Secukinumab for treating plaque psoriasis in children and young people [ID1669]

Produced by Aberdeen HTA Group

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Contribution of authors

Mari Imamura and Moira Cruickshank summarised and critiqued the clinical effectiveness evidence; Lorna Aucott and David Cooper checked and critiqued the statistical analyses presented in the company submission; Dwayne Boyers and Charlotte Kennedy reviewed and critiqued the cost-effectiveness evidence; Paul Manson checked and critiqued the company's search strategies; Tony Ormerod provided clinical guidance and comments on the draft report. Miriam Brazzelli coordinated all aspects of this appraisal. All authors contributing the writing of this report and approved its final version.

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List of abbreviations

BADBIR	British Association of Dermatologists' Biologic Interventions Register
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
CAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry
CDLQI	Children's Dermatology Life Quality Index
CHAQ©	Childhood Health Assessment Questionnaire
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
DERMBIO	Biological Treatment in Danish Dermatology
DIC	Deviance information criterion
DMC	Data monitoring committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medical Agency
EOF	End of follow-up
EOM	End of maintenance
EOT	End of treatment
ERG	Evidence Review Group
ETN	Etanercept
EU	European Union
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
IgG1	Immunoglobulin G1
IGA	Investigator's Global Assessment
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IL	Interleukin
MAP	Meta-analytive-predictive

MRI	Magnetic resonance imaging
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PASI	Psoriasis Area and Severity Index
PFS	Pre-filled syringe
PG	Pharmacogenetics
PGA	Physician’s Global Assessment
PK	Pharmacokinetics
PLA	Placebo
PUVA	Psoralen plus ultraviolet A
QFT	QuantiFERON TB-Gold test
SC	Subcutaneous
SD	Standard deviation
SEC	Secukinumab
sPGA	Static Physician’s Global Assessment
TA	Technology appraisal
TCS	Topical corticosteroids
TNFα	Tumour necrosis factor-alpha
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
WBC	White blood cell

1. Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred modelling assumptions.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on costs. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

The company submission (CS) focuses on secukinumab for treating children and young people aged 6 to <18 years with moderate to severe plaque psoriasis (as defined by the Psoriasis Area and Severity Index [PASI] score of 10 or more) who have failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated.

The clinical effectiveness evidence is provided by two ongoing multicenter, Phase 3 randomised controlled trials (RCT), A2310 and A2311. The A2310 study provides the primary source of evidence and was a good-quality, multicenter, double-blind placebo-controlled and single-blind active-controlled RCT comparing the two secukinumab dosing regimens (low and high dose) with placebo and etanercept in a total of 162 patients with severe plaque psoriasis (as defined by PASI ≥20). Supporting evidence comes from the A2311 study, an open-label RCT comparing secukinumab low dose with secukinumab high dose in [redacted] patients with moderate to severe plaque psoriasis (as defined by PASI ≥12). Results for secukinumab low and high dose from A2311 were also compared with placebo response rates from historical data.

The company reports the results from the data relating to the cut-off date at which the last patient underwent their Week 52 visit (18th September 2019 for A2310; 28th May 2020 for A2311). Efficacy was addressed using PASI 50/75/90/100, with the primary focus on PASI 75. The company also assessed the efficacy of secukinumab in terms of the Novartis Investigator's Global Assessment modified 2011 (IGA mod 2011) score 0 (clear) or 1 (almost clear). Meta-analysis was not performed.

In A2310, both secukinumab doses (low and high) were associated with statistically significant improvement compared with placebo in the study's primary outcomes in terms of PASI 75 response and IGA mod 2011 score 0 or 1 at Week 12. Compared with etanercept, secukinumab was associated with statistically significant improvement in IGA mod 2011 0 or 1, and numerical improvement in PASI 75 at Week 12. Secukinumab was also associated with statistically significant improvement compared with both placebo and etanercept in the key secondary outcome including PASI 90 at Week 12. In A2311, with the inclusion of participants with more moderate (less severe) psoriasis than in A2310, [redacted]

As there was no direct head-to-head evidence for secukinumab versus active comparators other than etanercept, a network meta-analysis was conducted to compare the relative efficacy of secukinumab with a network of two other biologics, ustekinumab and etanercept. The company chose not to include adalimumab listed in the NICE final scope as a comparator. [redacted]

Table 1. Summary of key issues

	Summary of issues	Report sections
Issue 1	Exclusion of adalimumab as comparator in the network meta-analysis and cost comparison model	Section 2.3 Section 3.4 Section 4.2.4

1.2 The decision problem: summary of the ERG's key issues.

The company's decision problem defined secukinumab in a narrower scope than its marketing authorisation. The ERG considers that this narrow scope reflects previous NICE technology assessments for plaque psoriasis and is consistent with relevant comparator treatments in children and young people (TA455) and also recommended use of secukinumab in adults (TA350). The ERG in consultation with their clinical expert considers the company's positioning of secukinumab in treatment pathway to be reasonable and in line with current clinical practice in the UK. The ERG's main issue of concern is the exclusion of adalimumab as a relevant comparator from the cost-comparison model. This issue is summarised below.

Issue 1: Exclusion of adalimumab as comparator in the network meta-analysis and cost comparison model

Report section	4.2.4 and 6.2
Description of issue and why the ERG has identified it as important	The company considers etanercept and ustekinumab to be the relevant comparators for this assessment, which is consistent with the NICE scope, TA455 and the NMA presented in the CS. However, the company have excluded adalimumab as a comparator from their base case analysis, only including it as a scenario analysis in response to clarification queries. The company justified adalimumab's exclusion because 1) it is not necessary to compare against all comparators from the scope in a FTA assessment, 2) there were no RCTs in a paediatric population that would allow connection to the NMA and 3) data in the paediatric population were limited. However, the ERG considers adalimumab to be a relevant comparator because it is used widely in clinical practice, is available as a generic low cost treatment, and consumes a significant market share (50%). The ERG believes the reasons for excluding adalimumab could have been overcome to enable its inclusion in the cost-comparison model.
What alternative approach has the ERG suggested?	The ERG prefers the inclusion of adalimumab in the cost-comparison model and has included adalimumab via a naïve indirect comparison to the adalimumab arm of the M04-717 trial which reports PASI-75 response data in a paediatric population. The ERG accepts that naïve indirect comparison are subject to limitations, but considers this the best available approach to consider adalimumab as a comparator for the cost-comparison analysis.
What is the expected effect on the cost-comparison case?	Including adalimumab as a comparator increases the uncertainty around the potential for secukinumab to be cost saving in the company's base case analysis. For example, adalimumab would be less costly than secukinumab in the 12-17 age subgroup in the company's base case analysis. However, the ERG's preferred base case analysis, including subsequent treatments following discontinuation of first line treatment suggests that secukinumab is cost saving compared to adalimumab for both age subgroups.
What additional evidence or analyses might help to resolve this key issue?	The ERG does not believe any additional evidence is required to resolve this issue and believe that the combination of scenarios provided by the company and the ERG is sufficient to describe the uncertainty regarding the comparison of secukinumab with adalimumab.

1.3 The cost-effectiveness evidence: summary of the ERG's key issues

The main issue of uncertainty for decision making is the choice of the most appropriate comparator for the cost-comparison case. The company considers etanercept and ustekinumab to be the relevant comparators for this assessment, but not adalimumab. The company justifies the position on three grounds:

- That the NICE process allows a choice of comparator for the assessment, so long as that comparator has been recommended by NICE. The ERG accepts that this is correct, but considers adalimumab to be a relevant comparator because it is widely used in clinical practice, has the largest market share, and is likely to be of lower treatment acquisition cost as it is available off patent,

- That there is a paucity of data for adalimumab in the paediatric population. However, the ERG has identified a study, the M04-717 trial. that compares adalimumab vs. methotrexate in the paediatric population and PASI 75 response data from the adalimumab arm could be used to populate the cost-comparison model.

- That paediatric data was not available to link adalimumab to the network. The ERG accepts this is correct but notes that adalimumab could still be included in the cost comparison case using a naïve indirect comparison to the M04-717 trial. The ERG does not consider it to be an essential requirement to conduct a NMA to derive response rates for the cost-comparison model.

1.4 Summary of ERG's preferred assumptions for the cost-comparison model, and resulting incremental costs

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- Inclusion of adalimumab as a comparator for the cost-comparison case because it consumes the largest market share, was recommended as part of TA455, is available as a generic equivalent which reduces costs and can be

included in the model through a naïve indirect comparison against an existing study.

- Correction of a minor error where ustekinumab 90mg, was assumed to be twice the list price of a 45mg dose, whereas the BNF lists both doses at the same price (£2,147 per vial).
- Use of adalimumab response rates sourced from a naïve indirect comparison of PASI-75 response rates using data from the M04-717 trial.
- a 12-year time horizon as opposed to company 5-year time horizon to capture the longer-term costs of treatment up to age 18

The ERG implemented further scenarios to address the uncertainty of the annual withdrawal rate assumption and explored the implication of the inclusion of subsequent treatment costs (weighted according to market share) following withdrawal from first-line biologic treatment. This could be considered more reflective of real-world clinical practice. These scenarios add greater face validity to the cost-comparison model predictions.

Table 2. ERG's preferred cost-comparison model assumptions (full population 6-17 years)

Preferred assumption	Section in ERG report	Incremental costs vs. etanercept	Incremental costs vs. ustekinumab	Incremental costs vs. adalimumab
ERG preferred assumptions				
Company base-case		[redacted]	[redacted]	[redacted]
All participants receive 45mg dosage regimen of ustekinumab equal to £2,147 per vial	*4.2.1*	[redacted]	[redacted]	[redacted]
PASI-75 response rates for adalimumab from M04-717 study[40]	*4.2.6*	[redacted]	[redacted]	[redacted]
12- year time horizon, up to age 18	*4.2.1*	[redacted]	[redacted]	[redacted]
ERG preferred base case		[redacted]	[redacted]	[redacted]
Additional scenario analyses applied to ERG preferred base case				
0% all cause annual withdrawal rate for all treatments	*4.2.2*	[redacted]	[redacted]	[redacted]
Withdrawal rates reported in clinical trials (see table X, section 4.2.2)	*4.2.2*	[redacted]	[redacted]	[redacted]
12/16-week PASI-75 response rates equal to 100% for all comparators	*4.2.2*	[redacted]	[redacted]	[redacted]
Inclusion of subsequent lines of biologic treatment	*4.2.2*	[redacted]	[redacted]	[redacted]

Results of the ERG's preferred analyses, split by age subgroup are provided in Chapter 6, together with several additional scenario analyses exploring different

assumptions around treatment discontinuation rates, response rates and whether treatment acquisition costs should be included for downstream treatments following first line treatment discontinuation.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for this submission is plaque psoriasis. The company's description of psoriasis in terms of prevalence and symptoms appears generally accurate and in line with the decision problem. The relevant intervention for this submission is Secukinumab (Cosentyx®, Novartis).

2.2 Background

Psoriasis is a distressing, chronic disease that affects skin and joints in children and adults. Plaque psoriasis is the most common form of psoriasis, occurring in 80-90% of cases,[1, 2] and is characterised as disfiguring, scaly red skin lesions (plaques) that may be painful or pruritic.[3, 4] Approximately 80% of the patients with psoriasis have mild to moderate disease, whereas 20% have moderate to severe psoriasis affecting more than 5% of the body surface area (BSA) or affecting crucial body areas such as the hands, feet, face or genitals.[4] Although aetiology or cause of psoriasis is unknown, genetic factors and the immune system play a key role in its development.[3] Psoriasis has been linked to genes associated with the immune response including tumour necrosis factor-alpha (TNFα), interleukin (IL)-23R, IL-12B and IL-17A.[5-7]

Psoriasis is estimated to affect between 1.30% and 2.60% of adults in the UK.[8] Among children, there is some evidence that prevalence is lower and increases linearly from the age of 1 to the age of 18.[9] Indeed, the prevalence in the UK is 0.55% for those aged 0 to 9 years, rising to 1.37% for those aged 10 to 17 years.[10]

Patients with psoriasis are associated with an increased risk of developing other cormorbid disease including metabolic syndrome and cardiovascular diseases.[2] An epidemiological study in Germany showed that children with psoriasis aged under 20 years were three to four times more likely to develop Crohn's disease, and nearly twice more likely to have hyperlipidemia, diabetes mellitus, hypertension and obesity, when compared with children who do not have psoriasis.[9] In a recent paediatric trial with 211 North American children with psoriasis, 37% of the participants (32% of 4-

to 11-year-olds and 41% of 12- to 17-year-olds) were obese (body mass index [BMI] ≥95th percentile of age- and sex-matched population).[11]

Diagnosis of psoriasis is usually made clinically. Measures commonly used to assess severity of psoriasis in adults such as the Physician's Global Assessment (PGA), the body surface area (BSA) affected, and the Psoriasis Area and Severity Index (PASI) are used in children, even though BSA and PASI are not validated for use in the paediatric population.[12] There is also no standardisation or consensus regarding thresholds that define mild, moderate or severe psoriasis in paediatric patients.[13, 14] A NICE technology assessment on paediatric psoriasis uses PASI ≥10 for severe psoriasis.[15] The European Medical Agency (EMA) guideline on clinical investigation for the medical treatment of psoriasis in both children and adults uses PASI score of >20 for severe psoriasis, score of 10 to 20 for moderate-to-severe psoriasis, and below that for moderate psoriasis.[13]

There is no cure for plaque psoriasis. The main aim of treatment is therefore to gain initial and rapid control of the disease process, decrease the percentage of body surface area involved, decrease plaque lesions, achieve and maintain long-term remission, minimize adverse events, and improve patient quality of life.[3, 16]

There is currently no psoriasis treatment pathway specific to children in the UK. The NICE guidance CG153 for all age groups recommends that children and young people have traditional topical therapies (such as corticosteroids, vitamin D and vitamin D analogues, dithranol and tar preparations) as first-line therapy.[12] If there is an inadequate response to treatment or if it is not tolerated or contraindicated, second-line therapy includes the phototherapies (broad- or narrow-band ultraviolet B light and psoralen plus UVA light [PUVA]) and systemic non-biological agents such as ciclosporin, methotrexate and acitretin. Third-line therapy includes systemic biological therapies.[12]

The NICE technology appraisal (TA) guidance 455 published in 2017 recommends adalimumab, etanercept and ustekinumab (Table 3) for the treatment of plaque psoriasis in children and young people when the following criteria are met:[15]

- the disease is severe, as defined by a total PASI of 10 or more and

- the disease has not responded to standard systemic therapy, such as ciclosporin, methotrexate or phototherapy, or these options are contraindicated or not tolerated.

