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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL (FTA)

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

Appraisal Committee Meeting – 4 August 2021
1st Committee meeting

The following documents are made available to the Committee:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from Novartis

2. **Clarification questions and company responses**
   2a. Clarification response
   2b. Further clarification response

3. **Patient group, professional group and NHS organisation submissions** from:
   a. British Association of Dermatologists; endorsed by Royal College of Physicians
   b. Psoriasis Association
   c. Psoriasis and Psoriatic Arthritis Alliance

4. **Evidence Review Group report** prepared by Aberdeen HTA Group

5. **Evidence Review Group report – factual accuracy check**

6. **Technical briefing**

7. **Appraisal Committee Meeting presentation slides**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

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

Document B

Company evidence submission

February 2021

File name	Version	Contains confidential information	Date
ID1669 secukinumab Document B_FINAL	1.0	Yes/no	09/02/21

Contents

Tables and figures

Abbreviations

BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
CDLQI	Children's Dermatology Life Quality Index
CHAQ©	Childhood Health Assessment Questionnaire
CI	Confidence interval
DIC	Deviance information criterion
DMC	Data monitoring committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOF	End of follow-up
EOM	End of maintenance
EOT	End of treatment
ETN	Etanercept
EU	European Union
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
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
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
TCS	Topical corticosteroids
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B

WBC	White blood cell

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

B.1.1.1 Population

The submission focuses on part of the technology's marketing authorisation: children and young people from the age of 6 years with PASI ≥10 who have failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated. The full marketing authorisation is for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

The proposed position in the treatment pathway is narrower than the marketing authorisation because:

- The published National Institute for Health and Care Excellence (NICE) technology appraisal guidance for the comparators specified in the NICE scope (TA455) recommends these for a subgroup of the population in the marketing authorisation (patients with PASI ≥10 and following failure of standard systemic therapies). Therefore, a cost-comparison case can be made only for this population.

- This position is aligned with the NICE recommendation for the use of secukinumab in the treatment of moderate to severe plaque psoriasis in adults (patients with PASI ≥10 and DLQI >10 and following failure of standard systemic therapies) (1).

The submission covers the full population for the comparators, as recommended by NICE (2).

B.1.1.2 Comparator(s)

The comparators considered within the cost comparison analysis are etanercept and ustekinumab, for the reasons described below.

Direct and indirect evidence is available vs etanercept and ustekinumab, respectively.

There is head-to-head trial data comparing secukinumab with etanercept in a paediatric population (Section B.3.6.1), making it a relevant comparator for the appraisal. In the pivotal head-to-head clinical trial (A2310), secukinumab demonstrated significantly higher IGA 0 (clear)/1 (almost clear) and PASI 90 response rates at Week 12 compared with etanercept. Furthermore, secukinumab demonstrated similar PASI 100 response rates at Week 12 compared with etanercept, and over time the mean PASI score was lower with secukinumab than etanercept. PASI 90 and 100 are now regarded as clinical treatment goals for paediatric patients with psoriasis, as the aim of therapy is ultimately to achieve clear skin (3).

[redacted]

Adalimumab does not connect to the evidence network.

Adalimumab could not be connected to the evidence network due to the lack of adalimumab trial data on children and/or young people. However, a comparison vs adalimumab was not considered necessary given that in-scope comparisons vs etanercept and ustekinumab can be made using paediatric data (and remain unaffected by the inclusion of adalimumab in the star-shape network). Moreover, it is appropriate to consider a subset of comparators in a fast-track appraisal (FTA) if the intervention offers similar or greater benefits at a similar or lower cost (4).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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 (2) • the NICE recommendation for secukinumab in the treatment of adults with moderate to severe plaque psoriasis (1). Further details are provided in Section B.1.1.
Intervention	Secukinumab	As per scope	Not applicable
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 (4)), that within an FTA it is acceptable to compare against a subset of the potential comparators, taking into account response rates. o Etanercept and ustekinumab are considered relevant comparators as head-to-head trial data are available for secukinumab vs etanercept,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			[redacted]. o 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.
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).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of	A cost-comparison analysis is presented assuming a 5-year time horizon. This is considered to be of	The technology is likely to provide similar or greater health benefits at

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	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. 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.	similar or lower cost than comparator technologies for the same indication.
Subgroups to be considered	Where the evidence allows, the following subgroups will be considered: • previous use of phototherapy and systemic non-biological therapy	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 (2), but the marketing authorisation is for	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.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• 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.	individuals aged 6 years and older (5).	
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.

Abbreviations: EMA, European Medicines Agency; FTA, fast track appraisal; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index.

B.1.2 Description of the technology being appraised

Table 2 outlines the technology being appraised. The summary of product characteristics (SmPC) and European public assessment report (EPAR) are provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Secukinumab (Cosentyx®)
Mechanism of action	Secukinumab is a high-affinity, recombinant, fully human monoclonal antibody that binds to and neutralises the activity of the proinflammatory cytokine IL-17A. IL-17A is the central lymphokine of a subset of inflammatory T cells, the Th17 cells, which, in several animal models, are pivotal in several autoimmune and inflammatory processes. IL-17A is mainly produced by memory effector CD4+ and CD8+ T lymphocytes. IL-17A is one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases, including PsO, PsA, nr-axSpA and AS. In PsO, IL-17 induces the expression and release of psoriasis-related proteins from keratinocytes, resulting in an inflammatory response that manifests as the symptoms of PsO. Neutralisation of IL-17 treats the underlying pathophysiology of the disease, and provides relief of symptoms. Currently, no IL-17A inhibitors are recommended by NICE for the treatment of moderate to severe plaque psoriasis in children and young people. The availability of secukinumab would offer a treatment option with an alternative mechanism to existing NICE-recommended treatments.
Marketing authorisation/CE mark status	Marketing authorisation has been granted by the European Commission for the paediatric plaque psoriasis indication (6).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The current indications for secukinumab (Cosentyx®) are (6): Adult plaque psoriasis Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Paediatric plaque psoriasis Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy. Psoriatic arthritis Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

<table>
<tr><td></td><td>Axial spondyloarthritis (axSpA)
Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)
Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.
Non-radiographic axial spondyloarthritis (nr-axSpA)
Cosentyx is indicated for the treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs).</td></tr>
<tr><td>Method of administration and dosage</td><td>Subcutaneous injection with a SensoReady Autoinjector pen or PFS. The recommended dose in children is based on body weight and administered by SC with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.

<table><tr><th>Body weight at time of dosing</th><th>Recommended dose</th></tr><tr><td><25 kg</td><td>75 mg (low dose†)</td></tr><tr><td>25 to <50 kg</td><td>75 mg (low dose†)</td></tr><tr><td>≥50 kg</td><td>150 mg (low dose†; may be increased to 300 mg [high dose‡] as some patients may derive additional benefit from the higher dose)</td></tr></table>
Each dose is given as one SC injection. [redacted] The 300 mg/2 mL PFS was approved by the EMA in November 2020 [redacted].</td></tr>
<tr><td>Additional tests or investigations</td><td>No additional tests or investigations are needed compared with current clinical practice.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>Acquisition cost (75 mg, 1 PFS, list price): [redacted]¶
Acquisition cost (150 mg, 1 PFS, list price): £609.39
Acquisition cost (300 mg, 1 PFS, list price): [redacted]¶
The average cost of a course of treatment is £12,880 (assuming the approach taken in Section B.4).</td></tr>
<tr><td>Patient access scheme/commercial arrangement (if applicable)</td><td>A PAS has been agreed with the Department of Health for the 150 mg and 300 mg doses. This scheme provides a variable rate discount on the NHS List Price to maintain a fixed purchase price. This is applied as a simple discount to the list price of secukinumab, with the discount applied at the point of purchase or invoice.

Acquisition cost (75 mg, 1 PFS, PAS price): [redacted]§
Acquisition cost (150 mg, 1 PFS, PAS price): [redacted]
Acquisition cost (300 mg, 1 PFS, PAS price): [redacted]</td></tr>
</table>

	The average cost of a course of treatment is [redacted] (cost-comparison results; Section B.4).

†Equivalent to the low dose of secukinumab administered in trials A2310 and A2311 (Section B.3.3). In the trials, there was a 150 mg high dose for patients with weight 25 to <50 kg, but in the licence there is no option to increase the dose to 150 mg in these patients; ‡Equivalent to the high dose of secukinumab administered in trials A2310 and A2311 (Section B.3.3); ¶Planned list price subject to PASAG and PASLU approval; §75 mg PAS not yet submitted to PASAG and PASLU.
Abbreviations: AS, ankylosing spondylitis; EMA, European Medicines Agency; IL, interleukin; JIA, juvenile idiopathic arthritis; NICE, National Institute for Health and Care Excellence; nr-axSpA; non-radiographic axial spondyloarthritis; PAS, patient access scheme; PFS, pre-filled syringe; PsA, psoriatic arthritis; PsO, psoriasis; SC, subcutaneous.

