutaneous; top = topical; Shaded = previously considered by the PBAC

* PI recommended dose

Efficacy

Table 74: Etanercept trials: efficacy results - proportion of patients achieving PASI 50, 75, 90 or 100 response

Trial	Time horizon	Arm	N	PASI 50; n (%)	PASI 75; n (%)	PASI 90; n (%)	PASI 100; n (%)
Etanercept versus placebo							
Leonardi (2003)	12 weeks	Etan ^{1*}	162	94 (58%)	55 (34%)	19 (12%)	NR
		Etan ²	164	121 (74%)	81 (49%)	36 (22%)	NR
		Pbo	166	24 (14%)	6 (4%)	1 (1%)	NR
Gottlieb (2003)	12 weeks	Etan ^{1*}	57	70%	17 (30%)	NR	NR
		Pbo	55	11%	1 (2%)	NR	NR
Papp (2005)	12 weeks	Etan ^{1*}	196	126 (64%)	67 (34%)	21 (11%)	NR
		Etan ²	194	150 (77%)	96 (49%)	40 (21%)	NR
		Pbo	193	18 (9%)	6 (3%)	1 (1%)	NR
van de Kerkhof (2008)	12 weeks	Etan ^{3*}	96	66 (69%)	36 (38%)	13 (14%)	NR
		Pbo	46	4 (9%)	1 (2%)	1 (2%)	NR
Tyring (2006)	12 weeks	Etan ²	311	229 (74%)	147 (47%)	65 (21%)	NR
		Pbo	307	43 (14%)	15 (5%)	4 (1%)	NR
OPT COMPARE	12 weeks	Etan ²	335	269 (80%)	197 (59%)	108 (32%)	NR
		Pbo	107	22 (21%)	6 (6%)	1 (1%)	NR
M10-114	12 weeks	Etan ²	141	NR	56%	NR	NR
		Pbo	68	NR	7%	NR	NR
M10-315	12 weeks	Etan ²	139	NR	40%	14%	6%
		Pbo	72	NR	7%	4%	0
Etanercept versus etanercept							
PRESTA	12 weeks	Etan ^{3*}	373	NR	36%	NR	NR
		Etan ²	379	NR	55%	NR	NR
PRISTINE	12 weeks	Etan ^{3*}	137	68%	37%	11%	NR
		Etan ²	136	88%	62%	29%	NR
Etanercept versus etanercept plus methotrexate							
Gottlieb (2012)	12 weeks	Etan ²	239	84%	54%	23%	NR

Etan = etanercept; NR = not reported; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; SE = standard error; *Italics* = (SE); Shaded = previously considered by the PBAC

^{1*} Etanercept 25 mg SC twice weekly (PI recommended dose)

² Etanercept 50 mg SC twice weekly

^{3*} Etanercept 50 mg SC once weekly (PI recommended dose)

Safety

Table 75: Etanercept trials: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Etanercept versus placebo														
van de Kerkhof (2008)	12 weeks	Etan ^{1*}	96	NR	NR	NR	NR	NR	9%	NR	NR	14%	15%	17%
		Pbo	46	NR	NR	NR	NR	NR	11%	NR	NR	2%	9%	2%
Tyring (2006)	12 weeks	Etan ²	312	28%	0	1%	1%	< 1%	4%	7%	NR	6%	NR	11%
		Pbo	306	23%	< 1%	< 1%	0	1%	5%	4%	NR	6%	NR	1%
OPT COMPARE	12 weeks	Etan ²	335	23%	1%	0	1%	< 1%	2%	8%	NR	NR	NR	15%
		Pbo	107	19%	0	0	0	0	0	9%	NR	NR	NR	8%
M10-114	12 weeks	Etan ²	141	24%	< 1%	1%	1%	0	6%	8%	NR	5%	NR	9%
		Pbo	68	19%	0	0	0	0	9%	3%	NR	3%	NR	4%
M10-315	12 weeks	Etan ²	139	28%	0	3%	2%	0	12%	8%	NR	NR	NR	NR
		Pbo	72	14%	0	1%	0	0	0	8%	NR	NR	NR	NR
Gottlieb (2003)	24 weeks	Etan ^{3*}	57	NR	0	NR	0	NR	35%	NR	NR	16%	NR	9%
		Pbo	55	NR	0	NR	0	NR	20%	NR	NR	13%	NR	0
Etanercept versus etanercept														
PRESTA	24 weeks	Etan ^{1*}	373	NR	1%	< 1%	< 1%	NR	NR	NR	NR	NR	NR	NR
		Etan ²	379	NR	< 1%	1%	< 1%	NR	NR	NR	NR	NR	NR	NR
PRISTINE	24 weeks	Etan ^{1*}	137	NR	< 1%	1%	0	NR	NR	NR	NR	NR	NR	NR
		Etan ²	136	NR	< 1%	0	0	NR	NR	NR	NR	NR	NR	NR
Etanercept versus etanercept plus methotrexate														
Gottlieb (2012)	24 weeks	Etan ²	239	NR	0	NR	0	NR	5%	11%	2%	9%	NR	8%

CVD = cardiovascular disease; Etan = etanercept; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; URTI = upper respiratory tract infection; Shaded = previously considered by the PBAC

^{1*} Etanercept 50 mg SC once weekly (PI recommended dose)

² Etanercept 50 mg SC twice weekly

^{3*} Etanercept 25 mg SC twice weekly (PI recommended dose)

Infliximab

Inclusion and exclusion criteria

Table 76: Infliximab trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Infliximab versus placebo		
Chaudhari (2001)	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 5%; - failure of topical corticosteroids 	<ul style="list-style-type: none"> - topical therapy within 14 days or systemic therapy within 28 days; - previous anti-TNF or biologicals; - HIV, Hep B/C, current alcohol or drug abuse, TB, malignancy
EXPRESS	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe plaque-type psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12 - candidate for systemic or phototherapy 	<ul style="list-style-type: none"> - previous infliximab or other TNF antagonist; - history or risk of serious infection, lymphoproliferative disease or active TB
Gottlieb (2004)	<ul style="list-style-type: none"> - ≥ 18 years; - plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12; - previous PUVA or systemic anti-psoriasis treatments 	<ul style="list-style-type: none"> - non-plaque forms of psoriasis; - history of chronic/opportunistic infection or active/latent TB; - pregnancy; - lymphoproliferative disease, malignancy
Menter (2007)	<ul style="list-style-type: none"> - ≥ 18 years; - BSA ≥ 10%, PASI ≥ 12; - candidate for systemic or phototherapy; 	<ul style="list-style-type: none"> - previous infliximab; - history of serious infection, lymphoproliferative disease or active TB
Torii (2010)	<ul style="list-style-type: none"> - mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12 	<ul style="list-style-type: none"> - history of serious infection, lymphoproliferative disease or active TB
Yang (2012)	<ul style="list-style-type: none"> - 18-65 years; - plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12; - failed to respond to systemic treatments 	<ul style="list-style-type: none"> - non-plaque psoriasis; - history of chronic/opportunistic infections; - serious infection within 2 months; - active/latent TB; - pregnancy; - lymphoproliferative disease; - active/history of malignancy
Infliximab versus methotrexate		
RESTORE	<ul style="list-style-type: none"> - 18-75 years; - mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12; - candidate for systemic or phototherapy 	<ul style="list-style-type: none"> - previous methotrexate, biologic or TNF antagonist within 3 months; - CHF; - history of chronic/recurrent infection or TB

Trial	Inclusion criteria	Exclusion criteria
Infliximab versus etanercept		
PIECE	<ul style="list-style-type: none"> - 18–75 years; - BSA \geq 10%, PASI \geq 10; - mod-to severe chronic plaque-type psoriasis; - unresponsive/contraindicated/intolerant to UV therapy, methotrexate or cyclosporin 	<ul style="list-style-type: none"> - pregnant or breastfeeding; - malignancy within 10 years; - active/chronic infections; - live vaccination within 3 months; - severe liver/kidney function disorders; - previous infliximab or etanercept stopped due to a lack of efficacy, contraindication or adverse event

BSA = body surface area; CHF = congestive heart failure; CRP = C-reactive protein; DMARD = disease modifying anti-rheumatic drug; Hep = hepatitis; HIV = human immunodeficiency virus; mod = moderate; m-PPASI = modified palmoplantar psoriasis areas and severity index; NSAID = non-steroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; PUVA = photochemotherapy; TB = tuberculosis; TNF = tumour necrosis factor; UV = ultraviolet; Shaded = previously considered by the PBAC

DRAFT

Treatment details

Table 77: Infliximab trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 5mg/kg at Weeks 0, 2, 6; then every 8 weeks (82)				
Infliximab versus placebo				
Chaudhari (2001)	10 weeks	Infliximab	IV	5 mg/kg at Weeks 0, 2, 6*
		Infliximab	IV	10 mg/kg at Weeks 0, 2, 6
		Placebo	IV	Matched placebo injections
EXPRESS	10 weeks/ 24 weeks	Infliximab	IV	5 mg/kg at Weeks 0, 2, 6; then every 8 weeks*
		Placebo	IV	Matched placebo injections
Gottlieb (2004)	10 weeks/ 30 weeks	Infliximab	IV	3 mg/kg at Weeks 0, 2, 6
		Infliximab	IV	5 mg/kg at Weeks 0, 2, 6*
		Placebo	IV	Matched placebo injections
Menter (2007)	10 weeks	Infliximab	IV	3 mg/kg at Weeks 0, 2, 6
		Infliximab	IV	5 mg/kg at Weeks 0, 2, 6*
		Placebo	IV	Matched placebo injections
Torii (2010)	10 weeks	Infliximab	IV	Infliximab 5 mg/kg at Weeks 0, 2, 6*
		Placebo	IV	Matched placebo injections
Yang (2012)	10 weeks	Infliximab	IV	5 mg/kg at Weeks at 0, 2, 6*
		Placebo	IV	Matched placebo injections
Infliximab versus methotrexate				
RESTORE	16 weeks	Infliximab	IV	5 mg/kg at Weeks at 0, 2, 6, 14*
		Methotrexate	Oral	15 mg weekly until Week 6; dose could then be increased to 20 mg weekly
Infliximab versus etanercept				
PIECE	12 weeks/ 24 weeks	Infliximab	IV	5 mg/kg at Weeks 0, 2, 6; and then every 8 weeks*
		Etanercept	SC	50 mg twice weekly

DB = double-blind; IV = intravenous; PBAC = Pharmaceutical Benefits Advisory Committee; PI = Product information; SC = subcutaneous; Shaded = previously considered by the PBAC

Efficacy

Table 78: Infliximab trials: efficacy results – proportion of patients achieving PASI 50, 75, 90 or 100 response

Trial	Seen by PBAC?	Time horizon	Arm	N	PASI 50; n (%)	PASI 75; n (%)	PASI 90; n (%)	PASI 100; n (%)
Infliximab versus placebo								
Chaudhari (2001)	Yes	10 weeks	Inf ¹	11	NR	9 (82%)	NR	NR
			Pbo	11	NR	2 (18%)	NR	NR
EXPRESS	Yes	10 weeks	Inf ¹	301	274 (91%)	242 (80%)	172 (57%)	NR
			Pbo	77	6 (8%)	2 (3%)	1 (1%)	NR
Gottlieb (2004)	No	10 weeks	Inf ¹	99	96 (97%)	87 (88%)	57 (58%)	NR
			Pbo	51	11 (22%)	3 (6%)	1 (2%)	NR
Menter (2007)	No	10 weeks	Inf ¹	314	NR	76%	45%	NR
			Pbo	208	NR	2%	1%	NR
Torii (2010)	No	10 weeks	Inf ¹	35	NR	69%	NR	NR
			Pbo	19	NR	0	NR	NR
Yang (2012)	No	10 weeks	Inf ¹	84	79 (94%)	68 (81%)	48 (57%)	NR
			Pbo	45	6 (13%)	1 (2%)	0	NR
Infliximab versus methotrexate								
RESTORE	No	16 weeks	Inf ¹	653	567 (87%)	508 (78%)	356 (55%)	NR
Infliximab versus etanercept								
PIECE	No	12 weeks	Inf ¹	25	24 (96%)	19 (76%)	5 (20%)	1 (4%)
			Etan ²	23	14 (61%)	5 (22%)	0	0