Adalimumab (Humira®, AbbVie) is a fully human immunoglobulin G1 (IgG1) monoclonal antibody that inhibits the activity of TNFα. Biosimilars for adalimumab are also available. Adalimumab has a marketing authorisation for treating 'severe chronic plaque psoriasis in children and adolescents from 4 years of age who have an inadequate response to or are inappropriate candidates for topical therapy and phototherapies'.[15, 17]

Etanercept (Enbrel®, Pfizer) is a recombinant human TNFα receptor fusion protein that inhibits the activity of TNF-alpha. Biosimilars for etanercept are also available. Etanercept has a marketing authorization for treating 'chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies'. [15, 18]

Ustekinumab (Stelara®, Janssen) is a fully human IgG1-kappa (IgG1κ) monoclonal antibody that acts as a cytokine inhibitor by targeting IL-12 and IL-23. The initial marketing authorization was for the treatment of 'moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies'.[15] An extension of indication was granted in December 2019 to include the treatment in children from the age of 6 years and older.[19, 20]

Table 3. Summary of marketing authorisation for systemic biological therapies in children and adolescents

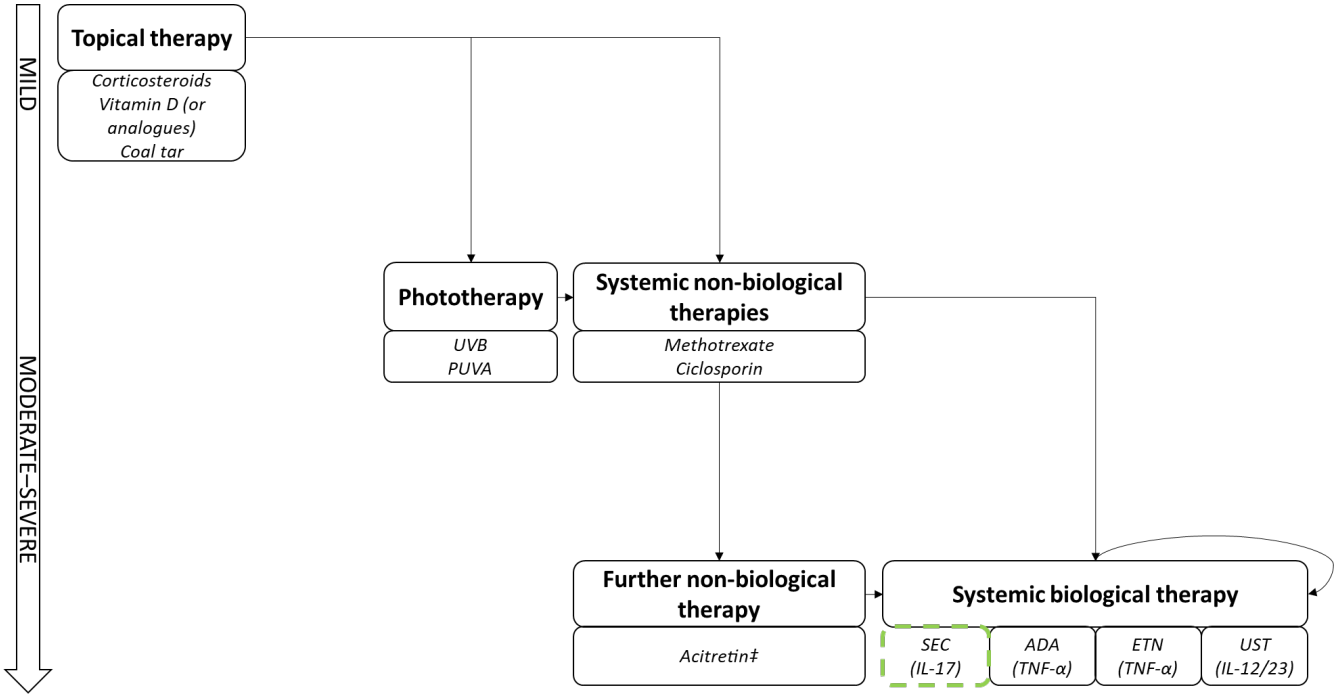
Treatment	Mechanism of action	Age range	Disease status	Dosage and schedules	Treatment pathway
Adalimumab	TNFα inhibitor	4 years and older	Severe chronic plaque psoriasis	0.8 mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	Where topical therapy and phototherapies are inadequate or inappropriate
Etanercept	TNFα inhibitor	6 years and older	Severe chronic plaque psoriasis	0.8 mg/kg up to a maximum of 50 mg weekly for up to 24 weeks	Where systemic therapies or phototherapies are inadequate or not tolerated
Ustekinumab	IL-12/IL-23 inhibitor	12 years and older (extended to 6 years and older since December 2019)	Moderate to severe plaque psoriasis	0.75 mg/kg for bodyweight <60 kg; 45 mg for bodyweight 60-100 kg; 90 mg for bodyweight >100 kg at weeks 0 and 4, then every 12 weeks thereafter	Where systemic therapies or phototherapies are inadequate or not tolerated

Source: NICE technology assessment guidance 455;[15] Table 1 of the Assessment Group's Report[21]

Secukinumab (Cosentyx®, Novartis) is a fully human IgG1κ monoclonal antibody that selectively binds to and neutralises IL-17A. Secukinumab 300 mg is already recommended by NICE in TA350 for treating adults with plaque psoriasis, only when:

- the disease is severe, as defined by a total PASI score of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10, and
- the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA, or these treatments are contraindicated or the person cannot tolerate them.[22]

The company's proposed positioning for secukinumab in the clinical care pathway in paediatric patients is presented in Figure 1 below. Secukinumab is presented as a treatment option in the third-line setting along with other biological therapies for children and young people with moderate to severe plaque psoriasis. The ERG's clinical advisor considers the company's positioning of secukinumab to be reasonable and in line with current clinical practice.



†The proposed positioning of secukinumab is indicated by a dashed green box; ‡acitretin is only prescribed to children and young people in exceptional cases.
Abbreviations: ADA, adalimumab; ETN, etanercept; IL-12/23, interleukin-12/23; IL-17, interleukin-17; PUVA, psoralen plus ultraviolet A; SEC, secukinumab; TNFα, tumour necrosis factor alpha; UST, ustekinumab; UVB, ultraviolet B.

Figure 1. Proposed treatment pathway with secukinumab† for psoriasis in paediatric patients [Reproduced from Figure 1, Section B.1.3.2.2 of the CS]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 4 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3.

Table 4. Summary of the company's decision problem

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Children and young people with severe plaque psoriasis (as defined by a total PASI score of 10 or more)	Children and young people with moderate to severe plaque psoriasis (PASI ≥10) who have failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated.	The proposed positioning aligns with: • the NICE recommendation for the comparators (TA455)[15] • the NICE recommendation for secukinumab in the treatment of adults with moderate to severe plaque psoriasis (TA350).[22] Further details are provided in Section **Error! Reference source not found.**.	The company's decision problem makes the case for use of secukinumab in a subset of the population specified in the NICE final scope and the marketing authorisation, and focuses on children and young people with moderate to severe plaque psoriasis, as defined by PASI ≥10, who have failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated. The definition of 'moderate to severe' disease in the company's decision problem aligns with the definition of 'severe' disease outlined in the NICE final scope and existing NICE guidance for children and young people (TA455).[15] The choice of this sub-population reflects previous NICE technology appraisals for the same disease indication (severe plaque psoriasis [PASI ≥10] who are inadequately controlled by, or are intolerant to, other systemic therapies), notably TA455 (adalimumab, etanercept and ustekinumab in children and young people) and TA350 (secukinumab in adults).[15, 22] The ERG considers that the

				patient population considered by the company is appropriate. The study populations in the two studies (A2310 and A2311) included in the evidence submitted by the company fit within the definition of 'severe' plaque psoriasis used by NICE (PASI ≥10). However, the severity of plaque psoriasis was defined differently between A2310 and A2311. The A2310 study included patients with a baseline PASI score of 20 or higher, reflecting 'very severe' psoriasis, while the A2311 study included patients with a baseline PASI score of 12 or higher. In general, the study populations in the company submission (CS) were narrower, and had higher disease severity, than those specified in the company's decision problem and the NICE final scope (PASI ≥10). The network meta-analysis (NMA) only included patients with very severe disease (PASI ≥20), with patients with PASI ≥12 included in a sensitivity analysis. [redacted] with the 12- to 17-year old age group representing 77% and [redacted] in A2310 and A2311,

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				respectively. The direct evidence in the CS may therefore be more relevant for older than younger children. Overall, however, the ERG's clinical advisor is of the opinion that the clinical evidence submitted by the company reflects the characteristics of the patient population who would be eligible for this treatment in the UK.
Intervention	Secukinumab	As per scope	Not applicable	The intervention described in the company's submission matches the intervention described in the final scope. Secukinumab (Cosentyx®, Novartis) gained marketing authorisation by the European Commission in January 2015 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. A variation for a new indication for children and adolescents received a CHMP (Committee for Medicinal Products for Human Use) positive opinion on 25th June 2020 with European marketing authorisation granted on 31st July 2020.[23, 24] The current approved indication is 'for the treatment of moderate to severe plaque psoriasis in children and

				adolescents from the age of 6 years who are candidate for systemic therapy'.[25,26] The Great Britain marketing authorisation for Cosentyx was automatically issued by MHRA (Medicines and Healthcare products Regulatory Agency) on 1 January 2021 and reflects the approval already granted for the EU marketing authorisation. The recommended dose is based on body weight and is 75 mg for <50 kg and 150 mg (with an option to increase to 300 mg) for ≥50 kg. Secukinumab is administered by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.[27] In the evidence submitted by the company, study participants in the secukinumab arm in both trials (A2310 and A2311) were stratified and randomised by body weight (<25 kg, 25 to <50kg, ≥50 kg) and age to receive 'low dose' (75/75/150 mg, respectively) or 'high dose' (75/150/300 mg, respectively). The company submission states that the use of secukinumab 150 mg in patients with 25 to <50 kg of body weight in the 'high dose' group is outwith the licensed dosage range, as there is no option in the

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				summary of product characteristics (SmPC) to increase the dosage to 150 mg for patients <50 kg.[27] In the NMA, only licensed doses were included in the analysis.
Comparator(s)	If systemic non-biological treatment or phototherapy is suitable: • systemic non-biological therapies (including methotrexate and ciclosporin) • phototherapy with or without psoralen. If conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated: • adalimumab • etanercept • ustekinumab • best supportive care.	If conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated: • etanercept • ustekinumab.	• Novartis wishes to pursue a recommendation alongside other biologics, so cost-effectiveness analyses vs systemic non-biological therapies or phototherapy are not presented. • Novartis understands following the decision problem meeting and based on previous FTAs in psoriasis (e.g. TA521[28]), that within an FTA it is acceptable to compare against a subset of the potential comparators, taking into account response rates.	In line with the proposed use of secukinumab in a subset of population within the NICE final scope, the company's decision problem focused on treatments targeted at this subset population and included biological therapies (etanercept and ustekinumab) as the only relevant comparators. The ERG clinical advisor considers the omission of non-biological treatment and phototherapy acceptable, for in UK clinical practice secukinumab is anticipated only to be used third-line after other systemic therapies or phototherapies. The ERG clinical advisor also agrees with the company that best supportive care is not a valid comparator, as biologics represent the standard of care in this population and few patients would be treated with the 'best supportive care' approach alone,

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			○ Etanercept and ustekinumab are considered relevant comparators as head-to-head trial data are available for secukinumab vs etanercept, [redacted] ○ Adalimumab is not included as a comparator as it does not connect to the NMA network (the trial comparator is methotrexate rather than placebo). • Best supportive care is not included as a comparator, as biologics represent the standard of care in this population.	unless all biologics have been tried and failed already. Secukinumab was directly compared with etanercept and placebo in the A2310 study in the CS. It is stated on page 42 of the CS that '*etanercept was chosen as an active comparator in accordance with EU Health Authority feedback, as it was the first biologic medication approved for use in children and adolescents with severe psoriasis in the European Union and elsewhere'*. Nevertheless, the ERG considers that the choice of etanercept as comparator may have increased the effect size in favour of secukinumab. In the NMA undertaken by the assessment group for TA455, etanercept was shown to be less effective than other biological therapies such as ustekinumab and adalimumab (PASI 75 relative risk at 12 weeks, mean [95% credible interval]: ustekinumab versus etanercept, 1.54 [1.28 to 1.92]; adalimumab versus etanercept, 1.47 [1.23 to 1.79]) (TA455, Section 4.8, Table 1).[15] The biological therapy comparators considered in the NMA in the company

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				submission were etanercept and ustekinumab. The company did not include adalimumab as a relevant comparator despite it was listed in the NICE final scope.
Outcomes	The outcome measures to be considered include: • severity of psoriasis • psoriasis symptoms on the face, scalp, nails and joints • mortality • response and remission rate • duration of response • relapse rate • adverse effects of treatment • health-related quality of life.	As per scope, except for: • psoriasis symptoms on the face, scalp, nails and joints.	The outcomes specified are broadly appropriate. However, psoriasis symptoms on the face, scalp, nails and joints are not measured outcomes within the secukinumab Phase III study (A2310).	The outcome of 'psoriasis symptoms on the face, scalp, nails and joints' specified in the NICE final scope was removed from the decision problem by the company, as it was not a measured outcome within the submitted evidence. The ERG clinical advisor considers that this outcome is not crucial when complete skin clearance is achieved. Nevertheless, the ERG notes that the omission could still be important for some patients. For example, psoriasis patients who responded to treatment and achieved near-complete skin clearance may still have symptoms of psoriasis in visible parts of the body, such as the face, where this still leads to an impairment on health-related quality of life. The outcome of 'duration of response' specified in the NICE scope was not explicitly reported in the CS. The company clarified that duration of response was

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				reported in terms of PASI response rates over time, PASI score over time, and IGA score over time. The ERG notes that the available data do not indicate any potential loss of treatment response, or fluctuation in response, at individual level over the length of treatment. The outcome of 'relapse rate' specified in the NICE final scope was not reported in the CS. Additional data on relapse rates were provided in the clarification response from the company.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	A cost-comparison analysis is presented assuming a 5-year time horizon. This is considered to be of sufficient duration in order to capture differences in costs between alternatives. A longer time horizon is tested in a scenario analysis in which all patients are modelled up to the age of 18 years, in line with the approach taken in TA455.[15] Costs are considered from an NHS and Personal Social Services perspective, and the availability of commercial arrangements for the intervention and comparators is taken into account.	The technology is likely to provide similar or greater health benefits at similar or lower cost than comparator technologies for the same indication.	

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups to be considered	Where the evidence allows, the following subgroups will be considered: • previous use of phototherapy and systemic non-biological therapy • previous use of biological therapy. Where the evidence allows, sequencing of different drugs and the place of secukinumab in such a sequence will be considered.	Subgroup cost-comparison analyses based on age (6– 11 years and 12–17 years) are presented, given that ustekinumab is recommended by NICE only in individuals aged 12 years and older, but the marketing authorisation is for individuals aged 6 years and older.	The subgroups in the scope are not included in the model as data are not available to inform these analyses, and Novartis wishes to pursue a recommendation alongside other biologics.	The subgroups specified in the NICE final scope were not reported for the assessment of clinical effectiveness in the company submission.

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Special considerations including issues related to equity or equality	Not discussed in draft scope.	See third column.	Since TA350 recommends secukinumab for adults with psoriasis and the paediatric licence wording is the same as for adults, there would be an equality issue for children and young people if the secukinumab paediatric recommendations were restricted vs those for adults.	No special considerations were specified in the NICE final scope. Given that use of secukinumab in children is being addressed in the current submission, the ERG has no comments on equality issues made by the company.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D.1.1 through to D.1.6.1 of the CS. The ERG's appraisal of the company's systematic review methods is summarised in Table 5 below.

Table 5. ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D.1 of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research, CDSR and HTA organisations for evidence syntheses, and relevant conference proceedings. Details provided in Appendix D.1.2 of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	
Was study selection conducted by two or more reviewers independently?	Yes	See Appendix D.1.4.1 and D.1.4.2 of the CS.