B.1.3 Health condition and position of the technology in the treatment pathway

Plaque psoriasis

- Plaque psoriasis is a chronic relapsing inflammatory skin disease characterised by the presence of dry, red patches of skin (plaques) covered in silver scales.
- The disease is a lifelong debilitating systemic inflammatory disease with periods of exacerbation and remission which may be aggravated by genetic, infectious, emotional and environmental factors (7).
- Moderate to severe disease affects approximately 20% of people with plaque psoriasis (15% moderate, 5% severe) (8), equating to 6,000 children (under 10 years) and 16,000 young people (aged 10–19 years) in England (9).
- There is no cure for plaque psoriasis. The aim of therapy is therefore to gain rapid control of the disease by decreasing the percentage of body surface involved, decreasing the number of plaque lesions, to achieve and maintain remission, and ultimately, clear skin (3).

Humanistic burden

- Children are a vulnerable population; the physical and psychosocial burden of psoriasis disrupts important formative years, thereby potentially having a lasting impact on children's development and well-being.

- Psoriasis impacts children psychologically by potentially affecting their social integration and self-esteem, with an increased risk of anxiety and depression (10, 11).

- Education can also be disrupted through school absensteeism due to appearance-related challenges and time-consuming treatments; young people have expressed concerns about job-related challenges and stress, leading to lower self-esteem and further psychological problems (12).

- Paediatric psoriasis also has a huge impact on parents and caregivers, leading to stress and anxiety (11).

Current treatment options

- If first-line topical therapy does not adequately control disease, treatment options include ultraviolet B (UVB) phototherapy and psoralen plus ultraviolet A (PUVA) irradiation.

- Systemic non-biological therapy is recommended if the disease cannot be controlled with topical therapy, it has a significant impact on physical, psychological or social wellbeing, and psoriasis is extensive, associated with significant functional impairment and or/distress, or phototherapy is ineffective or cannot be used (10).

- For patients with severe disease (Psoriasis Area and Severity Index [PASI] ≥10) who have not responded or are contraindicated to standard systemic therapy, NICE recommends TNFα inhibitors adalimumab (age ≥4 years) and etanercept (age ≥6 years), and the interleukin (IL)-12/23 inhibitor ustekinumab (age ≥12 years) as treatment options.

Secukinumab

- Secukinumab is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the IgG1/κ-class. Secukinumab binds to human IL-17A and neutralises the bioactivity of this cytokine, thereby offering an

alternative mechanism of action compared with existing NICE-recommended treatments that target TNFα and IL-12/23.

- Secukinumab is licensed for the treatment of moderate to severe plaque psoriasis in children and young people from the age of 6 years who are candidates for systemic therapy, including for patients weighing <25 kg.
- Secukinumab results in rapid and long-lasting skin clearance and has demonstrated superiority in adult studies vs etanercept and ustekinumab (13).

Equality

- Secukinumab is already NICE-recommended for adults with severe plaque psoriasis (PASI ≥10 and a Dermatology Life Quality Index [DLQI] >10) where the PAS price is available and the disease has failed to respond to standard systemic therapies (or these treatments are contraindicated or the person cannot tolerate them).
- There would be an equality issue for children and young people with plaque psoriasis if the secukinumab paediatric recommendations were restricted vs those for adults.

B.1.3.1 Disease overview

Plaque psoriasis is a chronic relapsing inflammatory skin disease characterised by the presence of dry, red patches of skin (plaques) covered in silver scales (14). It is the most common form of psoriasis, affecting about 90% of people with the condition (15). Plaques in children and young people can appear anywhere on the body including the face, scalp, buttocks, elbows, knees, and lower back. The disease is typically lifelong, with periods of exacerbation and remission which may be aggravated by genetic, infectious, emotional and environmental factors (7).

B.1.3.1.1 Prevalence

One study estimated that the prevalence of psoriasis in children and young people in the United Kingdom is approximately 0.55% in children under 10 years and 1.37% in

people aged between 10 and 19 years (16). Moderate to severe disease (affecting more than 5% of the body surface area [BSA] or affecting crucial body areas such as the hands, feet, face, or genitals) affects approximately 20% of people with plaque psoriasis (15% moderate, 5% severe) (8). This equates to 6,000 children (under 10 years) and 16,000 young people (aged 10 to 19 years) in England (9). There is a lack of reliable data on incidence (7).

B.1.3.1.2 Humanistic and economic burden

Plaque psoriasis can have a traumatic functional and psychological impact on children and young people, and on caregivers. Factors contributing to this include symptoms related to the skin (for example, chronic itch, bleeding, scaling and nail involvement), problems related to treatments, psoriatic arthritis, and the effect of living with a highly visible, stigmatising skin disease.

Psoriasis impacts children psychologically by potentially affecting their social integration and self-esteem, and increases the risk of anxiety and depression in paediatric patients (10). The condition also has a huge impact on parents and caregivers, leading to stress and anxiety; one study (N= 65) found that the amount of time spent caring for the child's skin and emotional distress were among the key drivers of reduced quality of life in caregivers of children with psoriasis (11).

Education can also be disrupted for children and young people with psoriasis; in a semi-structured interview study of young people, parents and health professionals, all three groups reported that some young people were challenged by school absenteeism threatening their educational goals, due to time-consuming treatments or appearance-related and psychological concerns. Young people primarily mentioned appearance-related challenges and were fearful that job-related challenges and stress could lead to lower self-esteem and further psychological problems. Parents and health professionals endorsed these concerns (12).

In children with at least one of 12 different skin diseases, children with psoriasis reported the greatest impairment to quality of life. Itch or pain was reported in the same study as the most significant problem affecting their health-related quality of life (17). Compared with a matched psoriasis-free control cohort in a study based on health services claims data in the USA, paediatric patients had an approximately 25% to 30%

greater risk of being given a diagnosis of any psychiatric disorder, depression, or anxiety following psoriasis diagnosis (18).

Given the profound functional and psychological burden, and lifelong time course of the disease, it is important to initiate treatment as soon as possible after diagnosis (19). Early treatment of children and young people with biological agents may prevent long-term multisystem morbidity (e.g. hypertension, cardiovascular disease, depression), which has a higher prevalence in adults with psoriasis than in the general population (20).

B.1.3.1.3 Co-morbidities

As described above, patients can experience anxiety and depression because of psoriasis. In one study (N=108), 70.3% of children with psoriasis had at least one psychiatric diagnosis, compared with 27.7% of children without psoriasis (p=0.0001) (21). Children with psoriasis were determined to have 9.21-fold greater risk of anxiety (p=0.0001) and a 6.65-fold greater risk of depression (p=0.0019) compared with the control group.

As in adults, paediatric psoriasis is also frequently associated with significant co-morbidities including diabetes mellitus, Crohn's disease, obesity, hypertension and high cholesterol (22). The overall rate of comorbid conditions in psoriasis patients under 20 years of age is double that of their peers without psoriasis (22). A paediatric study using an international cohort of patients with psoriasis found that a significantly higher percentage of children with psoriasis showed excess adiposity (37.9% vs 20.5%) or obesity (20.2% vs 7.3%) than the general paediatric population (23).

B.1.3.2 Diagnosis and monitoring

Diagnosis is usually clinical (7). NICE clinical guidelines state that children and young people should be referred to a specialist at presentation (10). The guidelines state that clinicians should assess:

- disease severity
- the impact of disease on physical, psychological and social wellbeing
- whether they have psoriatic arthritis

- the presence of comorbidities.

In general healthcare settings, severity is assessed using the Physician's Global (PGA) Assessment, the static Physician's Global Assessment (sPGA), the BSA affected, and the involvement of nails, high-impact and difficult-to-treat sites (e.g. the face and palms).

In specialist settings, the Psoriasis Area and Severity Index (PASI) is also used (24). The PASI is a composite score grading severity in four body regions according to erythema, scaling, thickness, and the total area of skin affected. Severity of each of erythema, scaling, and thickness is graded from 0 to 4, and the extent of body surface area involvement in each body region is graded categorically from 1 to 6 based on the percentage surface area covered. The final composite score ranges from 0 to 72, with a higher score indicating a greater severity of psoriasis.

Monitoring frequency depends on disease severity and the type of therapy administered. In general, patients with moderate to severe psoriasis are monitored at 3- to 6-month intervals (7).

B.1.3.2.1 Defining disease severity

There is inconsistency in the way NICE and the European Medicines Agency (EMA) define moderate and severe disease based on the PASI. The recommendation in TA350 for adults with severe disease (PASI ≥10) (1) aligns with the EMA's definition of moderate to severe disease (25) (Table 3).

In this submission, evidence is presented from trials A2310 (baseline PASI ≥20) and A2311 (baseline PASI ≥12).