Etan = etanercept; Inf = infliximab; IV = intravenous; NR = not reported; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; Shaded = previously considered by the PBAC

¹* Infliximab 5 mg/kg IV at Weeks 0, 2, 6; and then every 8 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

Safety

Table 79: Infliximab trials: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Infliximab versus placebo														
Chaudhari (2001)	10 weeks	Inf ^{1*}	11	9%	NR	NR	NR	NR	18%	NR	NR	9%	0	NR
		Inf ²	11	9%	NR	NR	NR	NR	27%	NR	NR	64%	0	NR
		Pbo	11	18%	NR	NR	NR	NR	36%	NR	NR	18%	18%	NR
Yang (2012)	10 weeks	Inf ^{1*}	84	NR	NR	NR	NR	NR	7%	NR	NR	NR	NR	4%
		Pbo	45	NR	NR	NR	NR	NR	9%	NR	NR	NR	NR	0
Menter (2007)	14 weeks	Inf ³	313	34%	NR	NR	NR	NR	16%	NR	NR	12%	NR	12%
		Inf ^{1*}	314	31%	NR	NR	NR	NR	13%	NR	NR	12%	NR	10%
		Pbo	208	30%	NR	NR	NR	NR	14%	NR	NR	5%	NR	6%
EXPRESS	24 weeks	Inf ^{1*}	298	42%	1%	1%	1%	NR	15%	NR	9%	14%	7%	3%
		Pbo	76	40%	0	0	0	NR	16%	NR	0	12%	7%	2%
Gottlieb (2004)	30 weeks	Inf ³	98	NR	0	NR	NR	NR	NR	NR	NR	NR	NR	18%
		Inf ^{1*}	99	NR	1%	NR	NR	NR	NR	NR	NR	NR	NR	22%
		Pbo	51	NR	0	NR	NR	NR	NR	NR	NR	NR	NR	2%
Infliximab versus methotrexate														
RESTORE	16 weeks	Inf ^{1*}	653	NR	NR	NR	NR	NR	NR	6%	NR	5%	NR	9%
		Mtx	215	NR	NR	NR	NR	NR	NR	5%	NR	7%	NR	0

CVD = cardiovascular disease; Etan = etanercept; Inf = infliximab; IV = intravenous; Mtx = methotrexate; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; URTI = upper respiratory tract infection; Shaded = previously considered by the PBAC

^{1*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; and then every 8 weeks (PI recommended dose)

² Infliximab 10 mg/kg IV at Weeks 0, 2, 6; and then every 8 weeks

³ Infliximab 3 mg/kg IV at Weeks 0, 2, 6; and then every 8 weeks

Ixekizumab

Inclusion and exclusion criteria

Table 80: Ixekizumab trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Ixekizumab versus etanercept versus placebo		
UNCOVER 1, 2, 3	<ul style="list-style-type: none"> - ≥ 18 years; - CPP for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, sPGA ≥ 3; - candidate for systemic and/or phototherapy 	<ul style="list-style-type: none"> - guttate, erythrodermic or pustular psoriasis; - history of drug-induced psoriasis; - clinically significant flare of psoriasis within 12 weeks; - previous etanercept or recent use of a biologic including natalizumab or agents that target alpha-4-integrin or IL-17 antagonists; - systemic non-biologic or phototherapy within 4 weeks; - topical treatment within 2 weeks; - allergy or hypersensitivity to any biologic therapy; - live vaccination within 12 weeks, vaccination with BCG within 12 months; - current or a history of lymphoproliferative disease, demyelinating disorder, uncompensated HF, fluid overload, or MI, or new-onset ischemic heart disease; - uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders, arterial hypertension or abnormal laboratory; - uncontrolled neuropsychiatric disorder/ suicide risk; - serious infection within 12 weeks, active or recent infection within 4 weeks, or evidence or suspicion of active or latent TB; uncontrolled; - HIV, Hep B/C; - breastfeeding

BCG = bacille Calmette-Guerin; BSA = body surface area; CPP = chronic plaque psoriasis; Hep = hepatitis; HF = heart failure; HIV = human immunodeficiency virus; IL = interleukin; MI = myocardial infarction; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; sPGA = static Physician's Global Assessment; TB = tuberculosis; **Shaded** = previously considered by the PBAC

Treatment details

Table 81: Ixekizumab trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 160 mg at Week 0, 80 mg at Weeks 2, 4, 6, 8, 10 and 12, then 80 mg every 4 weeks (83)				
Ixekizumab versus placebo				
UNCOVER 1	12 weeks	Ixekizumab	SC	160 mg at Week 0, 80 mg at Weeks 2, 4, 6, 8, 10*
		Ixekizumab	SC	160 mg at Week 0, 80 mg at Weeks 4, 8, 12 (plus matched placebo injections)
		Placebo	SC	Matched placebo injections
Ixekizumab versus etanercept versus placebo				
UNCOVER 2, 3	12 weeks	Ixekizumab	SC	160 mg at Week 0, 80 mg at Weeks 2, 4, 6, 8, 10 (plus matched placebo injections)*
		Ixekizumab	SC	160 mg at Week 0, 80mg at Weeks 4, 8, 12 (plus matched placebo injections)
		Etanercept	SC	50 mg twice weekly
		Placebo	SC	Matched placebo injections

DB = double-blind; PBAC = Pharmaceutical Benefits Advisory Committee; PI = Product Information; SC = subcutaneous; Shaded = previously considered by the PBAC

* PI recommended dose

Efficacy

Table 82: Ixekizumab trials: efficacy results – proportion of patients achieving PASI response of 50, 75, 90 or 100

Trial	Seen by PBAC?	Time horizon	Arm	N	PASI 50; n (%)	PASI 75; n (%)	PASI 90; n (%)	PASI 100; n (%)
Ixekizumab versus placebo								
UNCOVER 1	Yes	12 weeks	Ixe ¹	433	NR	89%	71%	35%
			Pbo	431	NR	4%	1%	0
Ixekizumab versus etanercept versus placebo								
UNCOVER 2	Yes	12 weeks	Ixe ¹	351	NR	315 (90%)	248 (71%)	142 (41%)
			Etan ²	358	NR	149 (42%)	67 (19%)	19 (5%)
			Pbo	168	NR	4 (2%)	1 (1%)	1 (1%)
UNCOVER 3	Yes	12 weeks	Ixe ¹	385	NR	336 (87%)	262 (68%)	145 (38%)
			Etan ²	382	NR	204 (53%)	98 (26%)	28 (7%)
			Pbo	193	NR	14 (7%)	6 (3%)	0

Etan = etanercept; Ixe = ixekizumab; NR = not reported; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SD = standard deviation; Shaded = previously considered by the PBAC

¹ Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

² Etanercept 50 mg SC twice weekly

Safety

Table 83: Ixekizumab trials: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Ixekizumab versus placebo														
UNCOVER 1	12 weeks	Ixe ¹	433	29%	NR	NR	NR	0	6%	12%	NR	4%	NR	NR
		Ixe ²	432	29%	NR	NR	NR	< 1%	5%	11%	NR	4%	NR	NR
		Pbo	431	31%	NR	NR	NR	0	4%	10%	NR	4%	NR	NR
Ixekizumab versus etanercept versus placebo														
UNCOVER 2, 3	12 weeks	Ixe ¹	734	26%	NR	NR	NR	0	4%	8%	NR	5%	2%	17%
		Ixe ²	729	26%	NR	NR	NR	< 1%	3%	8%	NR	5%	2%	13%
		Etan ³	739	22%	NR	NR	NR	< 1%	5%	7%	NR	4%	1%	16%
		Pbo	360	21%	NR	NR	NR	< 1%	3%	8%	NR	2%	1%	4%

CVD = cardiovascular disease; Ixe = ixekizumab; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; URTI = upper respiratory tract infection; Shaded = previously considered by the PBAC

¹ Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

² Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 4, 8

³ Etanercept 50 mg SC twice weekly

Secukinumab

Inclusion and exclusion criteria

Table 84: Secukinumab: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Secukinumab versus placebo		
ERASURE	<ul style="list-style-type: none"> - ≥ 18 years; - diagnosis of mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, IGA ≥ 3; - poorly controlled with topical, systemic or phototherapy, or a combination of these 	<ul style="list-style-type: none"> - other forms of psoriasis; - previous secukinumab or biologic targeting IL-17; - pregnancy or breastfeeding
FEATURE	<ul style="list-style-type: none"> - ≥ 18 years; - diagnosis of plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, IGA ≥ 3; - poorly controlled with topical, systemic or phototherapy 	<ul style="list-style-type: none"> - other forms of psoriasis; - unwillingness to limit UV light exposure during the study; - previous secukinumab or biologic targeting IL-17; - live vaccination within 6 weeks; - active ongoing inflammatory disease, immunocompromised or other significant medical problems; - active systemic infection within 2 weeks, ongoing/chronic/recurrent infectious disease, or TB; - HIV, Hep B/C; - history of lymphoproliferative disease or of known malignancy; - history of psychiatric conditions or alcohol or drug abuse within 6 months
JUNCTURE	<ul style="list-style-type: none"> - ≥ 18 years; - diagnosis of mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, IGA ≥ 3 - unresponsive to topical treatments, phototherapy, and/or systemic therapy 	<ul style="list-style-type: none"> - other forms of psoriasis; - previous secukinumab or biologic targeting IL-17; - active systemic infection within 2 weeks or active TB; - HIV, Hep B/C or if immunocompromised
Secukinumab versus secukinumab		
SCULPTURE	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe CPP for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, IGA ≥ 3; - unresponsive to topical, systemic, phototherapy, or a combination of these 	-

Trial	Inclusion criteria	Exclusion criteria
Secukinumab versus etanercept versus placebo		
FIXTURE	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, IGA ≥ 3; - unresponsive to topical, systemic, phototherapy, or a combination of these 	<ul style="list-style-type: none"> - other forms of psoriasis; - ongoing use of prohibited psoriasis treatments; - previous secukinumab or biologic IL-17; - pregnant or breastfeeding
Secukinumab versus ustekinumab		
CLEAR	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, IGA ≥ 3; - unresponsive to topical, systemic, phototherapy, or a combination of these 	<ul style="list-style-type: none"> - previous use of biologics directly targeting IL-17A or IL-12/IL-23

BSA = body surface area; CPP = chronic plaque psoriasis; Hep = hepatitis; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; IL = interleukin; mod = moderate; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; PUVA = photochemotherapy; TB = tuberculosis; UV = ultraviolet; Shaded = previously considered by the PBAC