Was data extraction conducted by two or more reviewers independently?	Yes	See Appendix D.1.4.3 of the CS.
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes (for A2310) Not applicable (for A2311)	For A2310, see Section B.3.5 and Appendix D.1.4.4 of the CS. The risk-of-bias assessment of the A2311 study was not reported in the CS.
Was risk of bias assessment conducted by two or more reviewers independently?	Possibly (for A2310) Not applicable (for A2311)	In Appendix D.1.4.4 of the CS, it is stated that the 'risk of bias' of the A2310 trial was conducted by one reviewer and 'was thoroughly checked' by the second reviewer. The risk-of-bias assessment of the A2311 study was not reported in the CS.
Was identified evidence synthesised using appropriate methods?	Not applicable	As the SLR identified only one trial that directly compared secukinumab against active comparator (etanercept), meta-analysis was not conducted.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria; results are presented in Table 6. Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be acceptable and in line with current methodological standards.

Table 6. Quality assessment of the company's systematic review of clinical effectiveness evidence (A2310 and A2311)

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes (A2310) No (A2311)
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The main evidence for secukinumab (Cosentyx®, Novartis Pharma AG, Basel, Switzerland) submitted by the company consisted of two ongoing, multicenter, Phase 3 randomised controlled trials (RCTs) sponsored by the company, A2310 (CAIN457A2310, NCT02471144)[29, 30] and A2311 (CAIN457A2311, NCT03668613).[31, 32] The A2310 double-blind trial provides the primary source of evidence and the A2311 open-label trial provides supporting evidence. Trials' characteristics are summarised in Table 4 and Table 5, Section B.3.2, of the CS and reproduced by the ERG as Table 7 below. The participant flow in the A2310 study is presented in Figure 14, Appendix D.1.7 of the CS. Participant flow of the A2311 study is not provided in the CS.

The study populations were in general narrower, and had higher disease severity, than those specified in the company's decision problem and the NICE final scope. There is inconsistency in the way NICE and the company define moderate and severe disease based on the PASI score. Severe plaque psoriasis as specified in the NICE final scope is defined as a PASI of ≥10,

while the company's definition of 'severe' psoriasis (PASI score ≥20) reflects the NICE definition of 'very severe' disease.[33] The company's definition of 'moderate-to-severe' disease (PASI score ≥12) does not encompass less severe disease (score 10 to <12) within the definition of 'severe' plaque psoriasis used by NICE (PASI ≥10).

Table 7. Clinical effectiveness evidence [Reproduced from Table 4 and Table 5, Section B.3.2 of the CS]

	Trial A2310 in patients with severe disease (PASI ≥20)	Trial A2311 in patients with moderate to severe disease (PASI ≥12)
Study	CAIN457A2310 (NCT02471144) – "A randomised, double-blind, placebo- and active controlled multicentre trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept (in a single-blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in patients from 6 to less than 18 years of age with severe chronic plaque psoriasis." (PASI ≥20)	CAIN457A2311 (NCT03668613) – "A randomised, open-label, multicentre trial to assess the efficacy of subcutaneous secukinumab after twelve weeks of treatment, and to assess the long-term safety, tolerability and efficacy in patients from 6 to less than 18 years of age with moderate to severe chronic plaque psoriasis" (PASI ≥12)
Study design	Multicentre, randomised, double-blind, parallel group, placebo- and active (etanercept)-controlled study	Randomised, open-label, parallel group, two-arm, multicentre study
Population	Key eligibility criteria: • Children and adolescents ≥6 and <18 years of age • Severe plaque psoriasis (PASI ≥20, IGA mod 2011 score 4, and BSA involvement ≥10%) • Candidates for systemic treatment (inadequate control of symptoms with topical treatment or failure to respond to or tolerate previous systemic treatment and/or UV therapy).	Key eligibility criteria: • Children and adolescents ≥6 and <18 years of age • Moderate to severe plaque psoriasis (PASI ≥12, IGA mod 2011 score ≥3, and BSA involvement ≥10%) • Candidates for systemic treatment.

Intervention(s)	Secukinumab low dose (equivalent to licensed dose) ≥50 kg: 150 mg 25 to <50 kg: 75 mg <25 mg: 75 mg Secukinumab high dose ≥50 kg: 300 mg 25 to <50 kg: 150 mg <25 kg: 75 mg To maintain blinding, patients ≥25 kg received two SC injections at each dose, and patients <25 kg received one SC injection. *The secukinumab arms were double-blind (patient, investigator, assessor) until the database lock for the Week 52 analysis.*	Secukinumab low dose (equivalent to licensed dose) ≥50 kg: 150 mg 25 to <50 kg: 75 mg <25 mg: 75 mg Secukinumab high dose ≥50 kg: 300 mg 25 to <50 kg: 150 mg <25 mg: 75 mg
Comparator(s)	Placebo Two SC injections at each dose, except for patients <25 kg who received one SC injection. *The placebo arm was double blind (patient, investigator, assessor) until the database lock for the Week 52 analysis.* Etanercept Weekly SC dose of 0.8 mg/kg (up to a maximum of 50 mg). *The etanercept arm was single-(assessor) blind until the database lock for the Week 52 analysis.*	Results for secukinumab low/high dose were compared with placebo response rates from historical data.
Indicate if trial supports application for marketing authorisation (yes/no)	Yes	Yes
Reported outcomes specified in the decision problem	Severity of psoriasis Response and remission rate Duration of response Relapse rate Adverse effects of treatment Health-related quality of life	Severity of psoriasis Response and remission rate Duration of response Relapse rate Adverse effects of treatment Health-related quality of life
All other reported outcomes	Physical development Pharmacokinetics Pharmacogenetics	Immunogenicity Physical development

Abbreviations: BSA, body surface area; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; SC, subcutaneous.

The A2310 study consisted of five periods: screening (up to 4 weeks), induction (randomisation to Week 12), maintenance (Week 12 to Week 52), extension treatment (open label, Week 52 until Week 236) and post treatment follow-up (16 weeks). The study is ongoing. Data presented in the submission related to the cut-off date at which the last patient underwent their Week 52 visit (18th September 2019). In A2310, a total of 162 participants were randomized in a 1:1:1:1 ratio to one of the treatment arms:

- low dose secukinumab (75 mg if weight <50 kg; 150 mg if weight ≥50 kg) (n = 40)
- high dose secukinumab (75 mg if weight <25 kg; 150 mg if weight ≥25 kg and <50 kg; 300 mg if weight ≥50 kg) (n = 40)
- placebo (n = 41)
- open-label etanercept (Enbrel®, 0.8 mg/kg up to a maximum of 50 mg per dose) (n = 41).

Randomisation was stratified by age (<12 years and ≥12 years) and weight (<25 kg, 25 to <50 kg, and ≥50 kg). Secukinumab was administered by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing thereafter. Placebo was administered subcutaneously in syringes matching the secukinumab syringes at Weeks 0, 1, 2, 3 and 4, and then 4 weeks later at Week 8. After the induction period, patients in the placebo arm switched to low- or high-dose secukinumab and continued into the maintenance period, if they did not achieve a PASI 75 response at Week 12. Placebo PASI 75 responders at Week 12 terminated their treatment and entered the post-treatment follow-up period. Etanercept was administered subcutaneously once weekly. Etanercept patients terminated their treatment at Week 52 and entered the post-treatment follow-up period. Patient, investigator and outcome assessor were blinded ('double-blind') in the secukinumab and placebo arms until Week 52, while in the etanercept arm only outcome assessor was blinded ('single-blind') until Week 52.

The A2311 study [redacted] The study is ongoing. Data presented in the CS relate to the cut-off date at which the last patient underwent their Week 52 visit (28th May 2020). [redacted]

- open-label secukinumab low dose (75 mg if weight <50 kg; 150 mg if weight ≥50 kg) ([redacted]) or
- open-label secukinumab high dose (75 mg if weight <25 kg; 150 mg if weight ≥25 kg and <50 kg; 300 mg if weight ≥50 kg) ([redacted]).

Secukinumab doses were identical to those used in the A2310 study. Randomisation was stratified by body weight (<25 kg, 25 kg to <50 kg, ≥50 kg) and disease severity (moderate [PASI score 12 to <20 and IGA 3 or 4, or PASI score ≥20 and IGA 3] or severe [PASI score ≥20 and IGA of 4]). [redacted] (34-36) [redacted] (11, 37)

The company performed a quality assessment of A2310 using eight criteria from the University of York Centre for Reviews and Dissemination (CRD) guidance (Table 16, Appendix D.1.8 of the CS).(38) Overall, the ERG generally agrees with the company's assessment of the A2310 study and considers that risk of bias was low for most domains for this study. The quality assessment of the A2311 study was not reported in the CS. Nevertheless, risk of bias for the comparison of secukinumab with a historical placebo in this study is likely to be high.

A2310 collected data from 19 countries with one patient recruited in the UK, while [redacted] A2310 was in general well balanced for baseline demographic and disease characteristics between the intervention groups (Tables 10 and 11, Section B.3.3.1.7 of the CS, reproduced as Tables 8 and 9 below). For A2311, [redacted]

[redacted] (Tables 15 and 16, Section B.3.3.2.6 of the CS, reproduced as Tables 8 and 9 below), [redacted]. In both trials, [redacted]. The 12- to 17-year-old age group represent 77% and [redacted] of participants in A2310 and A2311, respectively. The mean age of participants was 13.5 years in A2310 and [redacted] years in A2311. The body weight of participants was similar between the two trials (mean 53.47 kg and [redacted] kg for A2310 and A2311, respectively). Participants in A2310 had a mean baseline PASI score of 28.0, a mean BSA of 40.01%, and all but one participants had a IGA mod 2011 score of 4 (severe disease). Participants in the secukinumab low dose and high dose groups in A2311 had a mean baseline PASI score of [redacted], a mean BSA of [redacted]%, and [redacted] had a IGA mod 2011 score of [redacted]. Overall, the ERG's clinical advisor is of the opinion that the study populations are generally reflective of children and young people with severe chronic psoriasis who would be eligible for this treatment in the UK.

Table 8. Disease history and baseline disease characteristics of participants in the A2310 and A2311 trials [Reproduced from Table 11, Section B.3.3.1.7, and Table 16, Section B.3.3.2.6, Document B of the CS]

	A2310					A2311		
Disease characteristic	**Secukinumab low dose N=40**	**Secukinumab high dose N=40**	**Placebo N=41**	**Etanercept N=41**	**Total N=162**	**Secukinumab low dose**	**Secukinumab high dose**	**Total**
Baseline PASI score								
N	40	40	41	41	162			
Mean	27.6	28.0	28.0	28.4	28.0			
SD	6.89	8.67	8.09	9.05	8.15			
Median								
Min–Max								
Baseline PASI, n (%)								
≤ 20	0	1 (2.5)	0	0	1 (0.6)			
> 20	40 (100.0)	39 (97.5)	41 (100.0)	41 (100.0)	161 (99.4)			
Baseline total BSA affected by plaque-type psoriasis								
N	40	40	41	41	162			
Mean	37.59	40.26	38.99	43.13	40.01			
SD	13.860	17.559	17.647	19.557	17.258			
Median	36.65	36.75	34.50	37.70	36.00			
Min–Max	12.0–72.5	16.0–94.0	17.9–77.0	13.1–90.5	12.0–94.0			
Baseline IGA mod 2011 score, n (%)								
3 = Moderate disease	0	1 (2.5)	0	0	1 (0.6)			
4 = Severe disease	40 (100.0)	39 (97.5)	41 (100.0)	41 (100.0)	161 (99.4)			
Time since first diagnosis of plaque-type psoriasis (years)								
N	40	40	41	41	162			
Mean	4.85	5.44	6.03	4.55	5.22			
SD	4.291	4.665	5.093	3.733	4.468			

	A2310					A2311		
Disease characteristic	**Secukinumab low dose N=40**	**Secukinumab high dose N=40**	**Placebo N=41**	**Etanercept N=41**	**Total N=162**	**Secukinumab low dose**	**Secukinumab high dose**	**Total**
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis history, n (%)								
Generalised pustular psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palmoplantar pustular psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erythrodermic psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnosis of psoriatic arthritis, n (%)								
Yes	5 (12.5)	3 (7.5)	3 (7.3)	3 (7.3)	14 (8.6)	[redacted]	[redacted]	[redacted]
No	35 (87.5)	37 (92.5)	38 (92.7)	38 (92.7)	148 (91.4)			
Time since first diagnosis of psoriatic arthritis (years)								
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Previous psoriasis therapies, n (%)								
Yes	40 (100.0)	40 (100.0)	41 (100.0)	41 (100.0)	162 (100.0)	[redacted]	[redacted]	[redacted]
No	0	0	0	0	0	[redacted]	[redacted]	[redacted]

Abbreviations: BSA, body surface area; IGA mod 2011, Novartis Investigator's Global Assessment modified 2011; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Table 9. Demographics and background characteristics of participants in the A2310 and A2311 trials [Reproduced from Table 10, Section B.3.3.1.7, and Table 15, Section B.3.3.2.6, Document B of the CS]

	A2310					A2311		
Participant characteristic	**Secukinumab low dose N=40**	**Secukinumab high dose N=40**	**Placebo N=41**	**Etanercept N=41**	**Total N=162**	**Secukinumab low dose** [redacted]	**Secukinumab high dose** [redacted]	**Total** [redacted]
Sex, n (%)								
Male	13 (32.5)	17 (42.5)	19 (46.3)	16 (39.0)	65 (40.1)	[redacted]	[redacted]	[redacted]
Female	27 (67.5)	23 (57.5)	22 (53.7)	25 (61.0)	97 (59.9)			
Age group (years), n (%)								
<12	8 (20.0)	9 (22.5)	10 (24.4)	10 (24.4)	37 (22.8)	[redacted]	[redacted]	[redacted]
≥12	32 (80.0)	31 (77.5)	31 (75.6)	31 (75.6)	125 (77.2)	[redacted]	[redacted]	[redacted]
Age (years)								
N	40	40	41	41	162	[redacted]	[redacted]	[redacted]
Mean	13.7	13.2	13.7	13.5	13.5	[redacted]	[redacted]	[redacted]
SD	2.92	3.21	3.27	2.94	3.06	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Weight (kg)								
N	40	40	41	41	162	[redacted]	[redacted]	[redacted]
Mean	52.60	53.61	55.68	51.96	53.47	[redacted]	[redacted]	[redacted]
SD	15.263	20.179	22.280	19.430	19.345	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Weight strata (kg), n (%)								
<25	2 (5.0)	3 (7.5)	3 (7.3)	4 (9.8)	12 (7.4)	[redacted]	[redacted]	[redacted]
25 to <50	17 (42.5)	15 (37.5)	17 (41.5)	16 (39.0)	65 (40.1)	[redacted]	[redacted]	[redacted]
≥50	21 (52.5)	22 (55.0)	21 (51.2)	21 (51.2)	85 (52.5)	[redacted]	[redacted]	[redacted]
Race, n (%)								

	A2310					A2311		
Participant characteristic	**Secukinumab low dose N=40**	**Secukinumab high dose N=40**	**Placebo N=41**	**Etanercept N=41**	**Total N=162**	**Secukinumab low dose**	**Secukinumab high dose**	**Total**
Caucasian (or White)	34 (85.0)	34 (85.0)	36 (87.8)	30 (73.2)	134 (82.7)			
Black (or African American)								
Asian								
Vietnamese								
Native American (American Indian or Alaska Native)								
Other	1 (2.5)	0	1 (2.4)	0	2 (1.2)			
Ethnicity, n (%)								
Hispanic/Latino								
East Asian								
Southeast Asian								
South Asian								
West Asian								
Russian								
Mixed ethnicity								
Unknown								
Other								
Not Reported								
Child-bearing status, n (%)								
Pre-menarche								

Abbreviations: BMI, body mass index; SD, standard deviation.