Table 3: EMA and NICE definitions of moderate and severe disease

Guidelines	Definition	PASI	DLQI
NICE (1)	Severe	≥10	>10
	Very severe	≥20	≥18
EMA (25)	Moderate	≥10	-
	Severe	>20	-

Abbreviations: DLQI, dermatology life quality index; EMA, European Medicines Agency; NICE, National Institute for Health and Care Excellence; PASI, Psoriasis Area and Severity Index.

B.1.3.2.2 Clinical pathway of care

B.1.3.2.2.1 Overview

There is no cure for plaque psoriasis. The aim of therapy is therefore to gain rapid control of the disease by decreasing the percentage of body surface involved, decreasing the number of plaque lesions, to achieve and maintain remission, and ultimately, clear skin (3).

Treatment depends on plaque psoriasis severity, BSA affected, and area of involvement. Typically, topical therapies are used as first-line treatment to treat more mild and localised plaque psoriasis, whereas phototherapy, systemic therapy, and biological therapy are used for moderate to severe disease. These are discussed in further detail below, based on recommendations in NICE CG153 (10) and TA455 (2).

B.1.3.2.2.2 Moderate to severe disease

Treatment options for patients with disease that cannot be controlled by topical treatments alone include narrowband ultraviolet B (UVB) phototherapy and psoralen plus ultraviolet A (PUVA) irradiation. Systemic non-biological therapy (methotrexate, ciclosporin, and acitretin in exceptional cases) is recommended if the disease cannot be controlled with topical therapy and it has a significant impact on physical, psychological or social wellbeing, and one or more of the following apply:

- psoriasis is extensive (e.g. >10% of BSA affected or a PASI score >10), or
- psoriasis is localised and associated with significant functional impairment and/or high levels of distress (e.g. severe nail disease or involvement at high-impact sites), or
- phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as >50% of baseline disease severity within 3 months).

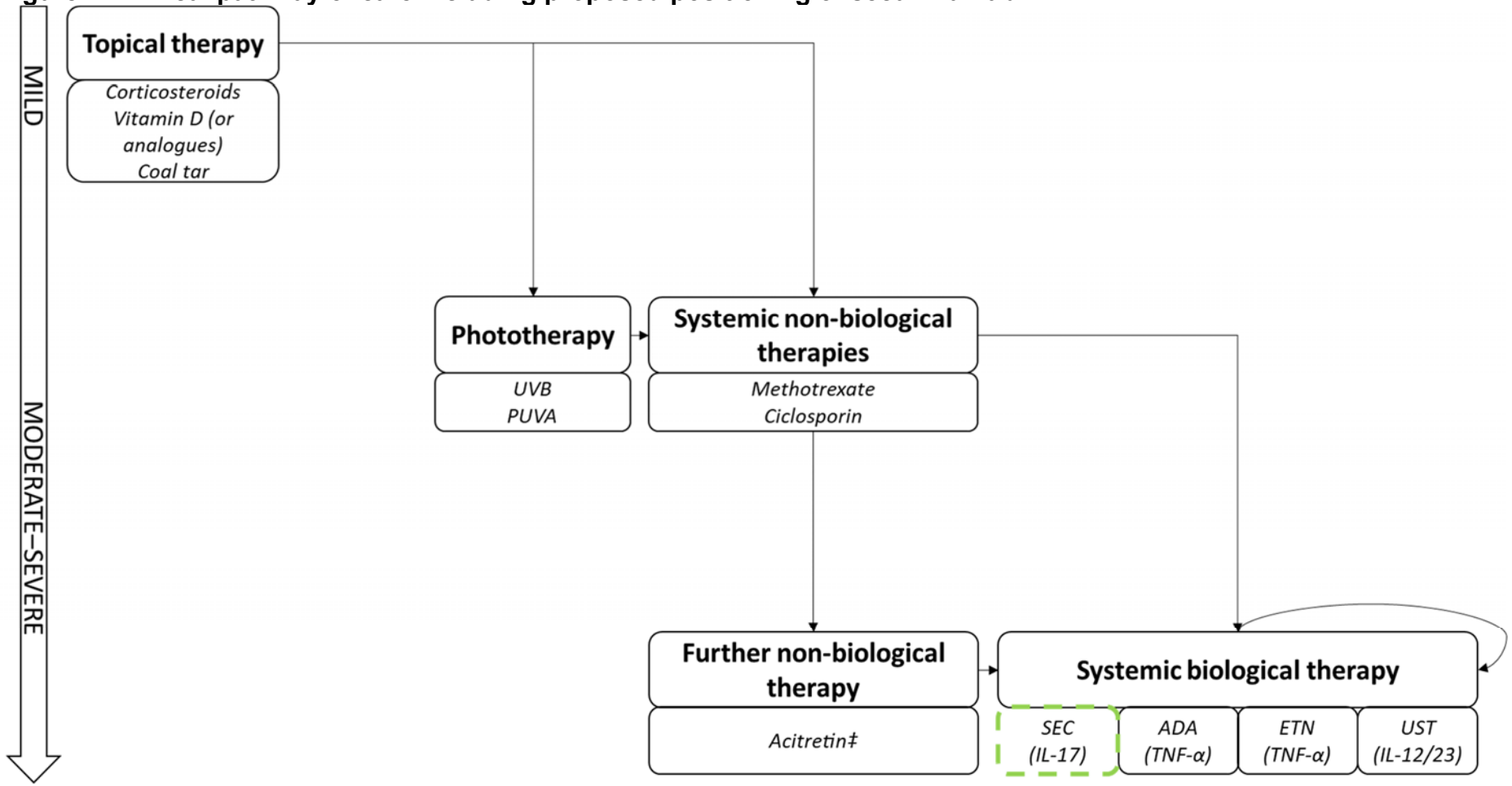
Adalimumab (age ≥4 years), etanercept (age ≥6 years) and ustekinumab (age ≥12 years) are NICE-recommended as options for treating plaque psoriasis in children and young people, only if the disease:

- is severe, as defined by a total PASI ≥10, and
- has not responded to standard systemic therapy, such as ciclosporin, methotrexate or phototherapy, or these options are contraindicated or not tolerated.

Etanercept treatment should be stopped at 12 weeks, and adalimumab and ustekinumab treatment at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as a 75% reduction in the PASI score from the start of treatment (PASI 75).

The clinical pathway of care in paediatric patients based on NICE CG153 (10) is presented in Figure 1. The figure highlights the proposed positioning of secukinumab in moderate to severe disease (termed 'severe' by NICE [Section B.1.3.2.1]).

Figure 1: Clinical pathway of care including proposed positioning of secukinumab†



†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.

B.1.3.2.3 Unmet need

Given the limited number of treatments available, there remains an unmet need for treatments with alternative mechanisms of action that can provide rapid relief of symptoms for children and young people. These will help to reduce the impact of psoriasis on physical and emotional development during a critical period of life.

Early clinical studies demonstrated the important role of TNF-α inhibitors in psoriasis, prompting the condition to be regarded as primarily driven by T-helper-1 (Th-1) cells (26). However, mounting evidence supports the pivotal involvement of T-helper cells producing interleukin (IL)-17 and IL-23 (27-29), which are now considered to be central to the pathogenesis of psoriasis as demonstrated by the efficacy of therapeutics inhibiting IL-23 or IL-17 pathways. IL-17 and IL-23 expression is increased in the serum, lesional skin, uninvolved skin and even in tear liquid of patients with psoriasis compared with patients without psoriasis (7).

IL-17-producing T cells in the skin produce several key cytokines, including IL-17. Acting alone or in concert with TNFα, IL-17 induces the expression and release of many psoriasis-related proteins from keratinocytes, which make up the outermost layer of the skin. The resulting inflammatory response contributes to the development of epidermal hyperplasia (excessive replication of cells) giving the skin a thickened, scaly appearance.

Neutralisation of IL-17 by secukinumab therefore treats the underlying pathophysiology of plaque psoriasis, and consequently provides relief of symptoms.

B.1.3.3 Secukinumab

Secukinumab is a recombinant high-affinity fully human monoclonal anti-human interleukin-17A (IL-17A) antibody of the IgG1/κ-class. Secukinumab binds to human IL-17A and neutralises the bioactivity of this cytokine, thereby offering an alternative mechanism of action compared with existing NICE-recommended treatments that target TNFα and IL-12/23.

Secukinumab is already recommended by NICE for the treatment of adults with severe plaque psoriasis (PASI ≥10 and DLQI >10) (1). In adult Phase 2/3 studies of plaque psoriasis, secukinumab 300 mg and 150 mg were shown to be efficacious with an

acceptable safety profile, with both doses superior to placebo over 12 weeks and etanercept over 52 weeks of treatment (13, 30, 31). Additionally, in a head-to-head double-blind study vs ustekinumab, secukinumab 300 mg demonstrated superior efficacy in clearing skin through Week 52, greater improvement in quality of life, and a comparable safety profile (32).