DRAFT

Treatment details

Table 85: Secukinumab trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 300 mg at Weeks 0, 1, 2, 3, 4; then every four weeks from Week 4 (84)				
Secukinumab versus placebo				
ERASURE	12 weeks	Secukinumab	SC	150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks
		Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks*
		Placebo	SC	Matched placebo injections
FEATURE	12 weeks	Secukinumab	SC	150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks
		Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks*
		Placebo	SC	Matched placebo injections
JUNCTURE	12 weeks	Secukinumab	SC	150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks
		Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks*
		Placebo	SC	Matched placebo injections
Secukinumab versus secukinumab				
SCULPTURE	12 weeks	Secukinumab	SC	150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks
		Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks*
Secukinumab versus etanercept versus placebo				
FIXTURE	12 weeks	Secukinumab	SC	150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks (plus matched placebo injections)
		Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks (plus matched placebo injections)*
		Etanercept	SC	50 mg twice weekly
		Placebo	SC	Matched placebo injections
Secukinumab versus ustekinumab				
CLEAR	16 weeks	Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks*
		Ustekinumab	SC	45 mg for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (plus matched placebo injections)

DB = double-blind; PBAC = Pharmaceutical Benefits Advisory Committee; PI = Product Information; SC = subcutaneous; Shaded = previously considered by the PBAC

* PI recommended dose

Efficacy

Table 86: Secukinumab trials: efficacy results – proportion of patients achieving PASI 50, 75, 90 or 100 response

Trial	Seen by PBAC?	Time horizon	Arm	N	PASI 50; n (%)	PASI 75; n (%)	PASI 90; n (%)	PASI 100; n (%)
Secukinumab versus placebo								
ERASURE	Yes	12 weeks	Sec ¹	245	NR	82%	59%	29%
			Pbo	248	NR	5%	1%	1%
FEATURE	Yes	12 weeks	Sec ¹	59	NR	76%	60%	43%
			Pbo	59	NR	0	0	0
JUNCTURE	Yes	12 weeks	Sec ¹	60	NR	87%	55%	27%
			Pbo	61	NR	3%	0	0
Secukinumab versus secukinumab								
SCULPTURE	No	12 weeks	Sec ¹	484	NR	90%	NR	NR
Secukinumab versus etanercept versus placebo								
FIXTURE	Yes	12 weeks	Sec ¹	327	NR	77%	54%	24%
			Etan ²	326	NR	44%	21%	4%
			Pbo	326	NR	5%	2%	0
Secukinumab versus ustekinumab								
CLEAR	No	16 weeks	Sec ¹	334	NR	311 (93%)	264 (79%)	148 (44%)
			Ust ³	335	NR	277 (83%)	193 (58%)	95 (28%)

Etan = etanercept; NR = not reported; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Sec = secukinumab; Ust = ustekinumab; Shaded = previously considered by the PBAC

¹ Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

³ Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

Safety

Table 87: Secukinumab trials: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Secukinumab versus placebo														
ERASURE	12 weeks	Sec ¹	245	27%	NR	NR	NR	NR	4%	9%	NR	5%	3%	NR
		Sec ^{2*}	245	29%	NR	NR	NR	NR	4%	9%	NR	5%	4%	NR
		Pbo	248	16%	NR	NR	NR	NR	0	8%	NR	3%	2%	NR
FEATURE	12 weeks	Sec ¹	59	NR	NR	0	NR	0	NR	5%	NR	7%	NR	NR

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
		Sec ^{2*}	59	NR	NR	0	NR	3%	NR	5%	NR	0	NR	NR
		Pbo	59	NR	NR	0	NR	0	NR	9%	NR	5%	NR	NR
JUNCTURE	12 weeks	Sec ¹	61	NR	NR	NR	NR	0	NR	23%	NR	8%	2%	0
		Sec ^{2*}	60	NR	NR	NR	NR	0	NR	32%	NR	5%	8%	5%
		Pbo	61	NR	NR	NR	NR	0	NR	16%	NR	5%	3%	0
Secukinumab versus secukinumab														
SCULPTURE	12 weeks	Sec ¹	482	NR	< 1%	0	NR	0	4%	10%	NR	5%	4%	NR
		Sec ^{2*}	483	NR	0	< 1%	NR	< 1%	4%	9%	NR	4%	2%	NR
Secukinumab versus etanercept versus placebo														
FIXTURE	12 weeks	Sec ¹	327	31%	NR	NR	NR	NR	3%	14%	NR	5%	4%	NR
		Sec ^{2*}	326	27%	NR	NR	NR	NR	2%	11%	NR	9%	3%	NR
		Etan ³	323	25%	NR	NR	NR	NR	2%	11%	NR	7%	3%	NR
		Pbo	327	19%	NR	NR	NR	NR	1%	8%	NR	7%	3%	NR
Secukinumab versus ustekinumab														
CLEAR	16 weeks	Sec ^{2*}	335	29%	NR	NR	NR	NR	NR	7%	NR	8%	NR	NR
		Ust ⁴	336	25%	NR	NR	NR	NR	NR	10%	NR	8%	NR	NR

CVD = cardiovascular disease; Etan = etanercept; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; sec = secukinumab; URTI = upper respiratory tract infection; Ust = ustekinumab; Shaded = previously considered by the PBAC

^a Adverse events for secukinumab arms receiving: 25 mg SC at Week 0; 25 mg SC at Weeks 0, 4, 8; and 75 mg SC at Weeks 0, 4, 8 were not included in the comparison

^b Adverse events for secukinumab arm receiving 150 mg SC at Week 0 was not included in the comparison

¹ Secukinumab 150 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks

^{2*} Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

³ Etanercept 50 mg SC twice weekly

⁴ Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

Ustekinumab

Inclusion and exclusion criteria

Table 88: Ustekinumab trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Ustekinumab versus placebo		
PHOENIX 1	<ul style="list-style-type: none"> - ≥ 18 years; - diagnosed plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12; - candidate for systemic or phototherapy; - no history of TB (latent TB if treatment initiated) 	<ul style="list-style-type: none"> - non-plaque forms of psoriasis; - recent serious systemic or local infection; - known malignancy (except basal- or squamous-cell skin cancer); - previous agents targeting IL-12 or IL-23; - biologic or investigational agents within 3 months; - systemic or phototherapy within 4 weeks, or topical treatment within 2 weeks
PHOENIX 2	<ul style="list-style-type: none"> - ≥ 18 years; - diagnosis of plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12; - candidate for systemic or phototherapy 	<ul style="list-style-type: none"> - non-plaque forms of psoriasis; - history/symptoms of active TB; - recent serious systemic or local infection; - known malignancy (except basal- or squamous-cell skin cancer); - previous agents targeting IL-12 or IL-23; - biologic or investigational agents within 3 months; - systemic or phototherapy within 4 weeks, or topical treatment within 2 weeks
PEARL	<ul style="list-style-type: none"> - Korean or Taiwanese ancestry; - diagnosis of mod-to-severe plaque psoriasis; - BSA ≥ 10%, PASI ≥ 12; - candidate for systemic or phototherapy; - no history of TB (latent TB if treatment initiated) 	<ul style="list-style-type: none"> - biologic psoriasis therapy within 3 months, systemic or phototherapy within 4 weeks, or topical treatment within 2 weeks of randomization; - history of chronic/recurrent infections; - history of malignancy
LOTUS	<ul style="list-style-type: none"> - ≥ 18 years; - Chinese ancestry; - diagnosis of plaque type psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12; - no history of TB (latent TB if treatment initiated) 	<ul style="list-style-type: none"> - non-plaque forms of psoriasis; - active TB; - current severe, progressive or uncontrolled medical conditions
Ustekinumab versus brodalumab versus placebo		
AMAGINE 2, 3	<ul style="list-style-type: none"> - 18 to 75 years; - stable mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3 	<ul style="list-style-type: none"> - other significant medical conditions; - medications with the potential to confound efficacy; - TB

Trial	Inclusion criteria	Exclusion criteria
Ustekinumab versus etanercept		
ACCEPT	<ul style="list-style-type: none"> - ≥ 18 years; - diagnosis of plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3; - candidate for systemic or phototherapy; - unresponsive/intolerant/contraindicated to ≥ 1 systemic agent 	<ul style="list-style-type: none"> - non-plaque or drug-induced psoriasis; - previous ustekinumab or etanercept; - recent serious infection or a history of chronic/recurrent infections; - known malignancy (except basal- or squamous-cell skin cancer or cervical cancer); - systemic or phototherapy within 4 weeks, topical treatments within 2 weeks, or investigational drugs within 4 weeks
Ustekinumab versus secukinumab		
CLEAR	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, IGA ≥ 3; - unresponsive to topical, systemic, phototherapy, or a combination of these 	<ul style="list-style-type: none"> - previous use of biologics directly targeting IL-17A or IL-12/IL-23

BCG = bacille Calmette-Guerin; BSA = body surface area; DMARD = disease modifying anti-rheumatic drug; Hep = hepatitis; HIV = human immunodeficiency virus; IL = interleukin; mod = moderate; NSAID = non-steroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; PUVA = photochemotherapy; TB = tuberculosis; TNF = tumour necrosis factor; Shaded = previously considered by the PBAC

Treatment details

Table 89: Ustekinumab trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 45 mg at Weeks 0, 4; then every 12 weeks. 90 mg at Weeks 0, 4; then every 12 weeks may be considered for patients > 100 kg (85)				
Ustekinumab versus placebo				
PHOENIX 1	12 weeks	Ustekinumab	SC	45 mg at Weeks 0, 4*
		Ustekinumab	SC	90 mg at Weeks 0, 4
		Placebo	SC	Matched placebo injections
PHOENIX 2	12 weeks	Ustekinumab	SC	45 mg at Weeks 0, 4*
		Ustekinumab	SC	90 mg at Weeks 0, 4
		Placebo	SC	Matched placebo injections
PEARL	12 weeks	Ustekinumab	SC	45 mg at Weeks 0, 4*
		Placebo	SC	Matched placebo injections
LOTUS	12 weeks	Ustekinumab	SC	45 mg at Weeks 0, 4*
		Placebo	SC	Matched placebo injections
Ustekinumab versus brodalumab versus placebo				
AMAGINE 2, 3	12 weeks	Brodalumab	SC	210 mg at Weeks 0, 1, 2, 4, 6, 8, 10
		Brodalumab	SC	140 mg at Weeks 0, 1, 2, 4, 6, 8, 10
		Ustekinumab	SC	45 mg at Weeks 0, 4 (plus matched placebo injections)*
		Placebo	SC	Matched placebo injections
Ustekinumab versus etanercept				
ACCEPT	12 weeks	Ustekinumab	SC	45 mg at Weeks 0, 4*
		Ustekinumab	SC	90 mg at Weeks 0, 4
		Etanercept	SC	50 mg twice weekly
Ustekinumab versus secukinumab				
CLEAR	16 weeks	Ustekinumab	SC	45 mg for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (plus matched placebo injections)*
		Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks

DB = double-blind; PBAC = Pharmaceutical Benefits Advisory Committee; PI = Product information; SC = subcutaneous; Shaded = previously considered by the PBAC

* PI recommended dose

Efficacy

Table 90: Ustekinumab trials: efficacy results – proportion of patients achieving PASI 50, 75, 90 or 100 response