3.2.2 Primary and secondary efficacy endpoints

The outcome measures to be considered as listed in the NICE final scope were: severity of psoriasis; psoriasis symptoms on the face, scalp, nails and joints (not measured in the company submission); mortality; response and remission rate; duration of response; relapse rate; adverse effects of treatment; and health-related quality of life.

Primary endpoints: A2310

The co-primary endpoints of A2310 were achieving PASI 75 and IGA mod 2011 0 or 1 response at week 12. The company submission reports these outcomes in terms of "n*/m", defined as "rounded mean number of responders for 100 imputations/number of patients evaluable", as opposed to actual observed counts of participants achieving the respective outcomes.

As such, Table 19 of the company submission reports exact logistic regression analyses of the primary outcomes at week 12 in the full analysis set (FAS) using multiple imputation as the main analyses. Any categorical missing data point (any of the PASI and IGA response rates) are replaced by multiple Bayesian draws from the conditional distributions based on observed data and covariates which are then incorporated into standard methods of analyses (no reference is given in the CS but the ERG presumes this would be comparable to MICE). A summary of the primary outcomes is presented in Table 10.

For PASI 75 at week 12, the odds ratio estimate (95%CI) for the low dose secukinumab vs placebo comparison was [redacted] and for the high dose secukinumab vs placebo comparison was [redacted] In both comparisons, the odds ratio estimates were statistically significant (p<0.001). The odds ratio estimates (95%CI) for the comparisons with etanercept of low dose secukinumab [redacted] and high dose secukinumab [redacted] were not statistically significant [redacted], respectively).

Table 10. A2310: Exact logistic regression analysis summarising the methods for IGA mod 2011 0 (clear) or 1 (almost clear), PASI 75 and PASI 90 response at Week 12 as well as secondary outcomes PASI 50 and PASI 100 response at Week 12

Response criterion	Imputation method	LD n*/m (%)	HD n*/m (%)	Placebo n*/m (%)	LD Odds ratio estimate (95% CI)†; p	HD Odds ratio estimate (95% CI)†; p	ETN n*/m (%)	LD Odds ratio estimate (95% CI)†; p	HD Odds ratio estimate (95% CI)†; p
IGA 0/1	MI #	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NRI $	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	MI #	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NRI $	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	MI #	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NRI $	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50	MI #	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NRI $£	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	MI #	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Response criterion	Imputation method	LD n*/m (%)	HD n*/m (%)	Placebo n*/m (%)	LD Odds ratio estimate (95% CI)†; p	HD Odds ratio estimate (95% CI)†; p	ETN n*/m (%)	LD Odds ratio estimate (95% CI)†; p	HD Odds ratio estimate (95% CI)†; p
	NRI $£	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n* for MI = rounded mean number of responders for 100 imputations; n* for NRI = the number of patients observed achieving the endpoint (i.e. responders); m = number of patients evaluable; †Odds ratio, 95% confidence interval, and p-value are from an exact logistic regression model with treatment group, baseline body-weight category and age category as factors; #Extracted from Document B Tables 19, 20 and 21. NB. some differ very slightly to Appendix I at 12 weeks; $Extracted from company clarification response Table 5 for the inputs for the NMA models page 13;£ Extracted from additional further clarification response Table 1.

Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; ETN, etanercept; FAS, full analysis set; PASI, Psoriasis Area and Severity Index; PLA, placebo; SEC, secukinumab; NRI, Pure non-responder imputation; MI, Multiple imputation; NE, not estimated: NR, not reported in the company submissions.

For IGA mod 2011 0 or 1 response at week 12, the odds ratio estimates (95%CI) were statistically significant (p<0.0001) for the low dose [redacted] and high dose [redacted] secukinumab groups, as compared to placebo. The odds ratio estimates (95% confidence interval [CI]) for the comparisons with etanercept with secukinumab low dose [redacted] and high dose [redacted] were also statistically significant [redacted], respectively).

It should be noted that sensitivity analyses of the above were also conducted using non-responder imputation (NRI) whereby those with missing data were imputed as not having reached that response rate category, regardless of the reason for missingness. These were the results eventually used in the NMA since the other studies also used this approach and were thus more comparable. See Table 10 above that summarizes both approaches for comparison for A2310.

At further clarification, the company provided what they stated were actual observed counts of participants achieving PASI 75 and IGA 0/1 at week 12. These were [redacted] for the low dose secukinumab group, [redacted] for the high dose secukinumab group, [redacted] for the placebo group and [redacted] for the etanercept group. Table 11 reports a summary of numbers of participants achieving the primary endpoints, in terms of “n*/m” (i.e., “rounded mean number of responders for 100 imputations/number of patients evaluable”), and “n/m” (i.e. “number of subjects observed achieving the endpoint/number of patients evaluable”). The ERG note that the denominator ‘m’ (number of participants evaluable) is different from actual number of participants observed and is based on ‘pure non-responder imputation’ where missing values were imputed with non-response regardless of the reason for missing data. The number of participants with missing data for PASI75 and IGA 0/1 at Week 12 as reported in CSR is: [redacted] for low-dose secukinumab, [redacted] for high-dose secukinumab, [redacted] for placebo and [redacted] for etanercept (Table 14.2 – 1.1.1, pages 252-253, Novartis A2310 Week 52 CSR).

Table 11. Summary of primary outcomes reported in terms of logistic regression analysis: mean number (n*) and actual observed counts (n) of participants achieving primary endpoints

Outcome	Low dose secukinumab (n=40)		High dose secukinumab (n=40)		Placebo (n=41)		Etanercept (n=41)	
	n*/m (%)	n/m (%)	n*/m (%)	n/m (%)	n*/m (%)	n/m (%)	n*/m (%)	n/m (%)
PASI 75	[redacted]							
IGA 0/1								

Note. n*: rounded mean number of responders for 100 imputations; n: number of participants achieving the endpoint; m: number of patients evaluable. Percentages as reported in the company submission

Secondary endpoints: A2310

The company also assessed PASI 90, PASI 50 and PASI 100. A summary of these outcomes is presented in Table 12. These outcomes were reported in the company submission in the multiple imputation format described above and [redacted].

At clarification, the company provided actual observed counts of participants achieving PASI 90, PASI 50 and PASI 100 at week 12. Table 12 presents a summary of the multiple imputation values reported for these outcomes in the company submission ("n*/m", i.e., "rounded mean number of responders for 100 imputations/number of patients evaluable") and the actual observed counts achieving these secondary endpoints (PASI 50/90/100) provided in the company's clarification response ("n/m", i.e. "number of subjects observed achieving the endpoint/number of patients evaluable"). The ERG note that the denominator 'm' (number of participants evaluable) is different from actual number of participants observed and is based on 'pure non-responder imputation' where missing values were imputed with non-response regardless of the reason for missing data. The number of participants with missing data for PASI 50/90/100 at Week 12 as reported in CSR is: [redacted] for low-dose

secukinumab, [redacted] for high-dose secukinumab, [redacted] for placebo and [redacted] for etanercept (Table 14.2 – 1.1.1, pages 252-253, Novartis A2310 Week 52 CSR).

Table 12. Summary of secondary outcomes (PASI 90, PASI 50 and PASI 100) reported in terms of logistic regression analysis: mean number (n*) and actual observed counts (n) of participants achieving secondary endpoints

Outcome	Low dose secukinumab (n=40)		High dose secukinumab (n=40)		Placebo (n=41)		Etanercept (n=41)	
	n*/m (%)	n/m (%)	n*/m (%)	n/m (%)	n*/m (%)	n/m (%)	n*/m (%)	n/m (%)
PASI 90	[redacted]							
PASI 50								
PASI 100								

Note. n*: rounded mean number of responders for 100 imputations; n: number of participants achieving the endpoint; m: number of patients evaluable. Percentages as reported in the company submission

The company for this trial attempted to address multiple testing issues by several methods including family wise error adjustment of the p-values for the six null hypotheses (all superiority with one-sided testing) defined in Document B page 67-69, which the ERG largely agree with.

- **Mortality:** No deaths were reported during the entire study period.
- **Response rate:** Response rates of PASI 75 and IGA mod 2011 0/1 at weeks 12 and 52 are presented in Table 13.

Table 13. Response rates at Weeks 12 and 52 [adapted from Tables 1 and 2, Appendix I of the CS]

Timepoint	Outcome	Low dose secukinumab (n=40)		High dose secukinumab (n=40)		Placebo (n=41)		Etanercept (n=41)	
		n*/m	%	n*/m	%	n*/m	%	n*/m	%
Week 12	PASI 75	[redacted]							
	IGA 0/1								
Week 52	PASI 75								
	IGA 0/1								

Note. n*: rounded mean number of responders for 100 imputations; m: number of patients evaluable. Percentages as reported in the company submission.
[a] Placebo group switching to low dose secukinumab at week 12.
[b] Placebo switching to high dose secukinumab at week 12.

For all groups, both PASI 75 and IGA 0/1 scores increased between week 12 and week 52. Scores for both variables were similar for the low and high dose secukinumab groups. Scores were lower for the etanercept group at both time points and the placebo group at week 12, but higher in the placebo group than both secukinumab groups at week 52 for both PASI 75 and IGA 0/1. The time courses of IGA mod 2011 0/1 and PASI 75 responders over time are presented in the company submission (Document B, Figure 7, Section B.3.6.1.3.2, page 81).

- **Remission rate:** Defined as PASI 100 response or complete clearing of psoriasis. At week 12, PASI 100 responses (multiple imputation) were achieved by [redacted] of the low dose secukinumab group, [redacted] of the high dose secukinumab group, [redacted] of the placebo group and [redacted] of the etanercept group. At week 52, these proportions (multiple imputation) were [redacted] and [redacted] for the low dose and high dose secukinumab groups, respectively, [redacted] for the etanercept group, [redacted] for the placebo-low dose secukinumab group and [redacted] for the high dose secukinumab group.
- **Duration of response:** The company submission reported duration of response in terms of PASI response rates over time, PASI score over time, IGA score over time and CDLQI 0/1 over time:

- PASI response rates over time: As reported in the company submission (Document B, Figure 7, Section B.3.6.1.3.2, page 81).
- PASI score over time: At week 52, the absolute mean change in score from baseline was [redacted] for the low dose secukinumab group, [redacted] for the high dose secukinumab group, [redacted] for the placebo-low dose secukinumab group [redacted] for the placebo-high dose secukinumab group and [redacted] for the etanercept group. The time course of percentage change from baseline in PASI score is presented in the company submission (Document B, Figure 9, Section 3.6.1.3.4, page 84).

- IGA score over time: [redacted] CDLQI 0/1 over time: Health-related quality of life was assessed by the Children's Quality of Life Index (CDLQI). Scores can range from 0 to 30 with higher scores representing greater impairment of quality of life. [redacted] The time course of CDLQI 0/1 achievement over time is presented in the company submission (Document B, Figure 10, Section B.3.6.1.4, page 87).

- **Relapse:** Defined as the reduction by >50% of the maximal PASI improvement from baseline. [redacted]

Primary endpoints: A2311

The co-primary endpoints were in line with those of trial A2310, i.e. achieving PASI 75 and IGA mod 2011 0 or 1 response at week 12, and were reported in the same format as those in A2310 (multiple imputation). [redacted]

At clarification, the company provided actual observed counts of participants achieving PASI 75 at week 12, as inputs for the NMA. These were [redacted] for the low dose secukinumab group and [redacted] for the high dose secukinumab group.

Secondary endpoints: A2311

[redacted]

Table 14 summarises their results based on NRI approach for missingness for the primary outcomes and the secondary outcomes.

Table 14. A2311: Exact logistic regression analysis summarising the methods for IGA mod 2011 0 (clear) or 1 (almost clear), PASI 75 and PASI 90 response at Week 12 as well as secondary outcomes PASI 50 and PASI 100 response at Week 12

Response criterion	Imputation method	LD n*/m (%)	HD n*/m (%)	Historical placebo n*/m (%)	LD Odds ratio estimate (95% CI)†; p	HD Odds ratio estimate (95% CI)†; p
IGA 0/1	NRI #	[redacted]	[redacted]	[redacted]	NR	NR
PASI 75	NRI #	[redacted]	[redacted]	NR	[redacted]	[redacted]
PASI 90	NRI #	[redacted]	[redacted]	NR	[redacted]	[redacted]
PASI 100	NRI $	[redacted]	[redacted]	NR	NR	NR

n* = rounded mean number of responders for 100 imputations, m = number of patients evaluable;
†Odds ratio, 95% confidence interval, and p-value are from an exact logistic regression model with treatment group, baseline body-weight category and age category as factors;
#Extracted from Document B, Overall summary, page 31;
$Extracted from company clarification response Table 5: inputs for the NMA models pg 13
NRI, Pure non-responder imputation; MI, Multiple imputation; NE, not estimated: NR, not reported in the company submissions
NE, not estimated

3.2.3 Subgroup analyses

The NICE final scope specifies the following subgroups to be considered:

- Previous use of phototherapy and systemic non-biological therapy
- Previous use of biological therapy.

The company submission does not report subgroup analyses, the rationale being that "*data are not available to pursue these analyses, and Novartis wishes to pursue a recommendation alongside other biologics*" [Document B, Table 1, page 13] and "*secukinumab provides similar or greater health benefits at similar or lower cost in the full population for whom the comparators have been recommended by NICE*" [Document B, Section B.3.7, page 92].

[redacted]

[redacted]

3.2.4 Adverse events

The safety set of A2310 included all patients who took at least one dose of the study drug during the treatment period. The methods used to assess safety are reported in Sections B.3.4.1 and B.3.10 of the company submission and are considered appropriate by the ERG. In general, the safety profile for secukinumab is as expected for patients with this clinical condition.

The majority of adverse events (AEs) reported throughout the entire treatment period were of mild to moderate severity. [redacted]

Table 15 reports a summary of treatment-emergent adverse events (TEAEs) at weeks 12 and 52 occurring in at least 5% of participants of the safety set in any group.

Adverse events possibly related to study medication were generally low, up to week 52: 11/40 (27.5) in the low dose secukinumab group, 13/40 (32.5%) in the high dose secukinumab group and 14/41 (34.1%) in the etanercept group. The most commonly reported SOC with AEs possibly related to study drug was infections and infestations (20% in low dose secukinumab group, 20% in high dose secukinumab group and 17.1% in etanercept group). Other SOCs with AEs possibly related to the study drug reported in >5% of any group were: ‘general disorders and administration site conditions’ (reported in 7.1%, 12.1% and 9.8% of the any low dose secukinumab, any high dose secukinumab and etanercept groups, respectively), ‘respiratory, thoracic and mediastinal disorders’ (1.8%, 8.6% and 2.4% in any low dose secukinumab,

any high dose secukinumab and etanercept groups, respectively) and ‘gastrointestinal disorders’ (reported in 7.1%, 6.9% and 4.9% of and low dose secukinumab, any high dose secukinumab and etanercept groups, respectively).