B.1.4 Equality considerations

Secukinumab 300 mg is already recommended by NICE in TA350 for treating adults with severe plaque psoriasis (defined as PASI ≥10 and DLQI >10) where the PAS price is available and the disease has failed to respond to standard systemic therapies (1). Any restrictions in the paediatric recommendation vs the adult recommendation would raise equality issues, as children and young people may not be able to access treatment until they reach 18 years of age.

Some patients with plaque psoriasis in England may currently have access to secukinumab under the Medicines for Children Policy. This covers patients who meet both the TA350 adult recommendation criteria (1) and the Policy criteria, which include discussion of drug use at a multidisciplinary team (MDT) meeting (33); at least two consultants in the subspeciality must be present (of whom at least one must be a consultant paediatrician), together with a paediatric pharmacist.

However, older paediatric patients (e.g. 16–17 year olds) who do not meet the requirements of TA350 (1) are often referred to adult services that also do not meet the Policy requirements. A consultant dermatologist (who preferred not to be named) highlighted the issue of patients falling in-between the strict criteria of the Policy and not being old enough for NICE TA350 to apply.

In addition, we understand that there are a number of paediatric services across England which do not meet the requirements of the Policy. For example, the lead paediatric dermatology consultant at a major centre (who preferred not to be named), does not have a paediatrician or a second paediatric dermatologist on the MDT; she is the only consultant with the relevant specialism in paediatric psoriasis. There are also several hospitals which see patients with psoriasis who are aged under 18, but which are part of the adult service; therefore, patients seen in this setting are not able

to access secukinumab via the policy. They may have to travel long distances with parents/carers in order to access a specialist paediatric service.

Clinicians have therefore expressed a need for a positive NICE recommendation (and the funding and resource mandate that follows) in the paediatric population, as this will ensure equity of access to secukinumab, the first recombinant high-affinity fully human monoclonal anti-human interleukin-17A (IL-17A) antibody of the IgG1/κ-class to be licensed for the treatment of paediatric psoriasis, thereby offering an alternative mechanism of action compared with existing NICE-recommended treatments that target TNFα and IL-12/23.

B.2 Key drivers of the cost effectiveness of the comparator(s)

- One previous NICE technology appraisal has been published for treatment of plaque psoriasis in children and young people (TA455).
- In TA455, the key clinical outcome used in the cost-effectiveness analysis was PASI 75; PASI 50 and PASI 90 were also considered in the NMA.
- Cost types considered in TA455 were drug acquisition and administration, monitoring, best supportive care (BSC) and adverse events; no concerns were raised by the committee on the types of costs considered in the appraisal.
    - Committee discussion topics for costs all related to BSC, which is not a relevant comparator for this appraisal.

B.2.1 Clinical outcomes and measures

Only one previous NICE technology appraisal relating to treatment for plaque psoriasis in children and young people has been published:

- Adalimumab, etanercept and ustekinumab for treating chronic plaque psoriasis in children and young people (TA455) (2).

In this appraisal, the key clinical outcome used in the cost-effectiveness analysis was PASI 75 (i.e. the proportion of patients achieving ≥75% improvement in their baseline PASI score by assessment of response), which the committee agreed was appropriate to assess response to treatment. This is in line with adult appraisals that have also used PASI 75 as a primary measure to assess response (1, 4, 34).

In addition to PASI 75, the NMA presented in TA455 also assessed PASI 50 and PASI 90 response rates. It is anticipated that patients not achieving PASI 75 may still derive benefit if they have achieved at least a PASI 50 response. Patients achieving PASI 90 have experienced more effective clearing of psoriasis, which the committee in TA350 acknowledged to be the most important outcome for patients.

The network meta-analysis (NMA) conducted for the current appraisal included PASI 50, PASI 75 and PASI 90 as outcomes (Section B.3.9.

B.2.2 Resource use assumptions

Resource use considered in TA455 included:

- Drug acquisition
- Drug administration
- Monitoring
- Best supportive care (BSC)
- Adverse events.

No concerns were raised by the committee on the types of costs considered in the appraisal. The above costs were considered for inclusion in the current cost comparison analysis; however, this analysis considers costs associated with drug acquisition only, on the basis that:

- In TA455, costs associated with administration, monitoring and BSC were assumed to be the same for all biologics (2)
- Differences in AE costs between biologics are expected to be minimal.

The committee discussed the most appropriate definition of BSC, hospitalisation days with BSC and the cost of hospitalisation for children. However, BSC is not included as a comparator in the current analysis and costs associated with BSC following biologic treatment are not considered; these issues are therefore not relevant to the current appraisal.

B.3 Clinical effectiveness

The efficacy and safety of secukinumab for the treatment of chronic plaque psoriasis in paediatric patients was assessed in two Phase 3 clinical trials.

- The trials evaluated low and high dose secukinumab, referring to a range of doses based on body weight:
    - Low dose (LD; equivalent to licensed dose [Table 2])
        - 75 mg for patients <50 kg
        - 150 mg for patients ≥50 kg
    - High dose (HD)
- 75 mg for patients <25 kg
        - 150 mg for patients 25 to <50 kg
        - 300 mg for patients ≥50 kg.
- A2310 is a randomised, Phase 3 trial that evaluated the efficacy and safety of low and high dose secukinumab vs placebo and etanercept, in paediatric patients with severe chronic plaque psoriasis (PASI ≥20, IGA mod 2011 score 4, and BSA involvement ≥10).
- A2311 is a randomised, open-label Phase 3 trial that evaluated the efficacy and safety of low and high dose secukinumab vs historical placeboa, in

[a] An historical placebo control was obtained using data from qualifying trials, and used as the comparator for the primary and key secondary endpoint analysis. This was in line with guidance from and discussions with the FDA and EMA, which suggested reducing placebo exposure, as well as

paediatric patients with moderate to severe chronic plaque psoriasis (PASI ≥12, IGA mod 2011 score ≥3, and BSA involvement ≥10%).

A2310 showed that in paediatric patients with severe chronic plaque psoriasis (PASI ≥20), secukinumab demonstrated a favourable safety profile and was effective in clearing skin and improving health-related quality of life, with significant improvements vs etanercept in IGA 0 (clear)/1 (almost clear) and PASI 90 outcomes.

- The co-primary objectives of the study (PASI 75 response and IGA mod 2011, 0 [clear] or 1 [almost clear] response at Week 12) were met with both secukinumab doses (LD and HD) showing superior efficacy compared with placebo (p<0.0001):
    - PASI 75 response (LD [redacted]; HD [redacted]; placebo [redacted]), and
    - IGA mod 2011, 0 or 1 response (LD [redacted]; HD [redacted]; placebo [redacted]).
- Importantly, both secukinumab doses also demonstrated statistically significant efficacy compared with etanercept in IGA 0 (clear)/1 (almost clear) and PASI 90 outcomes; PASI 90 and 100 are now regarded as clinical treatment goals for paediatric patients with psoriasis, as the aim of therapy is ultimately to achieve clear skin (3).
- Secukinumab also demonstrated numerical improvement vs etanercept in PASI 75 and PASI 100:
    - IGA mod 2011, 0 or 1 response (etanercept [redacted]; [redacted] and [redacted] for comparisons with LD and HD, respectively)
    - PASI 90 response (LD [redacted]; HD [redacted]; etanercept [redacted]; [redacted] and [redacted] for comparisons with LD and HD, respectively)

overall clinical trial burden for the paediatric population, and suggested/accepted the use of this extrapolation approach (35).

- PASI 75 response (etanercept [redacted], [redacted] and [redacted] for comparisons with LD and HD, respectively)
- PASI 100 response (LD [redacted]; HD [redacted]; etanercept [redacted]; [redacted] and [redacted] for comparisons with LD and HD, respectively).

- At Week 52, numerically higher efficacy rates were achieved with secukinumab (LD and HD) compared with etanercept as demonstrated by PASI and IGA response rates.
- The proportion of patients achieving CDLQI score of 0 or 1 at Week 52 in both secukinumab dose groups was numerically higher compared with etanercept (LD 60.6%; HD: 66.7%; etanercept 44.4%).
- Both doses of secukinumab demonstrated high and sustained efficacy rates up to Week 52 in clearing skin and improving health-related quality of life, with a favourable safety profile in paediatric patients with severe chronic plaque psoriasis.

[redacted]

[redacted]

B.3.1 Identification and selection of relevant studies

Appendix D provides full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.3.2 List of relevant clinical effectiveness evidence

The primary source of clinical effectiveness evidence in plaque psoriasis is A2310, a Phase 3 RCT comparing secukinumab with placebo and etanercept in patients with severe disease (PASI ≥20) (Table 4) (36). Supporting evidence comes from A2311, an open-label Phase 3 trial comparing secukinumab with historical placebo in patients with moderate to severe disease (PASI ≥12) (Table 5).