Trial	Time horizon	Arm	N	PASI 50; n (%)	PASI 75; n (%)	PASI 90; n (%)	PASI 100; n (%)
Ustekinumab versus placebo							
PHOENIX 1	12 weeks	Ust ^{1*}	255	213 (84%)	171 (67%)	106 (42%)	32 (13%)
		Ust ²	256	220 (86%)	170 (66%)	94 (37%)	28 (11%)
		Pbo	255	26 (10%)	8 (3%)	5 (2%)	0
PHOENIX 2	12 weeks	Ust ^{1*}	409	342 (84%)	273 (67%)	173 (42%)	74 (18%)
		Ust ²	411	367 (89%)	311 (76%)	209 (51%)	75 (18%)
		Pbo	410	41 (10%)	15 (4%)	3 (1%)	0
PEARL	12 weeks	Ust ^{1*}	61	51 (84%)	41 (67%)	30 (49%)	5 (8%)
		Pbo	60	8 (13%)	3 (5%)	1 (2%)	0
LOTUS	12 weeks	Ust ^{1*}	160	146 (91%)	132 (83%)	107 (67%)	38 (24%)
		Pbo	162	32 (20%)	18 (11%)	5 (3%)	1 (1%)
AMAGINE 2	12 weeks	Ust ^{1*}	300	NR	210 (70%)	NR	65 (22%)
		Pbo	309	NR	25 (8%)	NR	2 (1%)
AMAGINE 3	12 weeks	Ust ^{1*}	313	NR	217 (69%)	NR	58 (19%)
		Pbo	315	NR	19 (6%)	NR	1 (< 1%)
Ustekinumab versus etanercept							
ACCEPT	12 weeks	Ust ^{1*}	209	NR	141 (68%)	76 (36%)	NR
		Ust ²	347	NR	256 (74%)	155 (45%)	NR
		Etan ³	347	NR	197 (57%)	80 (23%)	NR
Ustekinumab versus secukinumab							
CLEAR	16 weeks	Ust ^{4*}	335	NR	277 (83%)	193 (58%)	95 (28%)
		Sec ⁵	334	NR	311 (93%)	264 (79%)	148 (44%)

Etan = etanercept; NR = not reported; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Sec = secukinumab; Ust = ustekinumab; Shaded = previously considered by the PBAC

^{1*} Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

² Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks

³ Etanercept 50 mg SC twice weekly

^{4*} Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

⁵ Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

Safety

Table 91: Ustekinumab trials: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Ustekinumab versus placebo														
PHOENIX 1	12 weeks	Ust ^{1*}	255	31%	0	0	0	< 1%	7%	10%	NR	6%	NR	NR
		Ust ²	256	26%	1%	0	0	0	6%	8%	NR	5%	NR	NR
		Pbo	255	27%	< 1%	0	0	0	6%	9%	NR	2%	NR	NR
PHOENIX 2	12 weeks	Ust ^{1*}	409	22%	0	0	0	0	4%	7%	NR	5%	NR	2%
		Ust ²	411	22%	< 1%	0	< 1%	< 1%	3%	7%	NR	5%	NR	2%
		Pbo	410	20%	< 1%	< 1%	< 1%	0	3%	7%	NR	4%	NR	< 1%
PEARL	12 weeks	Ust ^{1*}	61	33%	0	0	NR	0	12%	8%	NR	NR	8%	2%
		Pbo	60	23%	2%	0	NR	0	12%	5%	NR	NR	27%	5%
LOTUS	12 weeks	Ust ^{1*}	160	26%	0	0	NR	0	6%	12%	3%	NR	3%	NR
		Pbo	161	19%	0	0	NR	0	5%	8%	4%	NR	3%	NR
AMAGINE 2	12 weeks	Ust ^{1*}	300	NR	0	< 1%	NR	< 1%	7%	6%	NR	4%	NR	1%
		Pbo	309	NR	< 1%	0	NR	0	7%	5%	NR	3%	NR	1%
AMAGINE 3	12 weeks	Ust ^{1*}	313	NR	< 1%	NR	NR	NR	5%	5%	NR	4%	NR	3%
		Pbo	313	NR	< 1%	NR	NR	NR	5%	7%	NR	5%	NR	2%
Ustekinumab versus etanercept														
ACCEPT	12 weeks	Ust ^{1*}	209	31%	0	1%	1%	NR	6%	10%	NR	15%	6%	4%
		Ust ²	347	30%	1%	0	< 1%	NR	6%	10%	NR	12%	5%	4%
		Etan ³	347	29%	< 1%	0	0	NR	6%	9%	NR	11%	4%	25%
Ustekinumab versus secukinumab														
CLEAR	16 weeks	Ust ^{4*}	336	25%	NR	NR	NR	NR	NR	10%	NR	8%	NR	NR
		Sec ⁵	335	29%	NR	NR	NR	NR	NR	7%	NR	8%	NR	NR

CVD = cardiovascular disease; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PI = Product Information; SAE serious adverse event; SC = subcutaneous; URTI = upper respiratory tract infection; Ust = ustekinumab; Shaded = previously considered by the PBAC

^a Adverse events for ustekinumab arms receiving 45 mg and 90 mg SC at Week 0 were not included in the comparison

^b Adverse events for brodalumab arms not included in the comparison

^{1*} Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

² Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks

³ Etanercept 50 mg SC twice weekly

^{4*} Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

⁵ Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

Direct comparisons of PBS-listed biologics

Number of trials and treatment details

Table 92: Direct comparisons of PBS-listed biologics: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
Infliximab versus etanercept				
PIECE	12/24 weeks	Infliximab	IV	5 mg/kg at Weeks 0, 2, 6; and then every 8 weeks*
		Etanercept	SC	50 mg twice weekly
Ixekizumab versus etanercept versus placebo				
UNCOVER 2, 3	12 weeks	Ixekizumab	SC	160 mg at Week 0, 80 mg at Weeks 2, 4, 6, 8, 10 (plus matched placebo injections)*
		Ixekizumab	SC	160 mg at Week 0, 80mg at Weeks 4, 8, 12 (plus matched placebo injections)
		Etanercept	SC	50 mg twice weekly
		Placebo	SC	Matched placebo injections
Secukinumab versus etanercept versus placebo				
FIXTURE	12 weeks	Secukinumab	SC	150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks (plus matched placebo injections)
		Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks (plus matched placebo injections)*
		Etanercept	SC	50 mg twice weekly
		Placebo	SC	Matched placebo injections
Ustekinumab versus etanercept				
ACCEPT	12 weeks	Ustekinumab	SC	45 mg at Weeks 0, 4*
		Ustekinumab	SC	90 mg at Weeks 0, 4
		Etanercept	SC	50 mg twice weekly
Secukinumab versus ustekinumab				
CLEAR	16 weeks	Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks*
		Ustekinumab	SC	45 mg for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (plus matched placebo injections)*

DB = double-blind; IV = intravenous; PI = Product Information; SC = subcutaneous

* PI recommended dose

Baseline characteristics

Table 93: Direct comparisons of PBS-listed biologics: baseline characteristics

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Infliximab versus etanercept										
PIECE	Inf ^{1*}	25	45.9 (13.7)	72%	NR	NR	22 (13)	28% (22)	17.8 (9.7)	NR
	Etan ²	23	42.4 (13.2)	56%	NR	NR	18 (11)	21% (13)	15.9 (5.1)	NR

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Ixekizumab versus etanercept versus placebo										
UNCOVER 2	Ixe ^{3*}	351	45 (13)	63%	C: 94%	89 (22)	18 (12)	25% (16)	19 (7)	12 (7)
	Etan ²	358	45 (13)	66%	C: 94%	93 (22)	19 (12)	25% (16)	19 (7)	13 (7)
	Pbo	168	45 (12)	71%	C: 89%	92 (22)	19 (13)	27% (18)	21 (8)	13 (7)
UNCOVER 3	Ixe ^{3*}	385	46 (13)	66%	C: 94%	90 (23)	18 (12)	28% (17)	21 (8)	12 (7)
	Etan ²	382	46 (14)	70%	C: 92%	92 (24)	18 (12)	28% (17)	21 (8)	12 (7)
	Pbo	193	46 (12)	71%	C: 91%	91 (21)	18 (13)	29% (17)	21 (8)	13 (7)
Secukinumab versus etanercept versus placebo										
FIXTURE	Sec ^{4*}	327	44.5 (13.2)	69%	C: 69% A: 22%	83 (22)	16 (12)	34% (19)	23.9 (9.9)	NR
	Etan ²	326	43.8 (13.0)	71%	C: 67% A: 23%	85 (21)	16 (12)	34% (18)	23.2 (9.8)	NR
	Pbo	326	44.1 (12.6)	73%	C: 67% A: 22%	82 (20)	17 (12)	35% (19)	24.1 (10.5)	NR
Ustekinumab versus etanercept										
ACCEPT	Ust ^{5*}	209	45.1 (12.6)	64%	C: 92%	90 (21)	19 (12)	27% (18)	20.5 (9.2)	NR
	Ust ⁶	347	44.8 (12.3)	67%	C: 89%	91 (23)	19 (12)	26% (18)	19.9 (8.4)	NR
	Etan ²	347	45.7 (13.4)	71%	C: 91%	91 (21)	19 (12)	24% (14)	18.6 (6.2)	NR
Secukinumab versus ustekinumab										
CLEAR	Sec ^{4*}	337	45.2 (14.0)	68%	C: 89%	87 (20)	20 (13)	33% (18)	21.7 (8.5)	NR
	Ust ^{7*}	339	44.6 (13.7)	74%	C: 85%	87 (22)	16 (11)	32% (17)	21.5 (8.1)	NR

A = Asian; BSA = body surface area; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; Inf = infliximab; IV = intravenous; Ixe = ixekizumab; NR = not reported; PASI = Psoriasis Area and Severity Index; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; Sec = secukinumab; Ust = ustekinumab

^{1*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

² Etanercept 50 mg SC twice weekly

^{3*} Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

^{4*} Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

^{5*} Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

⁶ Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks

^{7*} Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

Safety

Table 94: Direct comparisons of PBS-listed biologics: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Ixekizumab versus etanercept versus placebo														
UNCOVER 2, 3	12 weeks	Ixe ^{1*}	734	26%	NR	NR	NR	0	4%	8%	NR	5%	2%	17%
		Ixe ²	729	26%	NR	NR	NR	< 1%	3%	8%	NR	5%	2%	13%
		Etan ³	739	22%	NR	NR	NR	< 1%	5%	7%	NR	4%	1%	16%
		Pbo	360	21%	NR	NR	NR	< 1%	3%	8%	NR	2%	1%	4%
Secukinumab versus etanercept versus placebo														
FIXTURE	12 weeks	Sec ⁴	327	31%	NR	NR	NR	NR	3%	14%	NR	5%	4%	NR
		Sec ^{5*}	326	27%	NR	NR	NR	NR	2%	11%	NR	9%	3%	NR
		Etan ³	323	25%	NR	NR	NR	NR	2%	11%	NR	7%	3%	NR
		Pbo	327	19%	NR	NR	NR	NR	1%	8%	NR	7%	3%	NR
Ustekinumab versus etanercept														
ACCEPT	12 weeks	Ust ^{6*}	209	31%	0	1%	1%	NR	6%	10%	NR	15%	6%	4%
		Ust ⁷	347	30%	1%	0	< 1%	NR	6%	10%	NR	12%	5%	4%
		Etan ³	347	29%	< 1%	0	0	NR	6%	9%	NR	11%	4%	25%
Secukinumab versus ustekinumab														
CLEAR	16 weeks	Sec ^{5*}	335	29%	NR	NR	NR	NR	NR	7%	NR	8%	NR	NR
		Ust ^{8*}	336	25%	NR	NR	NR	NR	NR	NR	10%	NR	8%	NR

CVD = cardiovascular disease; Etan = etanercept; Ixe = ixekizumab; PI = Product Information; NR = not reported; SC = subcutaneous; Sec = secukinumab; URTI = upper respiratory tract infection; Ust = ustekinumab

^{1*} Ixekizumab 160 mg SC Week 0; 80 mg Weeks 2, 4, 6, 8, 10 (PI recommended dose)