Table 15. Summary of TEAEs at weeks 12 and 52 experienced in at least 5% of participants of the safety set in any group [adapted from Table 29, Section B.3.10.1, p106, Document B of the CS; Table 12-3 of the week 24 CSR; Table 12-2 of the week 52 CSR]

System organ class, n (%)					
Week 12	**Low dose secukinumab (n=40)**	**High dose secukinumab (n=40)**	**Any dose secukinumab (n=80)**	**Placebo (n=41)**	**Etanercept (n=41)**
Any TEAE	**23 (57.5)**	**25 (62.5)**	**48 (60.0)**	**22 (53.7)**	**25/41 (61.0)**
Infections & infestations	13 (32.5)	15 (37.5)	28 (35.0)	16 (39.0)	11 (26.8)
Gastrointestinal disorders	6 (15.0)	7 (17.5)	13 (16.3)	6 (14.6)	10 (24.4)
General disorders & administration site conditions	4 (10.0)	5 (12.5)	9 (11.3)	3 (7.3)	4 (9.8)
Skin & subcutaneous tissue disorders	5 (12.5)	3 (7.5)	8 (10.0)	3 (7.3)	1 (2.4)
Respiratory, thoracic & mediastinal disorders	3 (7.5)	4 (10.0)	7 (8.8)	3 (7.3)	1 (2.4)
Nervous system disorders	3 (7.5)	3 (7.5)	6 (7.5)	5 (12.2)	1 (2.4)
Investigations	2 (5.0)	2 (5.0)	4 (5.0)	2 (4.9)	5 (12.2)
Reproductive system & breast disorders	1 (2.5)	2 (5.0)	3 (3.8)	1 (2.4)	2 (4.9)
Eye disorders	0 (0.0)	2 (5.0)	2 (2.5)	1 (2.4)	3 (7.3)
Musculoskeletal & connective tissue disorders	0 (0.0)	2 (5.0)	2 (2.5)	1 (2.4)	2 (4.9)
Week 52	**Low dose secukinumab** [redacted]	**High dose secukinumab** [redacted]	**Any dose secukinumab** [redacted]	**Any low dose** [redacted]**/**	**Etanercept** [redacted]

				Any high dose	
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections & infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin & subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders & administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic & mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal & connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning & procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system & breast disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood & lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal & urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE, treatment emergent adverse event

3.2.5 Meta-analyses

Secukinumab was compared directly against active comparator (etanercept) in only one trial (A2310), no meta-analyses were conducted.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

A systematic literature review conducted by the company identified no direct head-to-head evidence for secukinumab versus active comparators other than etanercept. The company's NMA indirectly compared secukinumab with ustekinumab and etanercept, but did not include adalimumab, despite this being listed in the NICE final scope.

The base case NMA included three studies:

- A2310
- CADMUS[37] comparing ustekinumab (standard or half-standard dosing) with placebo in children and young people (n = 110) aged 12 to 17 years with moderate-to-severe plaque psoriasis (defined as baseline PASI ≥12, a Physician's Global Assessment (PGA) ≥3 and BSA ≥10%, for ≥6 months) who were candidates for phototherapy or systemic treatment, or had psoriasis that was poorly controlled with topical therapy
- 20030211[11] comparing etanercept with placebo in children and young people (n = 211) aged 4 years to 17 years with moderate-to-severe plaque psoriasis (defined as PASI ≥12, a static PGA ≥3 and BSA ≥10%, for ≥6 months), who had previous or current treatment with phototherapy or systemic psoriasis therapy or had psoriasis that was poorly controlled with topical therapy.

A summary of the baseline characteristics of the trials include in the NMA as well as of the adalimumab trial versus methotrexate (M04-717) is presented in Table 16.

A sensitivity analysis was also conducted that included the A2311 study, connecting in its low and high dose secukinumab with those arms in the A2310 study.

The company conducted quality assessment of CADMUS and 20030211, using the University of York CRD guidance.[38] The company's assessment shows that risk of bias was low for most domains in these studies, although in the 20030211 study assessing etanercept versus placebo methods used for blinding was assessed by the company to be unclear.

Table 16. Summary of baseline characteristics of the studies included in the network meta-analysis (CADMUS, 20030211, CAIN457A2310, CAIN457A2311) and of the adalimumab study (M04-717) [adapted from Table 4 of the company's clarification response]

Study Name		CADMUS				20030211†		CAIN457A2310				CAIN457A2311		M04-717	
Author, year		Landells 2015[37]				Paller 2008[11]		Bodemer 2020[39]				Novartis data on file[31]		Papp 2017[40]	
Treatment arm		UST std. dose‡	UST half dose¶	UST both doses	PLA	ETN	PLA	SEC LD	SEC HD	ETN	PLA	SEC LD	SEC HD	ADA*	MTX
Randomised		36	37	73	37	106	105	40	40	41	41	[redacted]	[redacted]	38	37
Age (Years)	Mean	14.8	15.1	14.9	15.6	14†	13†	13.7	13.2	13.5	13.7	[redacted]	[redacted]	13.0	13.4
	SD	1.7	1.7	1.7	1.5	4–17†	4–17†	2.9	3.2	2.9	3.3	[redacted]	[redacted]	3.3	3.5
Gender	Male (%)	44.4	48.6	46.6	54.1	52	50	32.5	42.5	39	46.3	[redacted]	[redacted]	44.7	29.7
	Female (%)	55.6	51.4	53.4	45.9	48	50	67.5	57.5	61	53.7	[redacted]	[redacted]	55.3	70.3
Weight (kg)	Mean	62	68.2	65.1	64.7	59.6†	59.8†	52.6	53.6	51.9	55.6	[redacted]	[redacted]	50.8	53.1
	SD	17.1	24.5	21.2	14.7	17.7–168.3†	17.2–131.5†	15.2	20.1	19.4	22.2	[redacted]	[redacted]	19.9	18.7
Race (%)	White/ Caucasian	94.4	81.1	87.7	91.9	78	71	85	85	73.2	87.8	[redacted]	[redacted]	92.1	91.9
	Black	-	-	-	-	3	8	2.5	2.5	0	0	[redacted]	[redacted]	-	-
	Asian	-	-	-	-	8	6	2.5	5	7.3	2.4	[redacted]	[redacted]	-	-
	Native American	-	-	-	-	-	-	7.5	7.5	19.5	7.3	[redacted]	[redacted]	-	-
	Other	5.6	18.9	12.3	8.1	11	15	2.5	0	0	2.4	[redacted]	[redacted]	7.9	8.1
	Mean	21.7	21	21.3	20.8	16.7†	16.4†	27.6	28	28.4	28	[redacted]	[redacted]	18.9	19.2

Study Name		CADMUS				20030211†		CAIN457A2310				CAIN457A2311		M04-717	
Author, year		Landells 2015[37]				Paller 2008[11]		Bodemer 2020[39]				Novartis data on file[31]		Papp 2017[40]	
Treatment arm		UST std. dose‡	UST half dose¶	UST both doses	PLA	ETN	PLA	SEC LD	SEC HD	ETN	PLA	SEC LD	SEC HD	ADA*	MTX
PASI (0-72)	SD	10.4	8.5	9.4	8	12–51.6†	12–56.7†	6.9	8.7	9	8.1	[redacted]	[redacted]	10.0	10.0
BSA	Mean	31.9	33.6	32.7	27.4	21†	20†	37.6	40.3	43.1	40	[redacted]	[redacted]	27.7	30.3
	SD	23.2	21.4	22.1	16.4	10–90†	10-95†	13.9	17.6	19.6	17.7	[redacted]	[redacted]	20.4	21·2
Disease (plaque PsO) duration (Years)	Mean	5.6	5.9	5.7	6.2	6.8†	5.8†	4.8	5.4	4.5	6	[redacted]	[redacted]	5.0	5.1
	SD	3.8	4	3.9	5	0.3–17.9†	0.3–15.8†	4.3	4.7	3.7	5.1	[redacted]	[redacted]	3.8	3.8
Diagnosis of PsA	%	NR	NR	NR	NR	5	13	12.5	7.5	7.3	7.3	[redacted]	[redacted]	NR	NR
Prior systemic conventional therapy	%	47.2	37.8	42.5	43.2	58††	62††	65	52.5	46.3	48.8	[redacted]	[redacted]	36.8	24.3
Prior biologic therapy	%	8.3	10.8	9.6	13.5	0	0	7.5	0	2.4	0	[redacted]	[redacted]	10.5§	8.1§

†In study 20030211 median and range data were reported in place of mean and SD; ‡UST standard dosage: 0.75 mg/kg for patients weighing ≤60 kg, 45 mg for patients weighing >60 kg to ≤100 kg, and 90 mg for patients weighing >100 kg; ¶UST half-standard dosage: 0.375 mg/kg for patients weighing ≤60 kg, 22.5 mg for patients weighing >60 kg to ≤100 kg, and 45 mg for patients weighing >100 kg; ††systemic non-biologic therapy or phototherapy; *ADA dosage: 0.8 mg/kg, outcome data for ADA dosage 0.4 mg/kg not extracted in the table; §proportion of patients receiving prior etanercept therapy.
Abbreviations: ADA, adalimumab; BSA, body surface area; ETN, etanercept; HD, high dose; kg, kilogram; mg, milligram; LD, low dose; MTX, methotrexate; NR, not reported; PASI, psoriasis area and severity index; PLA, placebo; PsA, psoriatic arthritis; PsO, psoriasis; SD, standard deviation; SEC, secukinumab; std., standard; UST, ustekinumab.

Table 17. PASI scores at week 12 from the studies included in the network meta-analysis (CADMUS, 20030211, CAIN457A2310, CAIN457A2311) and the adalimumab study (M04-717) [adapted from Table 5 in the company's clarification response]

Study name	Time of assessment (weeks)	Treatment	PASI 50		PASI 75		PASI 90		PASI 100	
			n/N	%	n/N	%	n/N	%	n/N	%
CADMUS study[37]	12	Ustekinumab standard dose	32/36	88.9	29/36	80.6	22/36	61.1	14/36	38.9
		Ustekinumab half dose	30/37	81.1	29/37	78.4	20/37	54.1	8/37	21.6
		Placebo	11/37	29.7	4/37	10.8	2/37	5.4	1/37	2.7
20030211 study[11]	12	Etanercept	79/106	74.5	60/106	56.6	29/106	27.4	NA	NA
		Placebo	24/105	22.9	12/105	11.4	7/105	6.7	NA	NA
CAIN457A2310 study[39]	12	Secukinumab high dose	[redacted]							
		Secukinumab low dose	[redacted]							
		Etanercept	[redacted]							
		Placebo	[redacted]							
CAIN457A2311 study[31]	12	Secukinumab high dose	[redacted]							
		Secukinumab low dose	[redacted]							
M04-717 study[40]	16	Adalimumab 0.8 mg/kg	NA	NA	22/38	57.9	11/38	28.9	7/38	18.4
		Methotrexate	NA	NA	12/37	32.4	8/37	21.6	1/37	2.7

Abbreviations: NA, not available; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS base case NMA was conducted on three studies (CADMUS, 20030211 and CAIN457A2310) using NRI estimates for the A2310 study since this was the approach the other studies used. The CS did not include any information on the M04-717 study (i.e. potentially allowing for the inclusion of adalimumab as a comparator too). The ERG acknowledges that it is difficult how the M04-717 study might be easily included into the NMA since there are no common treatment arms to link with the other three studies.

The methodology used for the NMA is similar to example 6 in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) Guidelines DSU 2 document. The company state that they were not able to conduct any random effect (RE) models since there were convergence issues.

PASI NMA outcome results

Despite stating convergence issues the CS provides DIC's assessing the performance of both fixed effect (FE) and RE models at 12 weeks (indicating that the DIC for the FE and RE were possible). The company decided the FE model DIC was slightly less (although only within 3 points) and thus the preferred modelling approach. The ERG have some concern how RE DICs were assessed given the convergence problems.

The 12 weeks NMA fixed effect results showed that compared to low dose Secukinumab only the Placebo group was significantly worse with all other treatment arms from the included studies being not significantly different: (RR [Ctl 95%] [redacted] Figure 17 Document B page 97. The ERG was able to get similar results.

Along with the direct relative risks comparing each treatment arm throughout the network to each other, the CS also reports on the surface under the cumulative ranking curve (SUCRA) for the actual PASI scores (as apposed to the categorical 50, 75, 90, 100 cut offs). This is a numeric presentation of the overall ranking as a

single number showing associated with each treatment ranging from 0 to 100%. [redacted] These are also reflected in the rankogram Figure 21, Document B.

Table 18. SUCRA values and probabilities for each secukinumab dose to perform better than the comparators for PASI scores [adapted from Table 24 Document B of the CS]

Comparator	SUCRA	Probability for secukinumab to perform better	
		Secukinumab low dose	Secukinumab high dose
Ustekinumab standard	[redacted]	[redacted]	[redacted]
Secukinumab high	[redacted]	[redacted]	[redacted]
Secukinumab low	[redacted]	[redacted]	[redacted]
Ustekinumab half	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

Abbreviations: PASI, Psoriasis Area and Severity Index; SUCRA, surface under the cumulative ranking.

A source of strength in the CS is their comparison of their direct evidence from the NMA assessing the relationship estimates between etanercept vs placebo to indirect pairwise comparisons, based on the Bucher approach. Further, heterogeneity for each comparison using the Cochran's Q test and the I^2 statistic is reported and allows any inconsistencies to be evaluated for the closed loop containing 20030211 and A2310 (etanercept versus placebo comparison), as the main hub of the NMA since it is this interface that links all the studies together. They only assess the PASI 50, 75 and 90 outcomes, but none-the-less a degree of assurance may be derived from this assessment. The direct and indirect estimates are not seen to be significantly different (see Table 19) and there are no issues related to heterogeneity. Hence, the ERG agrees with the company that there is no significant evidence of inconsistency between these studies

Table 19. Results from inconsistency assessment for all PASI endpoints available (placebo versus etanercept) [adapted from Tables 27-28, Document B of the CS]

Placebo vs etanercept		Included trials	Ln0R (SE)	Z-score	p-value	I^2	p-value of Q
	PASI 50					[redacted]	[redacted]
Direct		20030211 A2310	[redacted]				
Indirect		A2310	[redacted]				
Indirect vs direct			[redacted]	[redacted]	[redacted]		
	PASI 75					[redacted]	[redacted]
Direct		[redacted]	[redacted]				
Indirect		A2310	[redacted]				
Indirect vs direct			[redacted]	[redacted]	[redacted]		
	PASI 90					[redacted]	[redacted]
Direct		20030211 A2310	[redacted]				
Indirect		A2310	[redacted]				
Indirect vs direct			[redacted]	[redacted]	[redacted]		

Abbreviations: OR, odds ratio; PASI, Psoriasis Area and Severity Index; SE, standard error.

The CS also presents a sensitivity analysis to include the A2311 study into the PASI NMA, results presented in Appendix D1.10, Figures 28-31, and 36. The ERG notes that these are very similar to the base case analyses results (albeit with marginally tighter credible limits) as were the direct vs indirect inconsistencies checks, the SUCRA assessment and rankogram.

Children's Quality of Life Index

CDLQI was reported across the base case studies (CADMUS, 20030211 and A2310) using the mean change from baseline (CFB) in quality of life (QoL) over time, as the main measure. Missing values for this outcome were imputed by last observation carried forward (LOCF). Baseline values were not carried forward. While not stated in the CS, the ERG assumes that a similar approach was used for all the NMA included studies.

At clarification the company provided mean change from baseline and associated SE for each treatment arm from studies CADMUS and 2003021. The A2310 equivalent summaries were extracted from various documents submitted by the company (see Table 20).