Table 4: Trial A2310 in patients with severe disease (PASI ≥20) (37, 38)

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)
Study design	Multicentre, randomised, double-blind, parallel group, placebo- and active (etanercept)-controlled 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).
Intervention(s)	<u>Secukinumab low dose (equivalent to licensed dose)</u> ≥50 kg: 150 mg 25 to <50 kg: 75 mg <25 mg: 75 mg <u>Secukinumab high dose</u> ≥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.*
Comparator(s)	<u>Placebo</u> 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.* <u>Etanercept</u> 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.*
Indicate if trial supports application	Yes

for marketing authorisation (yes/no)	
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
All other reported outcomes	Physical development Pharmacokinetics Pharmacogenetics

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

Table 5: Trial A2311 in patients with moderate to severe disease (PASI ≥12) (39, 40)

Study	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	Randomised, open-label, parallel group, two-arm, multicentre study
Population	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)	<u>Secukinumab low dose (equivalent to licensed dose)</u> ≥50 kg: 150 mg 25 to <50 kg: 75 mg <25 mg: 75 mg <u>Secukinumab high dose</u> ≥50 kg: 300 mg 25 to <50 kg: 150 mg <25 mg: 75 mg
Comparator(s)	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
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
All other reported outcomes	Immunogenicity Physical development

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

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Trial A2310 in patients with severe disease (PASI ≥20)

B.3.3.1.1 Trial design

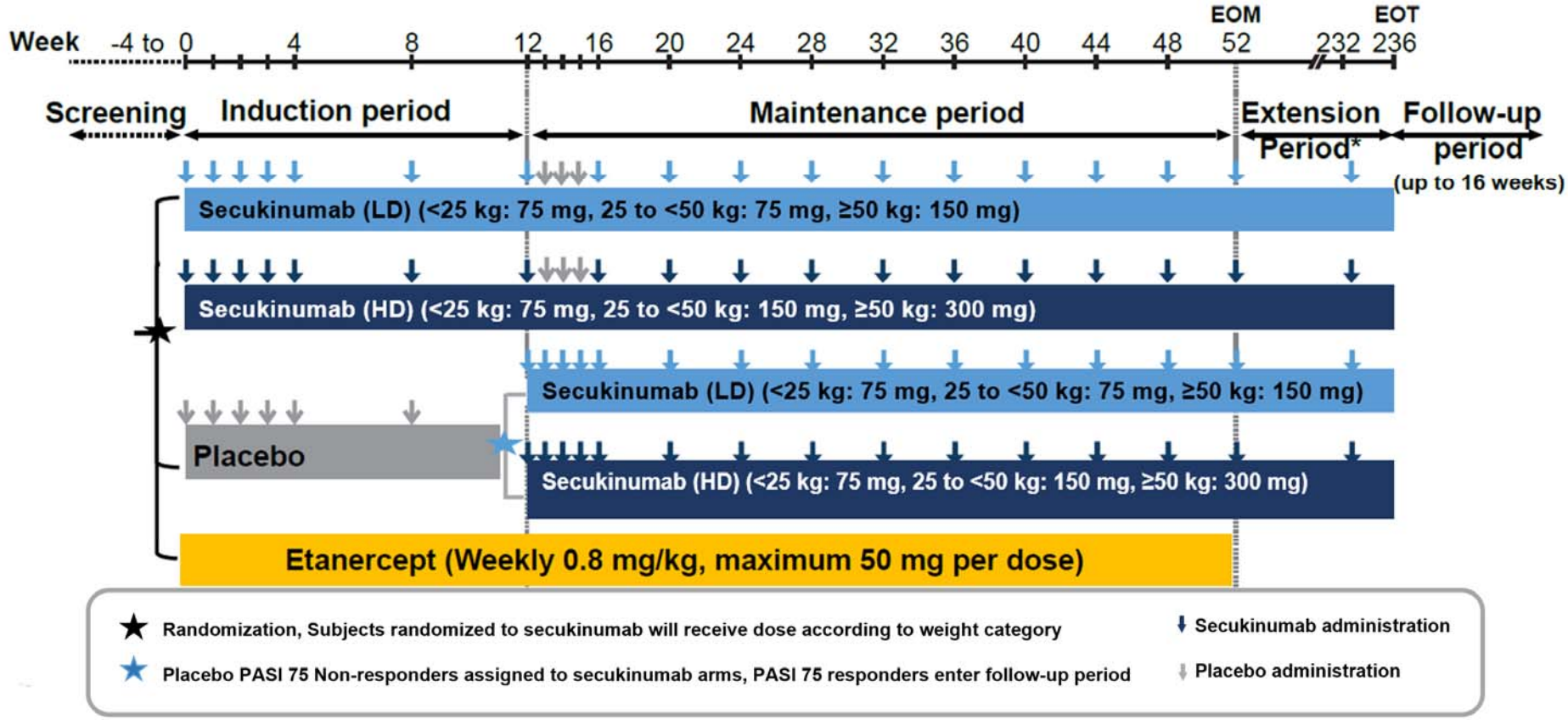
A2310 (NCT02471144) is a multicentre, randomised, double-blind, placebo- and active-controlled (etanercept in a single [assessor] blinded arm) study in paediatric patients aged 6–17 years with severe chronic plaque psoriasis (PASI ≥20) (36).

The primary objective was to demonstrate the superiority of secukinumab (low and high dose) in paediatric patients with severe chronic plaque psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared with placebo.

The study is ongoing; data presented in this submission relate to the cut-off date at which the last patient underwent their Week 52 visit (18th September 2019). The planned total duration of treatment in this study is 236 weeks (dosing up to Week 232) for all patients on secukinumab and 52 weeks (dosing up to Week 51) for patients on etanercept. For the Week 52 analysis, the actual duration of treatment for individual patients up to the data cut-off was variable.

Figure 2 presents an overview of the study design.

Figure 2: A2310 study design



*Secukinumab will be administered every 4 weeks during the extension treatment period until Week 232.
Abbreviations: EOM, end of maintenance; EOT, end of treatment; HD, high dose; LD, low dose; PASI, Psoriasis Area and Severity Index.

The study was split into five periods, described in further detail in Sections B.3.3.1.1.1 to B.3.3.1.1.5.

B.3.3.1.1.1 Screening (up to 4 weeks)

This was used to assess eligibility and to taper patients off prohibited medications.

B.3.3.1.1.2 Induction (12 weeks)

This period was both active- and placebo-controlled, with the co-primary endpoints of the study assessed at its completion (Week 12).

Patients were randomised at the start of the induction period using a 1:1:1:1 ratio into one of the treatment arms:

- secukinumab low dose (75 mg if weight <50 kg; 150 mg if weight ≥50 kg)
- secukinumab high dose (75 mg if weight <25 kg; 150 mg if weight ≥25 kg and <50 kg; 300 mg if weight ≥50 kg)
- etanercept (0.8 mg/kg up to a maximum of 50 mg)
- placebo.

Randomisation was stratified by age (<12 years or ≥12 years) and weight (<25 kg, 25 to <50 kg, and ≥50 kg).

Patients in the placebo arm were pre-assigned to either low- or high-dose secukinumab, which was to be administered if they did not achieve a PASI 75 response at Week 12. Week 12 placebo PASI 75 responders did not continue into the maintenance period, but entered the post-treatment follow-up period, with the first visit at F4 and the end of follow-up (EOF) visit 4 weeks later at F8 (Figure 2).

Details of study treatment formulation and dosing are provided in Section B.3.3.2.4.

B.3.3.1.1.3 Maintenance (40 weeks)

This period was active-controlled (all placebo patients had either moved onto low- or high-dose secukinumab treatment or entered the follow-up period), with the objective focused on the maintenance of the response.

In order to maintain the blind, patients in the secukinumab arms received weekly doses of secukinumab and/or placebo from Week 12 to Week 16 (inclusive) followed by doses every 4 weeks starting from Week 16 and up to Week 48 (Figure 2).

At the end of maintenance period (EOM; Week 52) visit, patients on secukinumab enter the extension treatment period and patients on etanercept enter the post-treatment follow-up period.

For patients who discontinued study treatment for any reason before the end of the maintenance period, the Week 52 visit was performed approximately 4 weeks after their last dose of study drug, after which the patients entered the post-treatment follow-up period.

B.3.3.1.1.4 Extension treatment (additional 184 weeks, open label)

In this period, all patients were to be treated with secukinumab, with the aim of collecting long-term safety and efficacy data. Patients who participated in the maintenance period but prematurely discontinued and patients who received etanercept were not able to enter the extension treatment period.