² Ixekizumab 160 mg SC Week 0; 80 mg Weeks 4, 8, 12

³ Etanercept 50 mg SC twice weekly

⁴ Secukinumab 150 mg SC Weeks 0, 1, 2, 3, 4; then every 4 weeks

^{5*} Secukinumab 300 mg SC Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

^{6*} Ustekinumab 45 mg SC Weeks 0, 4 (PI recommended dose)

⁷ Ustekinumab 90 mg SC Weeks 0, 4

^{8*} Ustekinumab 45 mg SC for patients ≤ 100kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

Appendix C – ToR 2: Network meta-analyses

Statistical analysis

PASI75 v 2.do - Printed on 15/09/2017 2:53:53 PM

```
1 display      newline(5)
2 display      "syntax executed at " c(current time) " on " c(current date)
3
4
5      * * * * *
6      *
7      *              Biologics in chronic plaque psoriasis
8      *              Syntax description
9      *
10     * * * * *
11
12
13 *set          output error // remove * when output starts to get too long
14 clear        all
15 set          more off // chose which one more on
16 version      12
17 set          linesize 80
18 set          varabbrev off, permanently
19 set          autotabgraphs on, permanently
20
21 /* SYNTAX REVISION HISTORY (include date and name)
22 created - 22/07/2017
23 modified - 10/09/2017
24
25 */
26 cd           ""
27
28 set          output proc
29 *-----*
30 *  o  o  o  o  o  o  o  o  o  o  o  o  o  o  o  o  o  o
31 *-----*
32 . import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow
33 . drop in 36/54
34 . replace dA = 1 if dA == 0
35 // Label drug names for output
36 . label variable nA "Placebo"
37
38 . label variable dA "Placebo"
39
40 . label variable nB "Adalimumab"
41
42 . label variable dB "Adalimumab"
43
44 . label variable nC "Efalizumab"
45
46 . label variable dC "Efalizumab"
47
48 . label variable nD "Etanercept - 2 weekly"
49
50 . label variable dD "Etanercept - 2 weekly"
51
52 . label variable nE "Etanercept - 1 weekly"
53
54 . label variable dE "Etanercept - 1 weekly"
55
56 . label variable nF "Ixekizumab"
57
58 . label variable dF "Ixekizumab"
59
60 . label variable nG "Secukinumab"
61
62 . label variable dG "Secukinumab"
63
64 . label variable nH "Ustekinumab - 45mg"
65
66 . label variable dH "Ustekinumab - 45mg"
67
68 . label variable nI "Ustekinumab - 90mg"
69
70 . label variable dI "Ustekinumab - 90mg"
71
72 . label variable nJ "Infliximab"
73
74 . label variable dJ "Infliximab"
```

```

75
76
77
78 //setup network
79 network setup d n, studyvar(study) or
80 // Run consistency model network
81 network meta c
82
83 // test for best intervention
84 mvmeta, pbest(max in 1, zero reps(9000)) noest
85
86 // run inconsistency model
87 network meta i
88
89 //test for inconsistency
90 network forest, l
91 // remove files before activating save -
92 graph save Graph "Network Analysis forest plot.gph"
93
94 //Convert to pairs for plot
95 network convert pairs
96 //Plot
97 networkplot t1 t2, lab (Placebo Adalimumab Efalizumab Etanercept-2-weekly Etanercept-1-
98 weekly Ixekizumab Secukinumab Ustekinumab-45mg Ustekinumab-90mg Infliximab) tit (PASI 75)
99 // remove files before activating save -
100 graph save Graph "Network Diagram.gph"
101
102 * HEADER
103 // sub-header
104
105 * -----
106 * Re-order Drugs
107 * -----
108 import excel "PASI75 12wks_placebo_recommend.xlsx", sheet("Sheet1") firstrow clear
109 . drop in 36/54
110 . replace dA = 1 if dA == 0
111 // reorder first to last
112 order dA nA, last
113 rename dA dK
114 rename nA nK
115 //setup network
116 network setup d n, studyvar(study) or
117 // Run consistency model network
118 network meta c
119
120 * -----
121 * Re-order Drugs
122 * -----
123 import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow clear
124 . drop in 36/54
125 . replace dA = 1 if dA == 0
126 // reorder first to last
127 order dA nA, last
128 rename dA dK
129 rename nA nK
130 // reorder first to last
131 order dB nB, last
132 rename dB dL
133 rename nB nL
134 //setup network
135 network setup d n, studyvar(study) or
136 // Run consistency model network
137 network meta c
138
139 * -----
140 * Re-order Drugs
141 * -----
142 import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow clear
143 . drop in 36/54
144 . replace dA = 1 if dA == 0
145 // reorder first to last
146 order dA nA, last
147 rename dA dK
148 rename nA nK

```

```
148 // reorder first to last
149 order dB nB, last
150 rename dB dL
151 rename nB nL
152 // reorder first to last
153 order dC nC, last
154 rename dC dM
155 rename nC nM
156 //setup network
157 network setup d n, studyvar(study) or
158 // Run consistency model network
159 network meta c
160
161 * -----
162 * Re-order Drugs
163 * -----
164 import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow clear
165 . drop in 36/54
166 . replace dA = 1 if dA == 0
167 // reorder first to last
168 order dA nA, last
169 rename dA dK
170 rename nA nK
171 // reorder first to last
172 order dB nB, last
173 rename dB dL
174 rename nB nL
175 // reorder first to last
176 order dC nC, last
177 rename dC dM
178 rename nC nM
179
180 // reorder first to last
181 order dD nD, last
182 rename dD dN
183 rename nD nN
184 //setup network
185 network setup d n, studyvar(study) or
186 // Run consistency model network
187 network meta c
188
189 * -----
190 * Re-order Drugs
191 * -----
192 import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow clear
193 . drop in 36/54
194 . replace dA = 1 if dA == 0
195 // reorder first to last
196 order dA nA, last
197 rename dA dK
198 rename nA nK
199 // reorder first to last
200 order dB nB, last
201 rename dB dL
202 rename nB nL
203 // reorder first to last
204 order dC nC, last
205 rename dC dM
206 rename nC nM
207
208 // reorder first to last
209 order dD nD, last
210 rename dD dN
211 rename nD nN
212 // reorder first to last
213 order dE nE, last
214 rename dE dO
215 rename nE nO
216 //setup network
217 network setup d n, studyvar(study) or
218 // Run consistency model network
219 network meta c
220
221 * -----
```

```
222 * Re-order Drugs
223 * -----
224 import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow clear
225 . drop in 36/54
226 . replace dA = 1 if dA == 0
227 // reorder first to last
228 order dA nA, last
229 rename dA dK
230 rename nA nK
231 // reorder first to last
232 order dB nB, last
233 rename dB dL
234 rename nB nL
235 // reorder first to last
236 order dC nC, last
237 rename dC dM
238 rename nC nM
239
240 // reorder first to last
241 order dD nD, last
242 rename dD dN
243 rename nD nN
244 // reorder first to last
245 order dE nE, last
246 rename dE dO
247 rename nE nO
248 // reorder first to last
249 order dF nF, last
250 rename dF dP
251 rename nF nP
252 //setup network
253 network setup d n, studyvar(study) or
254 // Run consistency model network
255 network meta c
256
257 *-----
258 * Re-order Drugs
259 * -----
260 import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow clear
261 . drop in 36/54
262 . replace dA = 1 if dA == 0
263 // reorder first to last
264 order dA nA, last
265 rename dA dK
266 rename nA nK
267 // reorder first to last
268 order dB nB, last
269 rename dB dL
270 rename nB nL
271 // reorder first to last
272 order dC nC, last
273 rename dC dM
274 rename nC nM
275
276 // reorder first to last
277 order dD nD, last
278 rename dD dN
279 rename nD nN
280 // reorder first to last
281 order dE nE, last
282 rename dE dO
283 rename nE nO
284 // reorder first to last
285 order dF nF, last
286 rename dF dP
287 rename nF nP
288 // reorder first to last
289 order dG nG, last
290 rename dG dQ
291 rename nG nQ
292 //setup network
293 network setup d n, studyvar(study) or
294 // Run consistency model network
295 network meta c
```

```
296
297 *-----
298 * Re-order Drugs
299 * -----
300 import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow clear
301 . drop in 36/54
302 . replace dA = 1 if dA == 0
303 // reorder first to last
304 order dA nA, last
305 rename dA dK
306 rename nA nK
307 // reorder first to last
308 order dB nB, last
309 rename dB dL
310 rename nB nL
311 // reorder first to last
312 order dC nC, last
313 rename dC dM
314 rename nC nM
315
316 // reorder first to last
317 order dD nD, last
318 rename dD dN
319 rename nD nN
320 // reorder first to last
321 order dE nE, last
322 rename dE dO
323 rename nE nO
324 // reorder first to last
325 order dF nF, last
326 rename dF dP
327 rename nF nP
328 // reorder first to last
329 order dG nG, last
330 rename dG dQ
331 rename nG nQ
332 // reorder first to last
333 order dH nH, last
334 rename dH dR
335 rename nH nR
336 //setup network
337 network setup d n, studyvar(study) or
338 // Run consistency model network
339 network meta c
340 *-----
341 * Re-order Drugs
342 * -----
343 import excel "PASI75 12wks placebo recommend.xlsx", sheet("Sheet1") firstrow clear
344 . drop in 36/54
345 replace dA = 1 if dA == 0
346 // reorder first to last
347 order dA nA, last
348 rename dA dK
349 rename nA nK
350 // reorder first to last
351 order dB nB, last
352 rename dB dL
353 rename nB nL
354 // reorder first to last
355 order dC nC, last
356 rename dC dM
357 rename nC nM
358
359 // reorder first to last
360 order dD nD, last
361 rename dD dN
362 rename nD nN
363 // reorder first to last
364 order dE nE, last
365 rename dE dO
366 rename nE nO
367 // reorder first to last
368 order dF nF, last
369 rename dF dP
```

```
370 rename nF nP
371 // reorder first to last
372 order dG nG, last
373 rename dG dQ
374 rename nG nQ
375 // reorder first to last
376 order dH nH, last
377 rename dH dR
378 rename nH nR
379 // reorder first to last
380 order dI nI, last
381 rename dI dS
382 rename nI nS
383 //setup network
384 network setup d n, studyvar(study) or
385 // Run consistency model network
386 network meta c
387
388 * -----
389 * end of Syntax01
390
```