Table 20 Change from baseline for CDLQI scores at week 12 [adapted from Table 6 of the company's clarification response]

Treatment arm	N	Mean CFB (SE)	Mean difference compared to Placebo (95% CI)
CADMUS study			
Ustekinumab standard dose [a]	32	–6.7 (0.9899)	–5.2 (–7.43, –2.97)
Ustekinumab half dose [a]	35	–5.6 (1.0818)	–4.1 (–6.49, –1.71)
Placebo [a]	32	–1.5 (0.5657)	N/A
20030211 study			
Etanercept [a]	106	–5.4 (0.5439)	–2.3 (–3.75, –0.85)
Placebo [a]	105	–3.1 (0.4977)	N/A
A2310 study			
Secukinumab low	[redacted]	[redacted]	NR
Secukinumab high	[redacted]	[redacted]	NR
Etanercept	[redacted]	[redacted]	NR
Placebo	[redacted]	[redacted]	N/A

Abbreviations: CFB, change from baseline; CI, confidence interval; SE, standard error; NR, not reported; N/A, not applicable
[a] Extracted from company's clarification response Table 6 page 14
[b] Extracted from Document B, summary 3.6.1.4.1., page 87
[c] ERG estimated from SDs from Table 11-5 on page 110 of the Novartis A2310 Week 52 CSR
[d] ERG Estimated from combined data for the two placebo groups at week 12, Table 11-5 on page 110 of the Novartis A2310 Week 52 CSR

These results were used by the ERG to replicate the NMA results presented in Figures 22- 23 and Table 25, Document B of the CS.

[redacted]

Table 21. NMA results comparing CFB for CDLQI scores at week 12 between secukinumab low dose and each of the other comparator treatments and the SUCRA and probability of being better [adapted from Figure 22 and Tables 25-26, Document B of the CS]

Treatment arm	Mean difference compared to secukinumab (95% CrI)[a]	SUCRA		Probability for secukinumab low dose being better	
		Base-Case [b]	Sensitivity analysis [c]	Base-Case [b]	Sensitivity analysis [c]
Ustekinumab standard dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab half dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab high	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; N/A, not applicable
[a] Extracted from Figure 22; [b] Extracted from Table 25, Document B; [c] Extracted from Table 2, Document B.

IGA mod 2011 0/1

Whilst the A2310 and A2311 studies reported results for IGA mod 2011 0/1, none of the reported outcomes within the CADMUS and 20030211 studies were sufficiently similar. Consequently, NMA analysis for IGA 0/1 was not possible.

3.5 Additional work on clinical effectiveness undertaken by the ERG

CDLQI score summary statistics for NMA:

- ERG extracted SDs from Table 11-5 on page 110 of the Novartis A2310 Week 52 CSR, then estimated SE - may have rounding errors.
- ERG estimated SEs by combining SDs from the two placebo groups at week 12 from Table 11-5 on page 110 of the Novartis A2310 Week 52 CSR. These were converted these into variances such that a combined SE could be estimated. May have rounding errors.

Unfortunately, the CS results could not be replicated by the ERG.

The ERG replicated the methods for the PASI outcomes for the NMA as the base case and sensitivity analyses and obtain similar results for the FE models.

3.6 Conclusions of the clinical effectiveness section

There were some differences between the trials included in the NMA with respect to their baseline demographics and characteristics. However, most of these were investigated by the company to assess if they could be treatment modifying effects. The ERG are satisfied that these concerns are mostly allayed.

With respect to the direct and indirect comparison of treatments, the submission contains assessments indicating thorough checking. The company have used relevant methods to assess secukinumab with respect to its treatment arms and to other comparator treatment groups.

The measure of disease severity for the A2310 and A2311 studies was IGA/0/1. This was not assessed by the comparator studies and so summaries can only be critiqued on each of two Novartis studies individually and no NMA was attempted. Both A2310 and A2311 indicate that the [redacted]

The PASI score results at the individual studies level for PASI 50, 75, 90 and 100 all show [redacted]

The CS NMA and score results for the QoL measure CDLQI saw [redacted]

The safety of secukinumab for the paediatric population is as would be expected and similar to the safety profile in adults.

The different studies all had slightly different demographic and characteristic profiles. While these were examined within the CS and not found to be have an impact, the ERG is of the opinion that the small sample sizes do not preclude this possibility, in particular with respect to the initial disease severity.

Overall, the outcomes measured within the individual studies A2310 and A2311 show that secukinumab to have a large benefit. [redacted]

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company have not provided a review of existing cost or cost-effectiveness evidence as part of their submission. Given that the company are seeking approval for secukinumab using a cost comparison model, the ERG does not consider it necessary to conduct a full systematic review of existing cost-effectiveness studies. The ERG notes that the most relevant existing information on cost-effectiveness of the comparators included in the company's assessment has been summarised as part of previous NICE guidance (TA455).[15] The committee's conclusions as part of TA455 were to recommend the use of etanercept and ustekinumab (included in the company's original cost comparison model) as well as adalimumab for treating plaque psoriasis in children and young people. Despite substantial uncertainty surrounding the ICER, the committee for TA455 guidance found that all three treatments could be considered a cost-effective use of resources with ICERs compared to best supportive care of:

- Etanercept: ICER between dominance and £29,177 per QALY gained.
- Adalimumab: ICER between £10,624 and £25,657 per QALY gained.
- Ustekinumab: ICER between £13,368 and £26,253 per QALY gained.

The ERG is satisfied that the information provided in TA455 is a sufficient basis on which to judge the relevance of the comparators included in the company's cost-comparison assessment.

4.2 Summary and critique of the company's submitted cost-comparison by the ERG

4.2.1 NICE reference case checklist

Table 22 below outlines the ERG's assessment of the NICE reference case with adaptions to reflect that this is a fast track appraisal (FTA) built on a cost-comparison case.

Table 22 NICE reference case checklist

Element of health technology assessment	Reference case (ERG adapted for FTA cost-comparison case)	ERG comment on company's submission
Perspective on costs	NHS and PSS	**Yes.**
Type of economic evaluation	Cost-comparison analysis with fully incremental analysis	**Yes**
Time horizon	Long enough to reflect all important differences in costs between the technologies being compared	**No,** the ERG raises two specific concerns: - The model assumes that there are no treatment costs incurred following treatment discontinuation. This does not reflect the clinical pathway of treatment, where patients would move to another biologic in clinical practice. - Company base case was for a 5-year time horizon. The ERG prefers a time horizon of 12 years from age 6-17 to capture all relevant costs.
Synthesis of evidence on health effects	Based on systematic review	**Partly.** Synthesis of response rates from NMA applied to calculate costs for secukinumab, etanercept and ustekinumab. ERG considers a naïve indirect comparison of response rates vs. adalimumab and a scenario where all response rates are equal across treatments.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the	**Yes.** The cost comparison case includes treatment acquisition costs for secukinumab and comparators, which

	prices relevant to the NHS and PSS	were appropriately sourced from the BNFc.[41] However, - Ustekinumab 90mg was not correctly costed, assuming a list price = twice that of 45mg. However, BNFc shows that the correct list price for both the 45mg and 90mg doses is £2,147.[42]. Furthermore, the recommended dose of ustekinumab is 45mg for all patients weighing 60-100kg and 90mg for patients who weigh ≥100kg (table 35, page 119, CS). No patients in the company's model weigh more than 100kg, therefore it is inappropriate for any patients to receive the 90mg dose in this context. - The model does not include any adverse event or monitoring costs. However, the ERG considers this to be acceptable because patient management and AE profiles are similar for all the treatments under consideration.
Discounting	Discounting is not required for a cost-comparison FTA.	**Yes.** Company base case is appropriate, and a 3.5% discount rate is applied in sensitivity analysis.
AE, Adverse events; FTA, fast track appraisal; PSS, personal social services		

4.2.2 Model structure

The company developed a simple model which compares the treatment acquisition costs of secukinumab, etanercept and ustekinumab in patients aged 6-17 years old. Adalimumab was added as a comparator scenario in response to clarification queries. The different treatment arms are modelled independently. Patients are assumed to incur treatment acquisition costs only for the period of which they are receiving the index treatment. It is assumed that once treatment is discontinued for any reason, no further treatment acquisition costs are incurred, and the patient is not assumed to move onto other treatments in the pathway. In the first year of the model, treatment discontinuation is assumed to be due to non-response to treatment, based on PASI-75 response rates obtained from the NMA at 12/16 weeks. For years two onwards, discontinuation is assumed to be 20% per year for all treatment

arms. There are two key limitations to the company's simplified modelling approach.

The first uncertainty relates to the assumption of 20% discontinuation annually for all treatments. The annual treatment discontinuation rate used in the company's base case analysis was obtained from NICE TA455 where the assessment report (page 164) lists the all-cause withdrawal rate as including lack of efficacy, presence of adverse events, non-compliance to treatment.[15] TA455 also acknowledges this parameter to be highly uncertain, especially in children as there is limited evidence to inform longer term treatment withdrawals. The ERG notes that the NIHR report associated with TA455 supports the 20% withdrawal rate. The NIHR report cites a study which used the BADBIR registry data and found drug survival of biologic therapies in adults to reduce from 77% in the first year to 53% in the third year which is approximate to assuming a 20% all-cause treatment discontinuation rate per year.[43] Furthermore, the NIHR report noted that there was no significant predictive relationship between age and treatment continuation in the child-CAPTURE and DERMBIO registry data which indicates that the adult data within the BADBIR registry could be extrapolated to children and young people. However, the ERG's clinical expert felt that a loss of response to secukinumab, once achieved was rare, and that the 20% withdrawal rate may be an overestimate based on the evidence. The ERG's clinical expert also notes that in practice, their experience is that ustekinumab tends to have lower withdrawal rates than etanercept or adalimumab. Evidence from CAIN457A2310 trial provided from the company at clarification stage (Company clarification response, page 23) suggests that not only is the assumed rate far higher than that observed in the trial, the all cause withdrawal is differential by treatment allocation between secukinumab and etanercept.[30] At 52 weeks post-randomisation, 2.5% and 14.6% of secukinumab and etanercept patients, who achieved PASI-75 response at week 12, had withdrawn due to any cause. However, data from the studies included in the NMA provided no comparable data for ustekinumab and adalimumab. Therefore, long-term adverse event withdrawal data presented in the NIHR report from the CADMUS (ustekinumab) and M04-

717(adalimumab) studies was used.[37, 40] These studies reported no withdrawals due to adverse events in the standard dosing arms so a rate of 0% was assumed. Given that withdrawal due to any cause was not reported in these studies, it is likely that this is an underestimation. The ERG, therefore, considers several different treatment specific withdrawal rates, described in Table 23 below, to explore this uncertainty. Table 23. Alternative annual treatment withdrawal rates for use in the model.

Table 23. Alternative annual treatment withdrawal rates for use in the model.

Scenario	Secukinumab	Etanercept	Ustekinumab	Adalimumab
Company BC	20%	20%	20%	20%
Assume responders remain on treatment	0%	0%	0%	0%
Short term data from trials extrapolated annually [A]	[redacted]	[redacted]	0%[A]	0%[A]

[A] 0 withdrawals due to AE reported in long term follow up of CADMUS and M04-717 trials in standard dosing arms (Table 12, page 26, Table 30 page 41)[21]

The second uncertainty regards the limitation that patients who discontinue treatment do not progress to other treatments to manage their condition, and thus accrue a £0 cost of treatment which is unlikely to reflect clinical practice. Furthermore, the assumption generates results with questionable face validity, whereby treatments with lower PASI-75 response rates are more likely to be cost saving. The ERG considers this to be counter intuitive. Whilst the choice of subsequent treatments is highly uncertain and the effectiveness for 2nd and subsequent rounds of treatment is uncertain, the ERG still considers it relevant to attempt to consider these costs for decision making. The ERG clinical expert advises that upon treatment discontinuation, the patient would normally receive an alternative biologic treatment. The ERG considers a scenario whereby patients discontinuing treatment receive one of the other biologics (etanercept, ustekinumab or adalimumab), according to the weighted

average market share assumed by the company. This assumes that all biologics have the same response rate on 2nd and subsequent rounds of treatment, which is a simplifying assumption, based on the ERG's expert opinion, in the absence of alternative data.

4.2.3 Population

Children and young people (aged 6-17) with moderate to severe plaque psoriasis (PASI≥10) who have failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated. This is mostly in line with the previous NICE recommendation TA455 for the comparators in this submission. However, the ERG notes that NICE (TA455) only recommends ustekinumab for patients aged 12 years and older in this population.

4.2.4 Interventions and comparators

Intervention

Secukinumab is included in the model as a low or high dose regimen, where patients receive a subcutaneous injection weekly for the first 5 doses then monthly thereafter. All patients weighing <50kg receive 75mg per dose, and those ≥50kg receive 150mg (low dose). Patients who weigh ≥50kg and achieve PASI 50-74 at week 12 receive an increase in dosage to 300mg where patients are reassessed for PASI-75 response at week 24. Patients receive treatment until non-response or withdrawal due to any cause.

Comparators

The company considers etanercept and ustekinumab to be the relevant comparators for this assessment and assume dosing regimens as described in the BNFC.[42, 44] Patients receive treatment until non-response or withdrawal due to any cause. The inclusion of etanercept and ustekinumab as comparators is consistent with the NICE scope, TA455 and the NMA presented in the CS. However, the ERG note that the company did not consider adalimumab to be a relevant comparator for this assessment because:

1. **NICE guidance notes for cost-comparison FTA's allows for the use of a subset of comparators with precedence from TA521 (table 1, page 10, Document B of CS). The cost-comparison TA521 assessed guselkumab versus adalimumab and ustekinumab for treating moderate to severe plaque psoriasis in adults.**[28] The ERG accepts that the company are permitted to select the most appropriate comparator from those currently recommended by NICE, but consider adalimumab to be the most appropriate comparator because; it is widely used in clinical practice, is available as a generic low cost treatment, and consumes a significant market share (50%).

   The ERG clinical expert and FAD for TA455 state that treatment would start with the lowest cost option, adalimumab is the least costly comparator in terms of treatment acquisition costs. Furthermore, the ERG notes that the company has chosen to compare secukinumab with the most expensive (ustekinumab) and least effective (etanercept) treatment options available, and this may overestimate the potential cost savings in this population. To include adalimumab, especially in the 6-11 age group where ustekinumab is not recommended by NICE, would give a more representative view of the cost savings that may be realised upon a positive recommendation of secukinumab.

2. **It was not possible to include adalimumab within the network due to a lack of placebo comparator in trials conducted in the paediatric population.** The ERG does not consider this to be a sufficient justification for the exclusion of adalimumab as a comparator. It is only necessary to show that the new treatment under consideration is likely to be at least as effective as the chosen comparator, and this could be achieved in a number of ways, either by utilising adult data within a network as was done for TA455, or through a naïve indirect comparison, as the ERG have reported in Chapter 3, which shows similar PASI-75 responses for adalimumab and secukinumab for the lower weight categories. The ERG does not consider the exclusion of

adalimumab due to the inability to connect it to the NMA network as a sufficient reason to exclude it as a comparator.

3. **There is a paucity of evidence of adalimumab compared to placebo in the paediatric population which was also highlighted in TA455 (see table 1, page 10, Document B of CS).[15]** The ERG accepts that this is true. However, adalimumab has marketing authorisation for treatment in children, which was obtained from a clinical trial comparing adalimumab with methotrexate. Therefore, the ERG does not consider it correct to assume that there is insufficient evidence to support the use of adalimumab in the paediatric population. A detailed comparison of the available adalimumab clinical evidence has been provided in Chapter 3.

4.2.5 Perspective, time horizon and discounting

The model reports costs in one-year increments, over a 5-year time horizon in the base case analysis. The model includes functionality to increase the time horizon up to age 18, and a scenario analysis reflecting this was provided by the company. Under the company approach, just 24% of patients who receive secukinumab treatment in year 1 at age 6 would remain on secukinumab for the full 5-year time horizon. Costs were not discounted in the model, which is in line with NICE guidance.[45]

4.2.6 Treatment effectiveness and extrapolation

The company's cost comparison model allows costs to depend on the PASI-75 response rates at 12 / 16 weeks for secukinumab and comparators based on the results of the NMA (see chapter 3 for further details of the NMA). The response rates are used to calculate the proportion of patients who discontinue treatment (1- treatment specific response rate) during the first year of the model. These rates can be found in table 34, page 117 of the company submission. The ERG's clinical expert confirms that PASI-75 is the most commonly considered definition of treatment response in clinical practice and is therefore relevant for decision making. It is also consistent with the measure of response used in the relevant clinical trials (for etanercept,

ustekinumab and adalimumab) and is the clinical effectiveness measure used to inform economic modelling and derivation of QALYs as part of TA455. Therefore, the ERG is confident that the outcome measures used for the cost-comparison case presented in the company's submission are consistent with those used for the NICE recommended comparators. The company has provided scenario analyses assuming equal response rates for all treatments.