For any patients who discontinued for any reason before the end of the extension treatment period, the EOT visit was be performed approximately 4 weeks after their last dose of secukinumab, after which the patients entered the post-treatment follow-up period.

B.3.3.1.1.5 Post-treatment follow-up (16 weeks)

This is a treatment-free period, which all patients who complete or discontinue treatment were expected to enter, unless they started another systemic anti-psoriatic treatment. Those who do were expected to return to site after the start of the systemic treatment and perform the EOF visit.

B.3.3.1.2 IRT dosing error (after Week 12)

In the trial, an interactive response technology (IRT) error led to additional dosing of patients after the co-primary endpoint (Week 12) assessment. Specifically, 36 patients who were assigned to the low dose (16 patients) and high dose (20 patients) secukinumab groups were dispensed active medication at the Week 13, 14 and 15

visits. At these visits, the patients who were randomised to active treatment groups were expected to receive placebo medication to maintain the blind. Sixteen patients in the secukinumab low dose group (≥50 kg/150 mg dose; N=21) were dispensed secukinumab 300 mg in error at these visits; five patients in the secukinumab high dose group (25 to <50 kg/150 mg dose; N=15) were dispensed secukinumab 150 mg in error at these visits; and 15 patients in the secukinumab high dose group (≥50 kg/300 mg dose; N=22) were dispensed secukinumab 300 mg in error at these visits.

B.3.3.1.3 Eligibility criteria

Study inclusion and exclusion criteria for trial A2310 are presented in Table 6.

Table 6: A2310 study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• 6 to less than 18 years of age at the time of randomisation • History of plaque psoriasis for ≥3 months • Written informed assent and parental permission obtained at screening before any assessment is performed • Severe plaque psoriasis, defined as a PASI score ≥20, and IGA mod 2011 score of ≥4, and BSA involvement of ≥10%, at randomisation • Regarded to be a candidate for systemic therapy because of: o inadequate control of symptoms with topical treatment; or o failure to respond to or tolerate previous systemic treatment and/or UV therapy	• Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) • Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel blockers or lithium) • Ongoing use of prohibited treatments and adherence to washout periods • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor, or to etanercept) • Use of any other investigational treatment within 4 weeks before randomisation, or within a period of five half-lives of the investigational treatment, whichever was longer • History of severe hypersensitivity reaction or anaphylaxis to any biological agents (human monoclonal antibody or soluble receptor) • Pregnant or nursing (lactating) females • Female patients (<18 years of age) of childbearing potential who did not agree to abstinence or, if sexually active, did not agree to the use of contraception • Female patients (who became ≥18 years of age during the study) of child-bearing potential unless they were using effective methods of contraception during dosing of study treatment and for a minimum of 16 weeks after stopping study treatment or longer if local label required it • Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab and/or etanercept therapy • Underlying condition which in the opinion of the investigator significantly immunocompromised the patient

Inclusion criteria	Exclusion criteria
	and/or placed the patient at unacceptable risk for receiving an immunomodulatory therapy • Investigator discretion was used for patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders • Patients with an eGFR, estimated by the Schwartz equation, of <60 mL/min/1.73 m^2 at screening • Patients with total WBC count <2,500/µL, or platelets <100,000/µL or neutrophils <1,500/µL or haemoglobin <8.5 g/dL at screening • Active systemic infections during the last 2 weeks (exception: common cold) prior to randomisation and any infections that reoccurred on a regular basis • Investigator/qualified site staff discretion was used regarding patients who had travelled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for patients with underlying conditions that could predispose them to infection, such as advanced or poorly controlled diabetes • History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection. If presence of latent tuberculosis was established, then treatment must have been initiated and maintained according to local country guidelines prior to randomisation • Known infection with HIV, hepatitis B or hepatitis C at screening • History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years prior to screening • Plans for administration of live vaccines during the study period or within 6 weeks prior to randomisation • Any medical or psychiatric condition which, in the investigator's opinion, could preclude the participant from adhering to the protocol or completing the study per protocol • Hypersensitivity or allergy to any of the ingredients of study treatments, including etanercept • History or evidence of ongoing alcohol or drug abuse, within the last 24 weeks before randomisation • Patients not willing to limit UV light exposure (e.g. sunbathing and/or the use of tanning devices) during the course of the study • Unwillingness to undergo repeated venepuncture or subcutaneous injections.

Abbreviations: BSA, body surface area; DMC, data monitoring committee; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; IL, interleukin; PASI, Psoriasis Area and Severity Index; UV, ultraviolet; WBC, white blood cell.

B.3.3.1.4 Settings and locations where the data were collected

In A2310, data were collected across 19 countries. One patient was in the UK.

B.3.3.1.5 Trial drugs and concomitant medications

Secukinumab and placebo were supplied by Novartis Global Clinical Supplies. In A2310, etanercept (Enbrel®) was provided centrally by a contract research organisation or purchased locally as available.

B.3.3.1.5.1 Secukinumab

Secukinumab was administered SC using prefilled syringes (150 mg in 1.0 ml and 75 mg in 0.5 ml). Patients received two SC injections at each dose, except for patients weighing <25 kg who received one SC injection. Patients in the secukinumab treatment groups received secukinumab SC weekly at Weeks 0, 1, 2, 3, and 4, followed by maintenance dosing every 4 weeks thereafter.

Dose was based on weight at randomisation and treatment arm (low vs high dose). If a patient moved into a higher or lower weight group at two consecutive visits with weight measurements[b] during the maintenance or extension treatment periods, the dose was revised according to the new weight group. Doses for each weight category and treatment arm are provided in Table 7.

Table 7: Secukinumab doses by weight category

Weight category	Dose	
	Low dose arm	High dose arm
≥50 kg	150 mg	300 mg
25 to <50 kg	75 mg	150 mg[†]
<25 mg	75 mg	75 mg

[†]The licensed dose for patients with weight 25 to <50 kg is 75 mg only (no option to increase to 150 mg). The other doses in this table align with the licence.

Secukinumab 300 mg and 150 mg were selected based on evidence from adult Phase 3 studies that demonstrated both doses to be safe and effective in treating moderate to severe plaque psoriasis. The doses selected for the high dose and low dose secukinumab arms were based on a population-pharmacokinetic (PK) model that was

[b] Excluding Weeks 13, 14 and 15 visits.

built based on the pool of key adult Phase 2/3 trials to predict exposure of secukinumab according to various body weights (13, 30, 31).

B.3.3.1.5.2 Placebo

In order to maintain the blind, placebo was administered in 1 ml and 0.5 ml prefilled syringes matching the secukinumab prefilled syringes. Patients in the placebo arm received placebo SC weekly at Weeks 0, 1, 2, 3 and 4, and then 4 weeks later at Week 8.

B.3.3.1.5.3 Etanercept

In the etanercept arm, patients received weekly weight-based dosing of Enbrel® (0.8 mg/kg up to a maximum of 50 mg per dose).

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. Due to the more frequent dosing of etanercept (once-weekly) compared with the monthly secukinumab dosing, it was agreed with the paediatric committee of the EMA that as an ethical approach the etanercept comparator arm should be single-blinded not double-blind. This way excessive weekly injections to all patients to maintain the blind were avoided. Instead only the efficacy assessor at each site was to remain blinded to the etanercept arm, to guarantee objectivity of the co-primary efficacy endpoint evaluation.

B.3.3.1.5.4 Concomitant medications

Concomitant medications in A2310 were allowed if not listed in Table 8. Patients who received treatments known to worsen psoriasis (e.g. beta-blockers) had to be on a stable dose for at least 4 weeks before randomisation.

After the screening period, the use of concomitant medication for psoriasis in all body regions was restricted to bland emollients (not supplied by Novartis) and other non-medicated interventions (not listed in Table 8). Once the patient was screened and if the patient had intolerable scaling and/or itching, the use of bland emollients was permitted. The use of bland emollients was to be avoided during the 12 hours preceding a scheduled study visit.

A topical corticosteroid (TCS) treatment of mild or moderate activity was allowed for the face, scalp, hands, feet and genitoanal area during the screening period, but not after the patient had been randomised (although they were permitted with restrictions after Week 12 [Footnote 5 in Table 8]). These TCS were not to be used during the 12 hours preceding the randomisation study visit.