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Efficacy

Adalimumab vs Placebo	LnOR	95%CI	
Kimball 2011	3.91	3.26	4.57
Cai 2017	3.30	2.99	4.00
Gordon 2006	3.35	1.82	4.88
Saurat 2007	2.93	2.05	3.80
Pooled	3.44	2.97	3.91
Efalizumab vs Placebo			
Dubertret, 2006	2.35	1.72	2.98
Gordon 2008	2.26	1.47	3.05
Leonardi 2005	3.27	2.23	4.31
Papp 2006	2.31	1.53	3.09
Pooled	2.46	2.02	2.91
Etanercept - twice vs placebo			
Bachelez, 2015	3.18	2.33	4.03
Leonardi, 2003	3.26	2.39	4.13
Gottlieb, 2011	2.78	1.81	3.75
Strober, 2011	4.02	3.02	5.02
Papp 2005	3.42	2.56	4.28
Tyring, 2006	2.85	2.29	3.42
Bagel, 2012	3.37	2.10	4.64
Griffith 2015	3.38	2.36	4.39
Griffith 2015	2.68	2.10	3.26
Langley 2014	2.72	2.17	3.27
Pooled	3.08	2.81	3.35
Etanercept - once vs placebo			
van de Kerkhof, 2008	3.30	1.27	5.32
Pooled	3.30	1.27	5.32
Ixekizumab vs placebo			
Griffith 2015	5.88	4.83	6.93
Griffith 2015	4.47	3.85	5.09
Gordon 2016	5.30	4.73	5.87
Pooled	5.19	4.80	5.57
Sekunumab vs placebo			
Langley 2014	4.56	3.88	5.25
Langley 2014	4.18	3.61	4.74
Blauvelt 2015	5.23	3.16	7.29
Paul 2015	5.26	3.66	6.85
Pooled	4.55	4.11	4.98
Ustekinumab - 45 vs placebo			
Leonardi 2008	4.14	3.39	4.89
Papp 2008	3.97	3.41	4.52
Landells 2015	3.40	2.10	4.70
Lebwohl 2015	3.28	2.80	3.76
Lebwohl 2015	3.56	3.04	4.08
Pooled	3.66	3.32	4.01
Ustekinumab - 90 vs placebo			
Leonardi 2008	4.11	3.36	4.86
Papp 2008	4.41	3.84	4.97
Landells 2015	3.53	2.21	4.86
Pooled	3.95	3.52	4.38
Infliximab vs placebo			
Reich, 2005	5.04	3.60	6.47
Torii, 2010	3.67	1.53	5.81
Yang 2012	5.23	3.18	7.29
Pooled	4.76	3.70	5.82

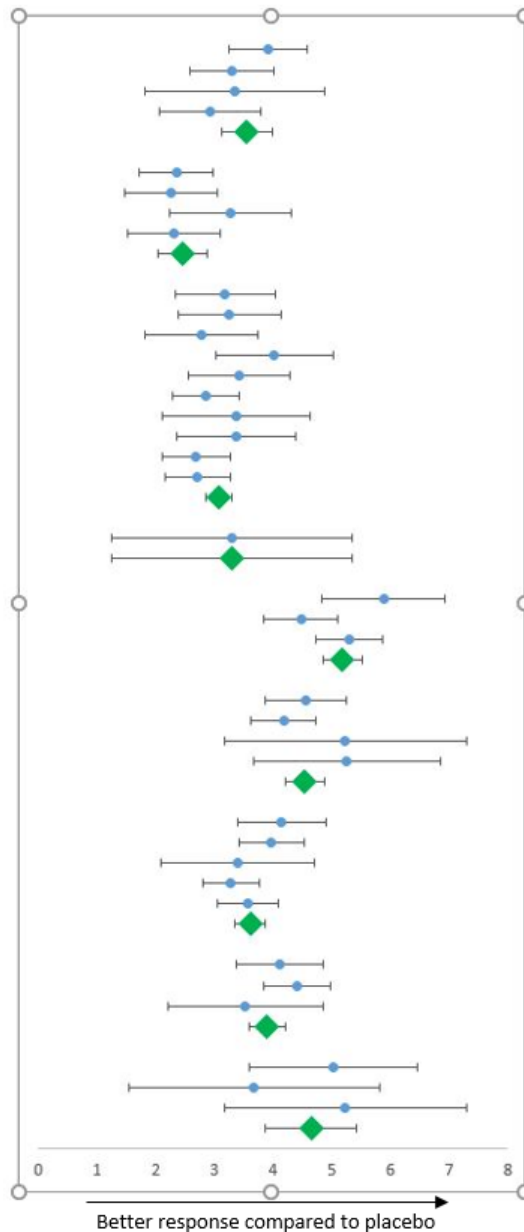


Figure 8: Forest plot of the LnOR (95% CI) for the proportion of patients achieving a PASI 75 response at 12 weeks – PBS-listed biologics versus placebo. Network diagram of dichotomous variable.

CI = confidence interval; Etanercept – once = etanercept 50 mg once weekly; Etanercept – twice = etanercept 25 mg twice weekly; LnOR = natural logarithm of the odds ratio; PASI = Psoriasis Area and Severity Index; PBS = Pharmaceutical Benefits Scheme; vs = versus

Appendix D – ToR 2: Treatment of children and adolescents with severe CPP

Risk of bias

Table 95: Biologics in children and adolescents trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
Papp (2017)	Low	Low	Low	Low	Low	Low	High
Paller (2008)	Unclear	Low	Low	Unclear	Low	Low	High
CADMUS	Low	Low	Low	Unclear	Low	Low	High

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Inclusion and exclusion criteria

Table 96: Biologics in children and adolescents: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Adalimumab versus methotrexate		
Papp (2017)	<ul style="list-style-type: none"> - ≥ 4 to < 18 years; - ≥ 13 kg; - plaque psoriasis for ≥ 6 months; - stable for ≥ 2 months; - no response to topical therapy; - patients ≥ 12 must not have responded to heliotherapy or phototherapy or have been intolerant/contraindicated to phototherapy; - PGA ≥ 4 OR BSA > 20% with > 10% with very thick lesion, OR PASI > 20 or > 10 and unresponsive to NSAIDs, CDLQI score > 10 or facial, foot, hand or genital involvement 	<ul style="list-style-type: none"> - biologics except etanercept within 4 weeks; - contraindication to methotrexate; - methotrexate within 12 months; - infection, dysplasia, cancer; - phototherapy
Etanercept versus placebo		
Paller (2008)	<ul style="list-style-type: none"> - 4-17 years; - stable, mod-to-severe plaque psoriasis; - history of psoriasis of ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3; - previous or current treatment with systemic or phototherapy or poorly controlled with topical therapy 	<ul style="list-style-type: none"> - guttate, erythrodermic or pustular psoriasis, - other skin conditions; - previous treatment with anti-TNF agents; - major concurrent medical conditions
Ustekinumab versus placebo		
CADMUS	<ul style="list-style-type: none"> - 12 to 17 years (inclusive); - diagnosis of mod-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3; - candidate for systemic or phototherapy or systemic treatment, or poorly controlled with topical therapy 	-

BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; mod = moderate; NSAID = non-steroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; TNF = tumour necrosis factor

Treatment details

Table 97: Biologics in children and adolescents: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
Adalimumab: PI recommended dose: < 40 kg – 20 mg every other week; ≥ 40 kg – 40 mg every other week				
Papp (2017)	16 weeks	Adalimumab	SC	0.4 mg/kg every other week
		Adalimumab	SC	0.8 mg/kg every other week
		Methotrexate	Oral	0.1-0.4 mg/kg once weekly
Etanercept: PI recommended dose: 0.8 mg/kg weekly (up to a maximum of 50 mg per dose)				
Paller (2008)	12 weeks	Etanercept	SC	0.8 mg/kg weekly*
		Placebo	SC	Matched placebo injections
Ustekinumab: PI recommended dose: -				
CADMUS	12 weeks	Ustekinumab	SC	0.375 mg/kg if ≤ 60 kg or 22.5 mg if 60-100 kg or 45 mg if > 100 kg at Weeks 0, 4
		Ustekinumab	SC	0.75 mg/kg if ≤ 60 kg or 45 mg if 60-100 kg or 90 mg if > 100 kg at Weeks 0, 4
		Placebo	SC	Matched placebo injections

DB = double-blind; PI = Product Information; SC = subcutaneous

* PI recommended dose

Safety

Table 98: Biologics in children: adverse events of interest; number of patients affected (%)

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Adalimumab versus methotrexate														
Papp (2017)	16 weeks	Ada ¹	39	56%	3%	NR	NR	NR	0	NR	NR	3%	3%	8%
		Ada ²	38	45%	0	NR	NR	NR	0	NR	NR	3%	0	11%
		Mtx	37	57%	0	NR	NR	NR	3%	NR	NR	3%	0	8%
Etanercept versus placebo														
Paller (2008)	12 weeks	Etan ^{3*}	210	NR	NR	0	NR	NR	90	52	NR	54	NR	NR
		Pbo	105	NR	NR	0	NR	NR	13	10	NR	18	NR	NR
Ustekinumab versus placebo														
CADMUS	12 weeks	Ust ⁴	37	32%	0	0	NR	NR	NR	NR	NR	NR	NR	NR
		Ust ⁵	36	22%	0	0	NR	NR	NR	NR	NR	NR	NR	NR
		Pbo	37	38%	0	0	NR	NR	NR	NR	NR	NR	NR	NR

Ada = adalimumab; CVD = cardiovascular disease; Etan = etanercept; Mtx = methotrexate; NR = not reported; Pbo = placebo; SC = subcutaneous; URTI = upper respiratory tract infection; Ust = ustekinumab; *Italics* = number of events

¹ Adalimumab 0.4 mg/kg SC every other week

² Adalimumab 0.8 mg/kg SC every other week

^{3*} Etanercept 0.8 mg/kg SC once weekly (PI recommended dose)

⁴ Ustekinumab 0.375 mg/kg if ≤ 60 kg or 22.5 mg if 60-100 kg or 45 mg if > 100 kg SC at Weeks 0, 4

⁵ Ustekinumab 0.75 mg/kg if ≤ 60 kg or 45 mg if 60-100 kg or 90 mg if > 100 kg SC at Weeks 0, 4

Appendix E – ToR 2: Longer-term safety of the PBS listed biologics for the treatment of severe CPP

Observational studies

Table 99: Observational studies: publication details for longer-term etanercept studies

Trial	Citation	Description	Seen by PBAC?
CRYSTEL	Ortonne JP, Griffiths CEM, Daudén E, et al. Efficacy and safety of continuous versus paused etanercept treatment in patients with moderate-to-severe psoriasis over 54 weeks: The CRYSTEL study. <i>Expert Review of Dermatology</i> . 2008; 3(6): 657-665.	Observational study: longer term safety	No
Elewski (2007)	Elewski B, Leonardi C, Gottlieb AB, et al. Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. <i>British Journal of Dermatology</i> . 2007; 156(1): 138-142.	OL extension of Leonardi (2003) and Papp (2005): longer-term, efficacy, safety	No
	Leonardi C, Strober B, Gottlieb AB, et al. Long-term safety and efficacy of etanercept in patients with psoriasis: an open-label study. <i>Journal of Drugs in Dermatology</i> . 2010; 9(8): 928-937.		No
Luger (2016)	Luger T, Schopf RE, Schwanke A, et al. An observational study to evaluate the long-term outcomes of treatment with etanercept in patients with plaque-type psoriasis. <i>Journal of the European Academy of Dermatology and Venereology</i> . 2016; 30(10): 1730-1741.	Observational study: longer-term safety	No
OBSERVE-5	Kimball AB, Pariser D, Yamauchi PS, et al. OBSERVE-5 interim analysis: an observational postmarketing safety registry of etanercept for the treatment of psoriasis. <i>Journal of the American Academy of Dermatology</i> . 2013; 68(5): 756-764.	Observational study: longer-term safety	No

OL = open label; PBAC = Pharmaceutical Benefits Advisory Committee

Table 100: Observational studies: inclusion and exclusion criteria for the longer-term etanercept studies

Trial	Inclusion criteria	Exclusion criteria
CRYSTEL	- ≥ 18 years; - active, stable plaque psoriasis; - ≥ 10% BSA, PGA ≥ 3; - unresponsive/intolerant/contraindicated to methotrexate, cyclosporin, PUVA or fumarates	- active skin condition other than psoriasis; - serious infection or TB; - severe comorbidities
Elewski (2007)	- completion of Leonardi (2003) or Papp (2005); - received ≥ 24 weeks of etanercept 25 mg twice weekly	-
Luger (2016)	- ≥ 18 years; - mod-to-severe plaque psoriasis; - unresponsive/intolerant/contraindicated to systemic treatments	- previous/ongoing etanercept; - participation in other clinical studies; - active infections; - demyelinating disease, CHF, uncompensated CHF
OBSERVE-5	- patients with plaque psoriasis; - etanercept indicated per prescribing information	- previous etanercept (before approval dates) or TNF inhibitor; - participation in previous etanercept trial; - contraindications to etanercept