The ERG notes that in response to clarification the company provided a scenario analysis where adalimumab was included in the cost-comparison on the assumption that its effectiveness was equal to ustekinumab. The ERG accepts that this is a simplifying assumption, but is consistent with the NICE AC's conclusions for TA455 concluded that the effectiveness of ustekinumab and adalimumab were broadly similar.[15] However, the ERG has identified a randomised controlled trial which compares adalimumab with methotrexate in the paediatric population (M04-717). The study was identified by the company's searches, but could not be included in their NMA as all other trials in the network compared against placebo, not methotrexate.[40] The ERG, prefers the use of the adalimumab arm from the M04-717 study to inform a naïve indirect comparison of adalimumab versus the other potential comparators to populate the cost-comparison model. A comparison of the company and ERG preferred response rates for use in the economic model are summarised in Table 24.

Table 24. PASI-75 response rates used in the economic model

Definition:	Secukinumab				Etanercept	Ustekinumab	Adalimumab
	<25 kg	25-50kg	≥50kg (Low dose)	≥50kg (High dose)			
Company preferred	[redacted]	[redacted]	[redacted]	[redacted]	64.6%	87.1%	-
Company base case (with adalimumab included)	[redacted]	[redacted]	[redacted]	[redacted]	64.6%	87.1%	87.1%[A]
ERG preferred	[redacted]	[redacted]	[redacted]	[redacted]	64.6%	87.1%	57.9%[B]

[A] The assumption of equal efficacy of adalimumab to ustekinumab was proposed by the ERG and executed by the company at the clarification stage. This was suggested as the committee in TA455 concluded that adalimumab and ustekinumab were of broadly similar effectiveness.(15)

[B] Taken from a naïve indirect comparison of adalimumab from study M04-717.(40) See Chapter 3, Table 17, for further information.

4.2.8 Resources and costs

Treatment acquisition costs

The PAS inclusive cost of secukinumab 150mg solution for injection is [redacted] representing a [redacted] reduction on the list price of £609.39. Etanercept is costed in the company model as the cheapest available biosimilar from the BNF, with a list price for 25mg / 0.5ml solution for injection in pre-filled syringes (Benepali®) of £328.00 for a pack of 4, or £82 per 25mg dose. Details of a confidential CMU price for etanercept are provided in a confidential appendix. Ustekinumab, 45mg solution for injection has a list price of £2,147.00. The company's cost-comparison model assumes that patients who require 90mg of ustekinumab (i.e. weight ≥100 kg) would incur twice the cost of a 45mg dose. However, inspection of the BNFc indicates that both the 45mg and 90mg doses of ustekinumab incur the same list price per vial (£2,147). Furthermore, the recommended dose of ustekinumab is 45mg for all patients weighing 60-100kg and 90mg for patients who weigh ≥100kg (table 35, page 119, CS). No patients in the company's model weigh more than 100kg, therefore it is inappropriate that any patients to receive the 90mg dose in this context. The ERG notes that assuming all patients receive the 45mg dose of ustekinumab in the model reduces the cost savings for secukinumab compared to ustekinumab, but the reduction is not sufficiently large to change overall conclusions. Adalimumab was included by the company in response to clarification queries at a cost of £68.27 for a 20mg dose, sourced from an NHS England letter which is publicly available.[46]

Treatment acquisition costs for a course of treatment depend on treatment price, dosages by weight, dosing frequency, treatment withdrawal rate (beyond year 1), and treatment response rates (i.e. PASI 75) in year 1, which impacts on the duration of treatment and hence the number of doses in a course of treatment. Total treatment acquisition costs (excluding any concomitant treatments or other resource use) for a one-year course of treatment, assuming a PASI 75 response is achieved, with no withdrawals for other reasons, are provided in Table 25 below for illustration. This illustration represents the treatment acquisition cost for one full year of treatment with all three comparator drugs and adalimumab, for which data were provided by the company at the clarification stage. For information, treatment acquisition costs are provided for four different patient weights (25kg, 40kg, 50kg,

75kg and 100kg) to illustrate the impact of weight-based dosing on results. The treatment acquisition cost for a full year of treatment for a responding patient on secukinumab is lower than both etanercept and ustekinumab. However, a full year's treatment cost on secukinumab is more expensive than adalimumab for the weight categories described below, which was included in the final scope for this assessment. The ERG notes that the treatment acquisition cost of adalimumab is higher than secukinumab for patients weighing between 30-50kg as secukinumab patients would continue to receive 75mg dose up to 50kg, whereas adalimumab patients would move onto the 40mg dose at 30kg.

Table 25. Treatment acquisition cost for one full year of continuous treatment

	Secukinumab (Year 1)	**Secukinumab (Years 2+)**	**Etanercept**	**Ustekinumab**	**Adalimumab**
Unit cost	[redacted]	[redacted]	£82.00	£2,147.00	£68.27
Per x mg	*150*	*150*	*25*	*45*	*20*
Dosage (25 kg)	75	75	20	19	20
Dosage (50 kg)	150	150	40	38	40
Dosage (75 kg)	150	150	50	45	40
Dosage (100 kg)	150	150	50	90[B]	40
Cost per dose (25 kg), with wastage	[redacted]	[redacted]	£82.00	£2,147.00	£68.27
Cost per dose (50 kg), with wastage	[redacted]	[redacted]	£164.00	£2,147.00	£136.54
Cost per dose (75 kg), with wastage	[redacted]	[redacted]	£164.00	£2,147.00	£136.54
Cost per dose (100 kg), with wastage	[redacted]	[redacted]	£164.00	£2,147.00	£136.54
Doses per year	16[A]	12	52	5	27
Acquisition cost for 1 year (25 kg)	[redacted]	[redacted]	£4,264.00	£10,735.00	£1,775.00
Acquisition cost for 1 year (50 kg)	[redacted]	[redacted]	£8,528.00	£10,735.00	£3,550.00
Acquisition cost for 1 year (75 kg)	[redacted]	[redacted]	£8,528.00	£10,735.00	£3,550.00
Acquisition cost for 1 year (100 kg)	[redacted]	[redacted]	£8,528.00	£10,735.00	£3,550.00

[A] Company adjusts exact annual dosage to reflect monthly usage, resulting in just over 16 doses per year on average, leading to calculated treatment acquisition costs in the company model of [redacted] for a full years treatment among responders for low dose (150mg secukinumab).

[B] Ustekinumab 90mg was costed as 2 x 45mg doses in the company submission. However, the BNFc indicates that both the 45mg and 90mg doses incur the same list price cost (£2,147 per vial).[42]

The ERG has cross-checked the dosing schedules, including recommended dosing and frequency of treatment administration against the relevant SmPCs in children and cross checked these against the BNFc dosing recommendations.[17-19, 27, 42, 44, 47, 48] The ERG is satisfied that the company has adopted all dosing and frequency schedules used in TA455 which were accepted by the committee. The ERG note however, that the SmPC for etanercept states that, for the paediatric population with plaque psoriasis: "The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks".[18] The SmPC also notes that repeat treatment courses may be considered. The ERG's clinical expert opinion is that, in clinical practice, the dosing schedule modelled by the company for etanercept is appropriate, and that paediatric patients would not be routinely removed from etanercept treatment at 24 weeks if they are continuing to achieve a response.

The additional costs of needles and syringes will be negligible if pre-filled vials are used. ERG expert opinion is that vial sharing does not occur within the NHS and that each vial would be used for a maximum of one dose only. ERG calculations presented above assume vial wastage for all treatments and the availability of 75mg / 150mg vials for secukinumab, 25mg vials for etanercept and 45mg / 90mg vials for ustekinumab.

Other costs (monitoring and adverse events)

The company's model considers only treatment acquisition costs and assumes that the administration and monitoring costs per injection are the same across all treatments considered. The ERG's clinical expert agrees that there are unlikely to be any differences in monitoring costs and it is reasonable to assume similar healthcare resource use across the comparators. However, the ERG would note that because etanercept is administered more frequently, and in cases where parents or children may have difficulty with administering / self-administering injections, there is a risk that any contact with secondary care might be greater for etanercept than for

treatments that require administration less frequently. The ERG is therefore confident that the administration / monitoring costs for secukinumab are likely to be similar to, or lower than etanercept. Any bias through the omission of administration / monitoring costs is likely to bias against secukinumab.

The company's cost-comparison model also assumes that there are no differences in AE costs between treatment arms. The ERG considers the assumption to be reasonable and notes that there is no evidence to suggest differential adverse events between the treatments. Furthermore, the ERG's clinical expert is of the opinion that the overall incidence and types of adverse events for secukinumab were within expected ranges and comparable to relevant biological therapies.

Overall, the ERG's clinical expert considers that the assumptions about monitoring and adverse event costs used in the company's cost-comparison model are reflective of UK clinical practice. The ERG can also confirm that whilst monitoring costs were included in TA455, they were assumed to be equal across all comparators, and their inclusion would not impact on the results of the company's cost comparison analysis. Adverse event costs were not considered included in TA455 due to a paucity of information (no statistically significant differences and short follow up). Therefore, the ERG is satisfied that the exclusion of adverse events costs from the cost-comparison analysis is reasonable and is also consistent with the approach taken in TA455.

5 COST-COMPARISON RESULTS

5.1 Company's cost comparison results

The company provided cost-comparison results for secukinumab compared to either etanercept or ustekinumab in their original submission (Tables 39 to 42 of the company submission). The inclusion of adalimumab as a comparator was added as a scenario in response to ERG clarification queries. Table 26 details all the company reported analyses, sourced from both the original submission and response to clarification queries. The ERG would have preferred all model amendments to be implemented as switches for ease of replication, but the ERG is broadly satisfied that the scenarios provided by the company are correct. The ERG notes that in all scenarios provided by the company, both in the original submission and in response to clarification queries, secukinumab generates substantial cost savings compared to both etanercept and ustekinumab. However, the magnitude of cost-savings in the company's base case model are substantially lower in the scenario where secukinumab is compared with adalimumab. This scenario assumes that adalimumab is equally effective (PASI-75 response) to ustekinumab. As the company model favours less clinically effective treatments in terms of cost, the magnitude of cost savings compared to adalimumab is likely substantially lower if PASI-75 response data from the M04-717 study is used as a naïve indirect comparison. This is presented as a scenario in Table 27, Chapter 6. The ERG notes that the company have not replicated the full set of scenario analyses with adalimumab included as a comparator. The ERG also provides this information in Chapter 6.

Table 26. Replication of company scenario analyses for secukinumab vs. etanercept and ustekinumab (reproduced from tables 40-41 of the CS and Tables 9, 10 and 12 of the company's response to clarification queries)

	Incremental costs (secukinumab vs. etanercept)	Incremental costs (secukinumab vs. ustekinumab)	Incremental costs (secukinumab vs. adalimumab)
Analyses from company original submission			
Base case	[redacted]	[redacted]	NR
Age 6-11 subgroup	[redacted]	[redacted]	NR
Age 12-17 subgroup	[redacted]	[redacted]	NR
Time horizon: up to 18 years	[redacted]	[redacted]	NR
Discount rate: 3.5%	[redacted]	[redacted]	NR
NMA including Trial A2311	[redacted]	[redacted]	NR
High dose response: 0% (bookend)	[redacted]	[redacted]	NR
High dose response: 100% (bookend)	[redacted]	[redacted]	NR
Efficacy of all comparators set to the low-dose, PASI-75 of all weight categories for secukinumab [redacted]	[redacted]	[redacted]	NR
Vial wastage excluded	[redacted]	[redacted]	NR
Withdrawal rate: 10%	[redacted]	[redacted]	NR
Withdrawal rate: 30%	[redacted]	[redacted]	NR
Analyses in response to clarification queries[A]			
Base case + including adalimumab as a comparator	[redacted]	[redacted]	[redacted]
Assume equivalent efficacy across all weight categories for secukinumab [redacted] [B]	[redacted]	[redacted]	NR

Table 26. Replication of company scenario analyses for secukinumab vs. etanercept and ustekinumab (reproduced from tables 40-41 of the CS and Tables 9, 10 and 12 of the company's response to clarification queries)

	Incremental costs (secukinumab vs. etanercept)	Incremental costs (secukinumab vs. ustekinumab)	Incremental costs (secukinumab vs. adalimumab)
Assume no patients on secukinumab transition to the higher 300mg dose	[redacted]	[redacted]	NR
Assuming all patients aged 12-17 weigh at least 50kg	[redacted]	[redacted]	NR
Increase all patient weight by 20%	[redacted]	[redacted]	NR

Abbreviations: NMA: network meta-analysis.

[A] Note that the ERG requested scenario analyses with treatment specific discontinuation rates from the trials. However, the company stated this was not possible because a treatment specific rate for ustekinumab was not available. The ERG conducts additional scenarios in Chapter 6.

[B] The ERG was not able to fully replicate these scenarios as functionality was not included in the model using switches, meaning it was not explicitly clear what model cells / what approach was used to implement the scenarios. However, in all cases the ERG's attempt to implement the noted scenarios resulted in minor differences to those reported by the company (less than £100 difference in incremental costs in all cases), and so has no meaningful impact on conclusions.

5.2 Model validation and face validity check

The ERG has conducted several black-box checks of model formulae to test the validity of the cost-comparison model's functionality (e.g. equalising all response rates and withdrawal rates, setting all probabilities to 1, setting all costs to £0). The ERG is satisfied that the company's cost-comparison model generates accurate estimates of incremental costs for secukinumab vs. the comparators.

However, the ERG has identified one potential error in the model's parameterisation. The costs of ustekinumab 90mg are assumed to be equal to the cost of 2 x 45mg vials, leading to treatment acquisition costs of £2,147 x 2 = £4,294 per 90mg dose. However, upon inspection of the BNF for children, the cost of a 90mg dose of

ustekinumab appears to be equal to the 45mg vial. Furthermore, the recommended dose of ustekinumab is 45mg for all patients weighing 60-100kg and 90mg for patients who weigh ≥100kg (table 35, page 119, CS). No patients in the company's model weigh more than 100kg, therefore it is inappropriate that any patients to receive the 90mg dose in this context. The implication is that the company appear to have over costed the treatment acquisition costs for ustekinumab. However, the magnitude of the error on incremental costs is not large because only a small proportion of patients, and only in the older age groups, are modelled to receive the higher 90mg dose, and the error is not sufficient to change base case conclusions (See Chapter 6).

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Additional analyses undertaken by the ERG

The ERG has re-produced all the company's scenario analyses from the original company submission and response to clarification queries, with adalimumab included as a comparator. The company's approach is to include adalimumab assuming it achieves equal PASI-75 response rates at 16 weeks to ustekinumab as the committee in TA455 concluded that they are similar in terms of effectiveness.[15] The results are provided in Table 27 below for the committee's information. In all but two scenarios, secukinumab remains cost saving compared to adalimumab. In the subgroup of patients aged 12-17, secukinumab is more costly than adalimumab under the company base case assumptions. The differential results by age subgroup is likely due to the higher secukinumab PASI-75 response rate in older children, and thus a lower proportion of patients discontinuing treatment leading to increased treatment acquisition costs in the older subgroup. Secukinumab is also more costly in a scenario where weight is increased by 20% above base case values.