Table 8: Prohibited treatment in A2310

Prohibited treatment	Wash-out period up to randomisation	Induction period (up to Week 12)[1,2]	Maintenance period (Weeks 13 to 52)[1,2]	Extension period (additional 184 weeks)[1,2]
Alefacept, briakinumab, efalizumab, ustekinumab	26 weeks	Not allowed	Not allowed	Not allowed
Biological immunomodulating agents other than above (e.g. adalimumab, infliximab)	12 weeks	Not allowed	Not allowed	Not allowed
Etanercept	No prior use allowed	-	-	-
Other systemic immunomodulating treatments (e.g. MTX, ciclosporin, corticosteroid, cyclophosphamide)	4 weeks	Not allowed	Not allowed	Not allowed
Photochemotherapy (e.g. PUVA)	4 weeks	Not allowed	Not allowed	Not allowed
Other systemic therapy for psoriasis (e.g. retinoids, fumarate)	4 weeks	Not allowed	Not allowed	Not allowed
Any other investigational treatment or participation in any interventional trial	4 weeks or five half-lives (whichever was longer)	Not allowed	Not allowed	Not allowed
Phototherapy (e.g. UVA, UVB)	2 weeks	Not allowed	Not allowed	Not allowed
Topical treatment[3] for psoriasis or any other skin condition (e.g. corticosteroids, vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids), except on the face, scalp, hand and feet and	2 weeks[4]	Not allowed	Not allowed[5]	Not allowed[5]

Prohibited treatment	Wash-out period up to randomisation	Induction period (up to Week 12)[1,2]	Maintenance period (Weeks 13 to 52)[1,2]	Extension period (additional 184 weeks)[1,2]
genitoanal area during screening				
Live virus vaccinations	6 weeks	Not allowed[6]	Not allowed[6]	Not allowed[6]
Killed virus vaccinations	None	Allowed	Allowed	Allowed

[1]If a prohibited treatment of psoriasis was used during the study, the patient was to discontinue use of the prohibited treatment if he/she wished to continue in the study.
[2]In case of undue safety risk for the patient, the patient was to discontinue study treatment at the discretion of the investigator.
[3]Including intra-articular or peri-articular injections. Note that inhaled corticosteroids as well as corticosteroid drops in the eye or ear or nasal sprays were permitted.
[4]Mild to moderate topical corticosteroids were allowed only during the screening period if used only on the face, scalp, hands and feet and/or genitoanal area and if not used during the 12 h preceding the randomisation visit.
[5]Topical corticosteroids and other topical treatments were allowed during maintenance and extension treatment period only if medication was started after the Week 12 visit was completed; medication was used for 14 consecutive calendar days or less; and medication was used for an indication other than psoriasis and not on the area affected with psoriasis.
[6]If the patient received a live virus vaccination during the study, the patient had to discontinue study treatment.
Abbreviations: MTX, methotrexate; PUVA, psoralen plus ultraviolet A; UVA, ultraviolet A; UVB, ultraviolet B.

B.3.3.1.6 Outcomes specified in the scope

B.3.3.1.6.1 Co-primary endpoint

In A2310, the primary objective was to demonstrate the superiority of secukinumab (low and high dose) with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared with placebo.

B.3.3.1.6.2 Secondary and exploratory outcomes

Table 14 presents a list of pre-specified secondary and exploratory trial endpoints related to outcomes specified in the scope. Note that psoriasis symptoms on the face, scalp, nails and joints, are not measured outcomes in A2310.

Table 9: Secondary and exploratory outcomes in A2310

Type of outcome	Secondary objectives (Section reference)	Exploratory objectives
Efficacy	• To demonstrate superiority of secukinumab (low and high dose) in patients with severe chronic plaque psoriasis with respect to PASI 90 response at Week 12, compared with placebo (Section B.3.6.1.1) • To assess efficacy of secukinumab in patients with severe chronic plaque psoriasis with respect to PASI 50 and PASI 100 at Week 12, compared with placebo (Section B.3.6.1.3.1) • To assess efficacy of secukinumab in patients with severe chronic plaque psoriasis with respect to PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 (clear) or 1 (almost clear) at Week 16 and over time up to Week 52 (Section B.3.6.1.3.2) • To assess the efficacy of secukinumab with respect to changes in PASI score and IGA mod 2011 score at Week 12, compared with placebo, and over time up to Week 52 (Section B.3.6.1.3.2.3 and Section B.3.6.1.3.5).	• To describe the efficacy of secukinumab compared with etanercept with respect to PASI 75, PASI 90, PASI 100 and IGA mod 2011 • To assess the efficacy of secukinumab with respect to onset of effect of secukinumab, compared with placebo and etanercept • To assess the long-term efficacy of secukinumab on severe chronic plaque-type psoriasis with respect to PASI 50/75/90/100 and IGA 0 (clear) or 1 (almost clear) response, after Week 52 • To assess the long-term efficacy of secukinumab on severe chronic plaque-type psoriasis with respect to PASI score and IGA mod 2011 score after Week 52.
Relapse/rebound	-	• To assess the occurrence of relapse† following secukinumab and etanercept therapy (during follow-up period) • To assess the occurrence of rebound‡ following secukinumab and etanercept therapy (during follow-up period).
Adverse effects of treatment	• To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, tolerability of SC injections, vital signs, clinical laboratory variables, ECGs, and adverse events monitoring, compared with placebo (Section B.3.9).	• To describe the safety of secukinumab compared with etanercept • To investigate the development of immunogenicity against secukinumab • To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain,

Type of outcome	Secondary objectives (Section reference)	Exploratory objectives
		tolerability of SC injections, vital signs, clinical laboratory variables, ECGs, and adverse events monitoring after Week 52.
Health-related quality of life.	• To investigate the effects of treatment with secukinumab with respect to changes in CDLQI at Week 12, compared with placebo, and over time up to Week 52 (Section B.3.6.1.4.1) • To investigate the effects of treatment of secukinumab with respect to CDLQI 0 or 1 achievement at Week 12, compared with placebo, and over time up to Week 52 (Section B.3.6.1.4.1) • To evaluate the effects of treatment of secukinumab on disability at Week 12 and over time up to Week 52 by use of the CHAQ©, for patients with history of psoriatic arthritis (not presented).	• To investigate the effects of treatment with secukinumab with respect to changes in CDLQI after Week 52 • To investigate the effects of treatment of secukinumab with respect to CDLQI 0 or 1 achievement after Week 52.
Outcomes not listed in NICE scope	-	• To assess impact of treatment with secukinumab on physical development in children and adolescents from ages 6–18 years, by use of the Tanner stages scale over time (Parts I and II) • To assess pharmacokinetic parameters • To perform exploratory PG assessments to examine whether individual genetic variation in genes relating to drug metabolism, psoriasis, and the drug target pathway confer differential response to secukinumab.

†Relapse is defined as when the achieved maximal PASI improvement from baseline is reduced by >50%.
‡Rebound is defined as when after last study treatment, PASI is increased to >125% of baseline PASI, or new pustular psoriasis, or new erythrodermic psoriasis, or more inflammatory psoriasis occurs.
Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CHAQ©, Childhood Health Assessment Questionnaire; ECG, electrocardiogram; IGA, Investigator's Global Assessment; IGA mod 2011, Investigator's Global Assessment modified 2011; PASI, Psoriasis Area and Severity Index; PG, pharmacogenetics; SC, subcutaneous.

B.3.3.1.7 Baseline participant characteristics

Demographics and background characteristics in A2310 were generally similar between treatment groups. The proportion of males was higher in the placebo group and that of females was higher in the secukinumab low dose group relative to the other groups. The etanercept group had a lower proportion of Caucasians and a higher proportion of Native American patients compared with other groups (Table 10).

Table 10: A2310 demographics and background characteristics

Participant characteristic	Secukinumab		Placebo N=41	Etanercept N=41	Total N=162
	Low dose N=40	High dose N=40			
Age group (years), n (%)					
<12	8 (20.0)	9 (22.5)	10 (24.4)	10 (24.4)	37 (22.8)
≥12	32 (80.0)	31 (77.5)	31 (75.6)	31 (75.6)	125 (77.2)
Age (years)					
N	40	40	41	41	162
Mean	13.7	13.2	13.7	13.5	13.5
SD	2.92	3.21	3.27	2.94	3.06
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)					
Male	13 (32.5)	17 (42.5)	19 (46.3)	16 (39.0)	65 (40.1)
Female	27 (67.5)	23 (57.5)	22 (53.7)	25 (61.0)	97 (59.9)
Race, n (%)					
Caucasian	34 (85.0)	34 (85.0)	36 (87.8)	30 (73.2)	134 (82.7)
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	1 (2.5)	0	1 (2.4)	0	2 (1.2)
Ethnicity, n (%)					
Hispanic/Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
East Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Southeast Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
South Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
West Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Russian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed ethnicity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Participant characteristic	Secukinumab		Placebo N=41	Etanercept N=41	Total N=162
	Low dose N=40	High dose N=40			
Weight (kg)					
N	40	40	41	41	162
Mean	52.60	53.61	55.68	51.96	53.47
SD	15.263	20.179	22.280	19.430	19.345
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)
25 to <50	17 (42.5)	15 (37.5)	17 (41.5)	16 (39.0)	65 (40.1)
≥50	21 (52.5)	22 (55.0)	21 (51.2)	21 (51.2)	85 (52.5)
Child-bearing status, n (%)					
Pre-menarche	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Baseline disease characteristics were also generally well balanced and comparable between treatment groups (Table 11).