BSA = body surface area; CHF = congestive heart failure; mod = moderate; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; PUVA = photochemotherapy; TB = tuberculosis; TNF = tumour necrosis factor

Table 101: Observational studies: baseline characteristics for the longer-term etanercept studies

Trial	Arm	N	Age, years; mean (SD)	Male; %	Race; %	Weight, kg; mean (SD)	DoD, years; mean (SD)	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
CRYSTEL	Etan ^{1*}	357	44.8 (11.8)	72%	NR	84 (18)	22 (11)	37% (22)	21.9 (10.3)	12.8 (7.3)
	Etan ²	363	45.3 (11.9)	72%	NR	85 (19)	22 (11)	40% (24)	22.8 (10.3)	13.8 (7.3)
Elewski (2007)	Etan ³	912	45.9 (11.9)	68%	C: 88%	91 (21)	20 (12)	NR	18.9 (8.5)	NR
Luger (2016)	Etan ⁴	720	46.7 (13.0)	63%	NR	NR	21 (14)	NR	NR	NR
OBSERVE-5	Etan ⁴	2,511	46.3 (13.6)	52%	C: 82%	NR	16 (13)	21% (20)	NR	NR

BSA = body surface are; C = Caucasian; DLQI = Dermatology Life Quality Index; DoD = duration of disease; Etan = etanercept; NR = not reported; PASI = Psoriasis Area and Severity Index; PI = Product Information; SC = subcutaneous; SD = standard deviation

^{1*} Etanercept 25 mg SC twice weekly (PI recommended dose)

² Etanercept 50 mg SC twice weekly until response, pause until relapse, then 25 mg twice weekly until response, then pause

³ Etanercept 50 mg SC once weekly for 12 weeks; then 50 mg once weekly or 50 mg twice weekly

⁴ Etanercept dose determined by study investigator

Table 102: Observational studies: treatment details for the longer-term etanercept studies

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 50 mg once weekly or 25 mg twice weekly (81)				
CRYSTEL	56 weeks	Etanercept	SC	25 mg twice weekly*
		Etanercept	SC	50 mg twice weekly until response, pause until relapse, then 25 mg twice weekly until response, then pause
Elewski (2007)	72 weeks	Etanercept	SC	50 mg once weekly for 12 weeks; then dose could be increased to 50 mg twice weekly until Week 72
Luger (2016)	36 months	Etanercept	SC	Dose and dosing regimen was determined by the study investigator
OBSERVE-5	3 years	Etanercept	SC	Dose and dosing regimen was determined by the study investigator

DB = double-blind; PI = Product Information; SC = subcutaneous; top = topical

* PI recommended dose

Efficacy

Table 103: Longer-term efficacy of the PBS-listed biologics in the treatment of CPP

Trial	Time horizon	Arm	N	PASI 50, %	PASI 75, %	PASI 90, %	PASI 100, %	Δ DLQI; mean (SD)
Adalimumab								
Gordon (2006)	60 weeks	Ada ^{1*}	45	64%	56%	33%	16%	NR
		Ada ²	50	66%	64%	48%	26%	NR
		Pbo + Ada ^{3*}	52	NR	45%	NR	19%	NR
Etanercept								
Leonardi (2003)	60 weeks	Etan ^{4*}	112	55%	23%	NR	NR	-9.9 (-54%)
Elewski (2007)	72 weeks	Etan ^{5*}	321	90%	60%	27%	NR	-55%
		Etan ⁶	591	83%	43%	10%	NR	-45%
Tyring (2006)	84 weeks	Etan ⁷	311	83%	51%	23%	NR	-8.6
		Pbo + Etan ⁸	307	79%	52%	23%	NR	-8.8
Infliximab								
Menter (2007)	50 weeks	Inf ^{9*}	134	72%	55%	34%	NR	-8.3 (7.4)
		Inf ¹⁰	134	74%	38%	10%	NR	-7.0 (7.7)
EXPRESS	50 weeks	Inf ^{9*}	301	NR	61%	45%	NR	-7.3 (8.0)
RESTORE	52 weeks	Inf ^{9*}	101	96%	80%	52%	NR	-10.4
		Inf ¹⁰	83	82%	47%	12%	NR	-6.3
	100 weeks	Inf ^{9*}	21	90%	86%	71%	NR	-9.6
		Inf ¹⁰	13	100%	69%	31%	NR	-6.0
Torii (2010)	66 weeks	Inf ^{9*}	30	83%	77%	57%	NR	-9.6 (7.1)
		Pbo + Inf ^{11*}	12	100%	75%	58%	NR	-6.9 (6.9)

Trial	Time horizon	Arm	N	PASI 50, %	PASI 75, %	PASI 90, %	PASI 100, %	Δ DLQI; mean (SD)
Ixekizumab								
Leonardi (2012)	52 weeks	Ixe ¹²	120	77%	68%	48%	NR	NR
Secukinumab (and etanercept)								
ERASURE 2	52 weeks	Sec ^{13*}	245	NR	66%	NR	NR	NR
		Sec ¹⁴	243	NR	52%	NR	NR	NR
FIXTURE	52 weeks	Sec ^{13*}	323	NR	65%	NR	NR	NR
		Sec ¹⁴	327	NR	55%	NR	NR	NR
		Ent ¹⁵	323	NR	32%	NR	NR	NR
Ustekinumab								
Igarashi (2012)	64 weeks	Ust ^{16*}	60	92%	65%	50%	NR	-7.4 (6.9)
		Ust ¹⁷	56	89%	79%	55%	NR	-7.9 (6.4)
PHOENIX 1	3 years	Ust ^{16*}	326	NR	62%	36%	NR	NR
		Ust ¹⁷	299	NR	72%	46%	NR	NR
	5 years	Ust ^{16*}	320	NR	63%	40%	22%	NR
		Ust ¹⁷	296	NR	72%	49%	26%	NR

Ada = adalimumab; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; Ent = etanercept; Inf = infliximab; IV = intravenous; Ixe = ixekizumab; NR = not reported; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; PBS = Pharmaceutical Benefits Scheme; Pbo = placebo; PI = Product Information; SC = subcutaneous; Sec = secukinumab; Ust = ustekinumab; *Italics = mean percentage change in DLQI score*

^{1*} Adalimumab 40 mg every other week (PI recommended dose)

² Adalimumab 40 mg weekly

^{3*} Placebo until Week 12; adalimumab 80 mg SC Week 13; then 40 mg every other week (PI recommended dose)

^{4*} Etanercept 25 mg SC twice weekly (PI recommended dose)

^{5*} Etanercept 50 mg SC once weekly (PI recommended dose)

⁶ Etanercept 50 mg SC once weekly until Week 12; then 50 mg twice weekly

⁷ Etanercept 50 mg SC twice weekly

⁸ Placebo until Week 12; then etanercept 50 mg SC twice weekly

^{9*} Infliximab 5 mg/kg IV every 8 weeks (PI recommended dose)

¹⁰ Infliximab 5 mg/kg IV when required

^{11*} Placebo until Week 14; infliximab 5 mg/kg IV Weeks 16, 18, 22; then every 8 weeks (PI recommended dose)

¹² Ixekizumab 120 mg SC every 4 weeks

^{13*} Secukinumab 300 mg SC every 4 weeks (PI recommended dose)

¹⁴ Secukinumab 150 mg SC every 4 weeks

¹⁵ Etanercept 50 mg SC twice weekly until week 12; then 50 mg once weekly

^{16*} Ustekinumab 45 mg SC every 12 weeks (PI recommended dose)

¹⁷ Ustekinumab 90 mg SC every 12 weeks

Appendix F – ToR 2: Efficacy and safety of the PBS-listed biologics in mild-to-moderate CPP

Risk of bias

Table 104: Mild-to-moderate psoriasis: risk of bias

Trial ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
Gisoni (2008)	Low	Low	High	Low	Low	Low	High

Inclusion and exclusion criteria

Table 105: Mild-to-moderate psoriasis: inclusion and exclusion criteria

Trial ID	Inclusion criteria	Exclusion criteria
Gisoni (2008)	- ≥ 18 years; - active, but stable, mod-to-severe plaque psoriasis	- psoriatic arthritis or other type of psoriasis (guttate, erythrodermic or pustular); - active or chronic infections including HIV, Hep B/C, latent TB; - previous malignancies; - severe haematological, renal or hepatic disorders, severe CHF or demyelinating disease; - previous biologics

CHF = congestive heart failure; Hep = hepatitis; HIV = human immunodeficiency virus; mod = moderate; TB = tuberculosis

Treatment details

Table 106: Mild-to-moderate psoriasis: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
PI recommended dose: 50 mg once weekly or 25 mg twice weekly (81)				
Gisoni (2008)	24 weeks	Etanercept	SC	25 mg twice weekly*
		Etanercept + acitretin	SC + oral	Etanercept: 25 mg twice weekly* Acitretin: 0.4 mg/kg daily
		Acitretin	Oral	0.4 mg/kg daily

PI = Product Information; SC = subcutaneous

* PI recommended dose

Appendix G – ToR 2: Treatment of severe CPP with concomitant PsA

Risk of bias

Table 107: Severe CPP and PsA trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
Mease (2000)	Low	Low	Low	Unclear	Low	Low	High
PRESTA	Unclear	Unclear	Low	Unclear	Low	Low	High
IMPACT 2	Low	Unclear	Low	Unclear	Low	Low	High
FUTURE 2	Low	Low	Low	Low	Low	Low	High

CPP = chronic plaque psoriasis; PsA = psoriatic arthritis

Inclusion and exclusion criteria

Table 108: Severe CPP and PsA trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Etanercept		
Mease (2000)	<ul style="list-style-type: none"> - 18-70 years; - active PsA (≥ 3 swollen joints and ≥ 3 tender or painful joints); - inadequate response to NSAIDs; - candidate for immunomodulatory therapy; - if on methotrexate, must be stable 	<ul style="list-style-type: none"> - other skin conditions; - treatment within 2 weeks with DMARDs
PRESTA	<ul style="list-style-type: none"> - ≥ 18 years; - active, stable plaque psoriasis; - BSA $\geq 10\%$; PGA > 2; - active PsA defined by ≥ 2 swollen joints, ≥ 2 tender or painful joints, or joint pain for > 3 months; - negative serum rheumatoid factor within 6 months 	<ul style="list-style-type: none"> - other skin conditions; - a tender, swollen joint not assessed by a rheumatologist as PsA; - severe comorbidities; - recent serious infection, TB
Infliximab		
IMPACT 2	<ul style="list-style-type: none"> - ≥ 18 years; - active PsA for ≥ 6 months; - active articular disease (≥ 5 swollen joints, ≥ 5 tender joints) and CRP levels ≥ 15 mg/L and morning stiffness ≥ 45 minutes; - unresponsive to DMARDs or NSAIDs; - active plaque psoriasis 	<ul style="list-style-type: none"> - previous TNF-inhibitors; - active/latent TB or chronic/clinically significant infection; - malignancy, CHF
Secukinumab		
FUTURE 2	<ul style="list-style-type: none"> - ≥ 18 years; - active PsA (≥ 3 swollen joints and ≥ 3 tender joints); - unresponsive to DMARDs, NSAIDs or anti-TNF agents 	<ul style="list-style-type: none"> - previous biologic use (other than anti-TNF agents); - other active inflammatory disease; - active infection within 2 weeks, or a history of ongoing, chronic or recurrent infections; - history of malignancy (except basal-cell skin carcinoma, cervical carcinoma or colon polyps); - pregnancy