Table 27. Replication of company scenario analyses for secukinumab vs. adalimumab (adapted from Tables 40-41 of the CS and Tables 9, 10 and 12 of the company's response to clarification queries)

Scenario	Incremental costs (secukinumab vs. adalimumab)
Analyses from company original submission	
Base case	[redacted]
Age 6-11 subgroup	[redacted]
Age 12-17 subgroup	[redacted]
Time horizon: (12 years, up to age 18)	[redacted]
Discount rate: 3.5%	[redacted]
NMA including Trial A2311	[redacted]
High dose response: 0% (bookend)	[redacted]
High dose response: 100% (bookend)	[redacted]
Efficacy of all comparators set to the low-dose, PASI-75 of all weight categories for secukinumab [redacted]	[redacted]
Vial wastage excluded	[redacted]
Withdrawal rate: 10%	[redacted]
Withdrawal rate: 30%	[redacted]
Analyses in response to clarification queries	
Assume equivalent efficacy across all weight categories for secukinumab [redacted] [A]	[redacted]
Assume no patients on secukinumab transition to the higher 300mg dose	[redacted]
Assuming all patients aged 12-17 weigh at least 50kg	[redacted]
Increase all patient weight by 20%	[redacted]

[A] The ERG was not able to fully replicate this scenario because functionality was not included in the model using switches, meaning it was not explicitly clear what model cells / what approach was used to implement the scenario. However, the ERG is satisfied that the discrepancy between the ERG and company approach is minor and does not impact on conclusions.

6.2 ERG's preferred assumptions

Following on from the critique of the company's submission provided in chapter 4, the ERG's preferred set of assumptions, together with a justification for these assumptions is provided below.

- ERG prefers to assume that all patients, regardless of age, receive a 45mg dose of ustekinumab consistent with the dosing regimen described table 35, page 199 of the CS and the BNF for children[42]
- ERG prefers the inclusion of adalimumab as a comparator because adalimumab:
    - consumes the largest market share as per the company's budget impact analysis,
    - was recommended by NICE as part of TA455,
    - is available as a generic equivalent off patent,
    - is commonly used in clinical practice and
    - can be included in the model with response rates obtained from a naïve indirect comparison in the paediatric population[40]
- ERG prefers the use of a naïve indirect comparison for adalimumab, using response rates from the M04-717 trial.
- ERG prefers a 12-year time horizon as opposed to company 5-year time horizon in order to follow patients until they are age 18.

The impact on the incremental costs for secukinumab compared to etanercept, ustekinumab and adalimumab are provided in tables 28-30 below for the full population (6-17 age group), 6-11 age group and 12-17 age group respectively.

Table 28. ERG's preferred cost-comparison model assumptions (Full population 6-17 years)

Preferred assumption	Section in ERG report	Incremental costs vs. etanercept	Incremental costs vs. ustekinumab	Incremental costs vs. adalimumab
ERG preferred assumptions				
Company base-case		[redacted]	[redacted]	[redacted]
All participants receive 45mg dosage regimen of ustekinumab equal to £2,147 per vial	*4.2.1*	[redacted]	[redacted]	[redacted]
PASI-75 response rates for adalimumab from M04-717 study[40]	*4.2.6*	[redacted]	[redacted]	[redacted]
12- year time horizon, up to age 18	*4.2.1*	[redacted]	[redacted]	[redacted]
ERG preferred base case		[redacted]	[redacted]	[redacted]
Additional scenario analyses applied to ERG preferred base case				
0% all cause annual withdrawal rate for all treatments	*4.2.2*	[redacted]	[redacted]	[redacted]
Withdrawal rates reported in clinical trials (see table 23, section 4.2.2)	*4.2.2*	[redacted]	[redacted]	[redacted]
12/16-week PASI-75 response rates equal to 100% for all comparators	*4.2.2*	[redacted]	[redacted]	[redacted]
Inclusion of subsequent lines of biologic treatment	*4.2.2*	[redacted]	[redacted]	[redacted]

Table 29. ERG's preferred cost-comparison model assumptions (6-11 years)

Preferred assumption	Section in ERG report	Incremental costs vs. etanercept	Incremental costs vs. ustekinumab	Incremental costs vs. adalimumab
ERG preferred assumptions				
Company base-case		[redacted]	[redacted]	[redacted]
All participants receive 45mg dosage regimen of ustekinumab equal to £2,147 per vial	*4.2.1*	[redacted]	[redacted]	[redacted]
PASI-75 response rates for adalimumab from M04-717 study[40]	*4.2.6*	[redacted]	[redacted]	[redacted]
12- year time horizon	*4.2.1*	[redacted]	[redacted]	[redacted]
ERG preferred base case		[redacted]	[redacted]	[redacted]
Additional scenario analyses applied to ERG preferred base case				
0% all cause annual withdrawal rate for all treatments	*4.2.2*	[redacted]	[redacted]	[redacted]
Withdrawal rates reported in clinical trials (see table X, section 4.2.2)	*4.2.2*	[redacted]	[redacted]	[redacted]
12/16-week PASI-75 response rates equal to 100% for all comparators	*4.2.2*	[redacted]	[redacted]	[redacted]
Inclusion of subsequent lines of biologic treatment	*4.2.2*	[redacted]	[redacted]	[redacted]

Table 30. ERG's preferred cost-comparison model assumptions (12-17 years)

Preferred assumption	Section in ERG report	Incremental costs vs. etanercept	Incremental costs vs. ustekinumab	Incremental costs vs. adalimumab
ERG preferred assumptions				
Company base-case		[redacted]	[redacted]	[redacted]
All participants receive 45mg dosage regimen of ustekinumab equal to £2,147 per vial	*4.2.1*	[redacted]	[redacted]	[redacted]
PASI-75 response rates for adalimumab from M04-717 study[40]	*4.2.6*	[redacted]	[redacted]	[redacted]
12- year time horizon	*4.2.1*	[redacted]	[redacted]	[redacted]
ERG preferred base case		[redacted]	[redacted]	[redacted]
Additional scenario analyses applied to ERG preferred base case				
0% all cause annual withdrawal rate for all treatments	*4.2.2*	[redacted]	[redacted]	[redacted]
Withdrawal rates reported in clinical trials (see table X, section 4.2.2)	*4.2.2*	[redacted]	[redacted]	[redacted]
12/16-week PASI-75 response rates equal to 100% for all comparators	*4.2.2*	[redacted]	[redacted]	[redacted]
Inclusion of subsequent lines of biologic treatment	*4.2.2*	[redacted]	[redacted]	[redacted]

6.3 Conclusions of the cost comparison section

The company submission demonstrates that secukinumab offers substantial cost savings compared to etanercept and ustekinumab in all patient subgroups between the ages of 6-17 in this indication. This finding is robust to a range of scenario analyses undertaken by both the company (Chapter 5) and the ERG (Chapter 6).

However, there is greater uncertainty surrounding the cost saving case for secukinumab compared to adalimumab. Adalimumab has a lower treatment acquisition cost for a full year of treatment among responders (apart from the 30kg-50kg weight category) and has lower costs than secukinumab in the company's and ERG's base case analysis for the subgroup of the population aged 12-17. In the ERG's preferred base case analysis for the full population, secukinumab is [redacted] more costly compared to adalimumab. This is primarily driven by the lower PASI-75 response rates for adalimumab and a longer time horizon over which adalimumab cost savings can accrue in the ERG's base case assumptions.

In order to explore the uncertainty of the model bias towards less efficacious treatments (patients who discontinue treatment incur £0 cost for the remaining model time horizon), the ERG explored several scenarios. Importantly, the inclusion of treatment costs of remaining biologics following first line treatment discontinuation (according to their assumed market share) leads to secukinumab being cost saving in all populations.

Across the range of plausible scenarios explored by the ERG, secukinumab offers substantial cost savings to the comparators ustekinumab and etanercept. However, the magnitude of the incremental cost of secukinumab compared to adalimumab ranges from between [redacted] (0% all cause annual withdrawal rate for all treatments) to [redacted] (Inclusion of subsequent lines of biologic treatment) in the full population (6-17 age group).

7 References

1. Lebwohl M. Psoriasis. Lancet. 2003;361(9364):1197-204.

2. Boehncke WH, Schön MP. Psoriasis. Lancet. 2015;386(9997):983-94.

3. Chiricozzi A. Psoriasis 2020. Available from: https://bestpractice.bmj.com/topics/en-gb/74 (Accessed 17 January 2020).

4. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826-50.

5. Prieto-Pérez R, Cabaleiro T, Daudén E, Ochoa D, Roman M, Abad-Santos F. Genetics of psoriasis and pharmacogenetics of biological drugs. Autoimmune Dis. 2013;2013:613086.

6. Pușcaș AD, Cătană A, Pușcaș C, Roman, II, Vornicescu C, Șomlea M, et al. Psoriasis: Association of interleukin-17 gene polymorphisms with severity and response to treatment. Exp Ther Med. 2019;18(2):875-80.

7. Lønnberg AS, Zachariae C, Skov L. Targeting of interleukin-17 in the treatment of psoriasis. Clin Cosmet Investig Dermatol. 2014;7:251-9.

8. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-85.

9. Augustin M, Glaeske G, Radtke MA, Christophers E, Reich K, Schäfer I. Epidemiology and comorbidity of psoriasis in children. Br J Dermatol. 2010;162(3):633-6.

10. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. Arch Dermatol. 2005;141(12):1537-41.

11. Paller AS, Siegfried EC, Langley RG, Gottlieb AB, Pariser D, Landells I, et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med. 2008;358(3):241-51.

12. National Institute for Health and Care Excellence. Psoriasis: assessment and management [CG153] 2012. Available from: https://www.nice.org.uk/guidance/cg153 (Accessed 18 January 2020).

13. European Medicines Agency. Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis 2004. Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-

clinical-investigation-medicinal-products-indicated-treatment-psoriasis_en.pdf (Accessed 6 January 2021).

14. Lavaud J, Mahé E. [Severity scores for childhood psoriasis: A systematic literature review]. Ann Dermatol Venereol. 2019;146(12):771-82.

15. National Institute for Health and Care Excellence. Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people [TA455] 2017. Available from: https://www.nice.org.uk/guidance/ta455 (Accessed March 2021).

16. Lebwohl M. A clinician's paradigm in the treatment of psoriasis. J Am Acad Dermatol. 2005;53(1 Suppl 1):S59-69.

17. European Medicines Agency. Adalimumab summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/humira (Accessed 21 April 2020).

18. European Medicines Agency. Etanercept summary of product characteristics 2009. Available from: https://www.ema.europa.eu/documents/product-information/enbrel-epar-product-information_en.pdf (Accessed 18 September 2020).

19. European Medicines Agency. Ustekinumab summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf (Accessed March 2021).

20. European Medicines Agency. Summary of opinion (post authorisation) Stelara ustekinumab. Amsterdam; 2019. Report No.: EMA/CHMP/645416/2019. Available at: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-stelara-ii-73_en.pdf.

21. Duarte A, Mebrahtu T, Goncalves PS, Harden M, Murphy R, Palmer S, et al. Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people: systematic review and economic evaluation. Health Technol Assess. 2017;21(64):1-244.

22. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis [TA350] 2015. Available from: https://www.nice.org.uk/guidance/ta350 (Accessed March 2021).

23. European Commission. Union Register of medicinal products for human use: Cosentyx 2015. Available from: https://ec.europa.eu/health/documents/community-register/html/h980.htm (Accessed 21 April 2021).

24. European Commission. COMMISSION IMPLEMENTING DECISION of 31.7.2020 amending the marketing authorisation granted by Decision C(2015)203(final) for “Cosentyx - secukinumab”, a medicinal product for human use. Brussels; 2020. Available at: https://ec.europa.eu/health/documents/community-register/2020/20200731148746/dec_148746_en.pdf.

25. European Medicines Agency. Summary of opinion (post authorisation) Cosentyx secukinumab. Amsterdam; 2020. Contract No.: EMA/CHMP/171152/2020. Available at: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-cosentyx-ii-57_en.pdf.

26. National Institute for Health and Care Excellence. Secukinumab for treating plaque psoriasis in children and young people Final scope. London/Manchester; 2020.

27. European Medicines Agency. Secukinumab summary of product characteristics. Amsterdam; 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/cosentyx-epar-product-information_en.pdf.

28. National Institute for Health and Care Excellence. Guselkumab for treating moderate to severe plaque psoriasis [TA521] 2018. Available from: https://www.nice.org.uk/guidance/ta521 (Accessed March 2021).

29. Novartis Pharmaceuticals. CAIN457A2310 Clinical Study Report Week 24 Analysis [Data on file]. E. Hanover, USA; 2019.

30. Novartis Pharmaceuticals. CAIN457A2310 Clinical Study Report Week 52 Analysis [Data on file]. E. Hanover, USA; 2020.

31. Novartis Pharmaceuticals. CAIN457A2311 Clinical Study Report Week 24 Analysis [Data on file]. E. Hanover, USA; 2020.

32. Novartis Pharmaceuticals. CAIN457A2311 Clinical Study Report Week 52 Analysis [Data on file] E. Hanover, USA; 2020.

33. National Institute for Health and Care Excellence. Infliximab for the treatment of adults with psoriasis [TA134] 2008. Available from: https://www.nice.org.uk/guidance/TA134 (Accessed March 2021).

34. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014;371(4):326-38.

35. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015;172(2):484-93.

36. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015;29(6):1082-90.

37. Landells I, Marano C, Hsu MC, Li S, Zhu Y, Eichenfield LF, 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. J Am Acad Dermatol. 2015;73(4):594-603.

38. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking systematic reviews in health care. University of York: 2009. Available from: URL: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm.

39. Bodemer C, Kaszuba A, Kingo K, Tsianakas A, Morita A, Rivas E, et al. Secukinumab demonstrates high efficacy and a favourable safety profile in paediatric patients with severe chronic plaque psoriasis: 52-week results from a Phase 3 double-blind randomized, controlled trial. J Eur Acad Dermatol Venereol. 2021;35(4):938-47.

40. Papp K, Thaçi D, Marcoux D, Weibel L, Philipp S, Ghislain PD, 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. Lancet. 2017;390(10089):40-9.

41. Medicines Complete. Briitsh National Formulary for Chldren 2021. Available from: https://about.medicinescomplete.com/publication/british-national-formulary-for-children/ (Accessed April 2021).

42. Medicines Complete. British National Formulary for children - ustekinumab 2021. Available from: https://bnfc.nice.org.uk/drug/ustekinumab.html (Accessed March 2021).

43. Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker J, Burden AD, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-40.

44. Medicines Complete. British National Formulary for children - etanercept 2021. Available from: https://bnfc.nice.org.uk/medicinal-forms/etanercept.html (Accessed March 2021).

45. National Institute for Health and Care Excellence. User guide for company evidence submission template: Fast track appraisal: cost-comparison case [PMG32] 2017. Available from: https://www.nice.org.uk/process/pmg32/chapter/cost-comparison-analysis (Accessed 18 September 2020).

46. NHS England, NHS Improvement. Reference Prices for Adalimumab. London; 2019. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/04/reference-prices-for-adalimumab-letter.pdf.

47. Medicines Complete. British National Formulary - secukinumab 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/secukinumab.html (Accessed March 2021).

48. Medicines Complete. British National Formulary for Children - adalimumab 2021. Available from: https://bnfc.nice.org.uk/drug/adalimumab.html (Accessed March 2021).