BSA = body surface area; CHF = congestive heart failure; CPP = chronic plaque psoriasis; CRP = C-reactive protein; DMARD = disease modifying anti-rheumatic drug; NSAID = non-steroidal anti-inflammatory drug; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; TB = tuberculosis; TNF = tumour necrosis factor

Treatment details

Table 109: Severe CPP and PsA trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
Etanercept: PI recommended dose for CPP and PsA: 50 mg once weekly or 25 mg twice weekly (81)				
Mease (2000)	12 weeks	Etanercept	SC	25 mg twice weekly*
		Placebo	SC	Matched placebo injections
PRESTA	12 weeks/ 24 weeks	Etanercept	SC	50 mg once weekly (plus matched placebo injections)*
		Etanercept	SC	50 mg twice weekly
Infliximab: PI recommended dose for CPP and PsA: 5 mg/kg at Weeks 0, 2, 6; then every 8 weeks (82)				
IMPACT 2	16 weeks/ 24 weeks	Infliximab	IV	Infliximab 5 mg/kg at Weeks 0, 2, 6, 14, 22*
		Placebo	IV	Matched placebo injections
Secukinumab: PI recommended dose for CPP: 300 mg at Weeks 0, 1, 2, 3, 4; then 300 mg every 4 weeks PI recommended dose for PsA: 150 mg at Weeks 0, 1, 2, 3, 4; then 150 mg every 4 weeks				
FUTURE 2	16 weeks	Secukinumab	SC	75 mg Weeks 0, 1, 2, 3, 4; then every 4 weeks
		Secukinumab	SC	150 mg Weeks 0, 1, 2, 3, 4; then every 4 weeks
		Secukinumab	SC	300 mg Weeks 0, 1, 2, 3, 4; then every 4 weeks*
		Placebo	SC	Matched placebo injections

CPP = chronic plaque psoriasis; IV = intravenous; PI = Product Information; PsA = psoriatic arthritis; SC = subcutaneous

* PI recommended dose

Safety

Table 110: Severe CPP and PsA trials: summary of adverse events

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Etanercept							
Mease (2000)	12 weeks	Etan ^{1*}	30	NR	0	NR	NR
		Pbo	30	NR	1 (3%)	NR	NR
PRESTA	24 weeks	Etan ^{2*}	373	190 (51%)	11 (3%)	0	NR
		Etan ³	379	213 (56%)	15 (4%)	0	NR
Infliximab							
		Pbo	52	33 (65%)	1 (2%)	NR	NR
IMPACT 2	24 weeks	Inf ^{4*}	150	100 (67%)	13 (9%)	0	6 (4%)
		Pbo	97	65 (67%)	6 (6%)	0	1 (1%)
Secukinumab							
FUTURE 2	16 weeks	Sec ^{5*}	100	57 (57%)	1 (1%)	0	0
		Sec ^{6*}	100	56 (56%)	5 (5%)	0	2 (2%)
		Pbo	98	57 (58%)	2 (2%)	0	3 (3%)

AE = adverse event; CPP = chronic plaque psoriasis; Etan = etanercept; Inf = infliximab; IV = intravenous; NR = not reported; Pbo = placebo; PI = Product Information; PsA = psoriatic arthritis; SAE = serious adverse event; SC = subcutaneous; Sec = secukinumab

^{1*} Etanercept 25 mg SC twice weekly (PI recommended dose)

^{2*} Etanercept 50 mg SC once weekly (PI recommended dose)

³ Etanercept 50 mg SC twice weekly

^{4*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

^{5*} Secukinumab 150 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose, PsA)

^{6*} Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose, CPP)

Table 111: Severe CPP and PsA trials: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Etanercept														
Mease (2000)	12 weeks	Etan ^{1*}	30	NR	0	NR	NR	NR	57%	NR	NR	13%	NR	20%
		Pbo	30	NR	0	NR	NR	NR	57%	NR	NR	10%	NR	3%
PRESTA	24 weeks	Etan ^{2*}	373	NR	1%	< 1%	< 1%	NR	NR	NR	NR	NR	NR	NR
		Etan ³	379	NR	< 1%	1%	< 1%	NR	NR	NR	NR	NR	NR	NR
Infliximab														
IMPACT II	24 weeks	Inf ^{4*}	150	NR	0	NR	0	NR	10%	NR	6%	6%	NR	7%
		Pbo	97	NR	0	NR	1%	NR	14%	NR	1%	5%	NR	6%
Secukinumab														
FUTURE 2	16 weeks	Sec ⁵	99	23%	NR	NR	2%	1%	10%	6%	1%	2%	NR	NR
		Sec ^{6*}	100	30%	NR	NR	1%	0	8%	4%	0	4%	NR	NR
		Sec ^{7*}	100	29%	NR	NR	0	0	4%	6%	0	7%	NR	NR
		Pbo	98	31%	NR	NR	0	0	7%	8%	0	4%	NR	NR

CVD = cardiovascular disease; Etan = etanercept; Inf = infliximab; IV = intravenous; NR = not reported; Pbo = placebo; PI = Product Information; PsA = psoriatic arthritis; SC = subcutaneous; Sec = secukinumab; URTI = upper respiratory tract infection

^{1*} Etanercept 25 mg SC twice weekly (PI recommended dose)

^{2*} Etanercept 50 mg SC once weekly (PI recommended dose)

³ Etanercept 50 mg SC twice weekly

^{4*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

⁵ Ustekinumab 90 mg SC at Weeks 0, 1, 2, 3

^{6*} Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose, PsA)

^{7*} Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose, CPP)

Appendix H – ToR 2: Treatment of CPP with hands, face and/or feet involvement

Risk of bias

Table 112: CPP with hands and/or feet involvement trials: risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Other
REACH	Low	Low	Low	Low	Low	Low	High
Bissonnette (2011)	Low	Low	Low	Unclear	Low	Low	High
GESTURE	Low	Low	Low	Unclear	Low	Low	High

CPP = chronic plaque psoriasis

DRAFT

Inclusion and exclusion criteria

Table 113: CPP with hands and/or feet involvement trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Adalimumab		
REACH	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe CPP of hands/feet for ≥ 6 months; - hf PGA ≥ 3; - psoriatic disease on ≥ 1 other area 	<ul style="list-style-type: none"> - treatment with adalimumab; - palmoplantar pustulosis
Infliximab		
Bissonnette (2011)	<ul style="list-style-type: none"> - ≥ 18 years; - non-pustular palmoplantar psoriasis; - total surface of palms and soles affected ≥ 10%, m-PPASI ≥ 8; - evidence of psoriasis elsewhere 	<ul style="list-style-type: none"> - pregnancy; - opportunistic, serious, chronic, recurrent infections; - Hep B/C, malignancies, TB, lymphoproliferative disease; - high aspartate/alanine aminotransferase levels
Secukinumab		
GESTURE	<ul style="list-style-type: none"> - ≥ 18 years; - mod-to-severe palmoplantar psoriasis; - pp-IGA ≥ 3; - ≥ 1 additional plaque outside of palms and soles 	<ul style="list-style-type: none"> - non-plaque forms of psoriasis; - previous secukinumab or IL-17A antagonists

BSA = body surface area; CPP = chronic plaque psoriasis; Hep = hepatitis; hf = hands and/or feet; IGA = Investigator's Global Assessment; mod = moderate; m-PPASI = modified Palmoplantar Psoriasis Area and Severity Index; NAPSI = Nail Psoriasis Severity Index; NPPFS = Nail Psoriasis Physical Functioning Severity; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; pp = palmoplantar; PSSI = Psoriasis Scalp Severity Index; PUVA = photochemotherapy; SSA = scalp surface area; TB = tuberculosis

Treatment details

Table 114: CPP with hands and/or feet involvement trials: treatment details

Trial	Time horizon	Treatment	Delivery	Dose
Adalimumab: PI recommended dose: 80 mg at Week 0; 40 mg every other week from Week 1 (80)				
REACH	16 weeks	Adalimumab	SC	80 mg at Week 0; 40 mg every other week from Week 1*
		Placebo	SC	Matched placebo injections
Infliximab: PI recommended dose: 5 mg/kg at Weeks 0, 2, 6; then every 8 weeks (82)				
Bissonnette (2011)	14 weeks	Infliximab	IV	5 mg/kg weeks at 0, 2, 6; then every 8 weeks*
		Placebo	IV	Matched placebo injections
Secukinumab: PI recommended dose: 300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks (84)				
GESTURE	16 weeks	Secukinumab	SC	150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks
		Secukinumab	SC	300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks*
		Placebo	SC	Matched placebo injections

CPP = chronic plaque psoriasis; DB = double-blind; IV = intravenous; PI = Product Information; SC = subcutaneous

* PI recommended dose

Safety

Table 115: CPP with hands and/or feet involvement trials: summary of adverse events; number of patients affected (%)

Trial	Time horizon	Arm	N	All AEs	All SAEs	Death	Discontinued trial
Adalimumab							
REACH	16 weeks	Ada ^{1*}	49	31 (63%)	0	0	3 (6%)
		Pbo	23	16 (70%)	1 (4%)	0	2 (9%)
Infliximab							
Bissonnette (2011)	14 weeks	Inf ^{2*}	12	32	1 (8%)	NR	1 (8%)
		Pbo	12	20	0	NR	0
Secukinumab							
GESTURE	16 weeks	Sec ³	68	44 (65%)	4 (6%)	0	1 (2%)
		Sec ^{4*}	69	40 (58%)	2 (3%)	0	2 (3%)
		Pbo	68	34 (30%)	2 (3%)	0	2 (3%)

Ada = adalimumab; AE = adverse event; CPP = chronic plaque psoriasis; Inf = infliximab; IV = intravenous; NR = not reported; Pbo = placebo; SAE = serious adverse event; SC = subcutaneous; *Italics = number of events*

^{1*} Adalimumab 80 mg SC Week 0; the 40 mg every other week from Week 1 (PI recommended dose)

^{2*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

³ Secukinumab 150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks

^{4*} Secukinumab 300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

Table 116: Hands and/or feet psoriasis trials: adverse events of interest

Trial	Time horizon	Arm	N	Infection	Serious infection	Malignancy	Skin cancer	CVD	URTI	Nasopharyngitis	Liver enzyme changes	Headache	Pruritus	Administration site disorders
Adalimumab														
REACH	16 weeks	Ada ^{1*}	49	35%	0	0	0	NR	NR	NR	2%	NR	NR	NR
		Pbo	23	44%	0	4%	0	NR	NR	NR	0	NR	NR	NR
Infliximab														
Bissonnette (2011)	14 weeks	Inf ^{2*}	12	42%	8%	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Pbo	12	42%	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Secukinumab														
GESTURE	16 weeks	Sec ³	68	NR	0	NR	NR	0	6%	7%	NR	6%	NR	NR
		Sec ^{4*}	69	NR	0	NR	NR	0	4%	3%	NR	10%	NR	NR
		Pbo	68	NR	0	NR	NR	0	4%	6%	NR	9%	NR	NR

Ada = adalimumab; CVD = cardiovascular disease; Inf = infliximab; IV = intravenous; NR = not reported; Pbo = placebo; SC = subcutaneous; URTI = upper respiratory tract infection

^{1*} Adalimumab 80 mg SC Week 0; 40 mg every other week from Week 1 (PI recommended dose)

^{2*} Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

³ Secukinumab 150 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks

^{4*} Secukinumab 300 mg at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)