Table 11: A2310 disease history and baseline disease characteristics

Disease characteristic	Secukinumab		Placebo N=41	Etanercept N=41	Total N=162
	Low dose N=40	High dose N=40			
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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)

Disease characteristic	Secukinumab		Placebo N=41	Etanercept N=41	Total N=162
	Low dose N=40	High dose N=40			
Diagnosis of plaque-type psoriasis, n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis history, n (%)					
Generalised pustular psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palmoplantar pustular psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erythrodermic psoriasis	[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)
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]
Mean	[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)
No	0	0	0	0	0

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

B.3.3.2 Trial A2311 in patients with moderate to severe disease (PASI ≥12)

B.3.3.2.1 Trial design

A2311 (NCT03668613) is a randomised, Phase 3, open-label, parallel group, two-arm, multicentre study in paediatric patients aged 6–17 years with moderate to severe chronic plaque psoriasis and who are candidates for systemic therapy. The primary

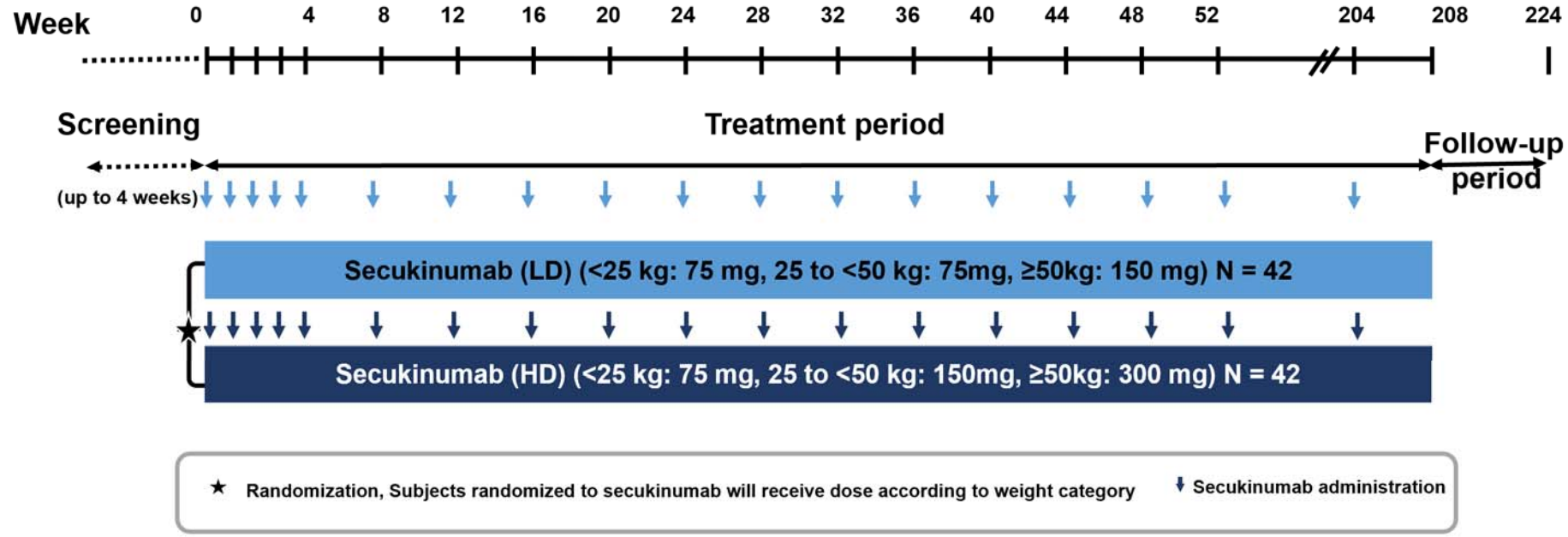
objective was to demonstrate the superiority of secukinumab (low and high dose) in paediatric patients with severe chronic plaque psoriasis with regards to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared with placebo (historical control [Section 0]).

Randomisation of patients 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).

The study is ongoing; data presented in this submission relate to the cut-off date at which the last patient underwent their Week 52 visit (28th May 2020). The planned total duration of treatment in this study is 224 weeks (dosing up to Week 208). For the Week 52 analysis, the actual duration of treatment for individual patients up to the data cut-off was variable.

An outline of the study design is presented in Figure 3.

Figure 3: A2311 study design



Abbreviations: HD, high dose; LD, low dose.

[redacted]

B.3.3.2.1.1 Screening period

[redacted]

B.3.3.2.1.2 Treatment period

[redacted]

B.3.3.2.1.3 Follow-up period

[redacted]

B.3.3.2.1.4 Historical placebo

[redacted]

B.3.3.2.2 Eligibility criteria

Study inclusion and exclusion criteria are presented in Table 12.

Table 12: A2311 study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• 6 to less than 18 years of age at the time of randomisation • [redacted] Written informed assent and parental permission obtained at screening before any assessment is performed • Moderate to severe plaque psoriasis, defined as a PASI score ≥12, and IGA mod 2011 score of ≥3, and BSA involvement of ≥10%, at randomisation • Regarded as a candidate for systemic therapy due to: o Inadequate control of symptoms with topical treatment, or o Failure to respond or tolerate previous systemic treatment and/or UV therapy	• Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) • Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel blockers or lithium) • Ongoing use of prohibited treatments and non-adherence to washout periods • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor • [redacted] Pregnant or nursing (lactating) females • Female patients (<18 years of age) of childbearing potential who did not agree to abstinence or, if sexually active, did not agree to the use of contraception • Female patients (who became ≥18 years of age during the study) of child-bearing potential unless they were using effective methods of contraception during dosing of study treatment and for a minimum of 16 weeks after stopping study treatment or longer if local label required it • [redacted]

Inclusion criteria	Exclusion criteria
	[redacted] • Patients with total WBC count <2,500/μL, or platelets <100,000/μL or neutrophils <1,500/μL or haemoglobin <8.5 g/dL at screening • [redacted]

Abbreviations: BSA, body surface area; DMC, data monitoring committee; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; IL, interleukin; PASI, Psoriasis Area and Severity Index; UV, ultraviolet; WBC, white blood cell.

B.3.3.2.3 Settings and locations where the data were collected

[redacted]

B.3.3.2.4 Trial drugs and concomitant medications

[redacted]

B.3.3.2.4.1 Concomitant medications

Concomitant medications were allowed if not listed in Table 13. Dose adjustments of these medications were avoided during the study. Patients who received treatments known to worsen psoriasis had to be on a stable dose for at least 4 weeks before the randomisation visit.

After the screening period, the use of concomitant medication for psoriasis in all body regions was restricted to bland emollients (not supplied by Novartis) and other non-medicated interventions (not listed in Table 13). Once the patient was screened and if the patient had intolerable scaling and/or itching, the use of bland emollients was permitted. The use of bland emollients was to be avoided during the 12 hours preceding a scheduled study visit.

A topical corticosteroid (TCS) treatment of mild or moderate activity was allowed for the face, scalp, hands, feet and genitoanal area during the screening period, but not after the patient had been randomised (although they were permitted with restrictions after Week 12 [Footnote 5 in Table 13]). These TCS were not to be used during the 12 hours preceding the randomisation study visit.

Table 13: A2311 prohibited treatment

Prohibited treatment	Wash-out period up to randomisation	Treatment period[1,2]
Secukinumab	No prior use allowed	Used as study treatment
Any biologic drug directly targeting IL-17 or the IL-17 receptor (other than secukinumab [e.g. rodalumab, ixekizumab])	No prior use allowed	Not allowed

Prohibited treatment	Wash-out period up to randomisation	Treatment period[1,2]
Any biologic directly targeting IL-12/23 or IL-23, e.g. briakinumab, stekinumab, guselkumab, tildrakizumab	26 weeks	Not allowed
Alefacept, efalizumab	26 weeks	Not allowed
Etanercept	4 weeks	Not allowed
Biological immunomodulating agents other than above (e.g. adalimumab, infliximab)	12 weeks	Not allowed
Other systemic immunomodulating treatments (e.g. methotrexate, cyclosporine A, corticosteroid, cyclophosphamide)	4 weeks	Not allowed
Photochemotherapy (e.g. PUVA)	4 weeks	Not allowed
Other systemic therapy for psoriasis (e.g. retinoids, fumarates, apremilast)	4 weeks	Not allowed
Any other investigational treatment or participation in any interventional trial	4 weeks or five half-lives (whichever is longer)	Not allowed
Phototherapy (e.g. UVA, UVB)	2 weeks	Not allowed
Topical treatment[3] for psoriasis or any other skin condition (e.g. corticosteroids, vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids), except on the face, scalp, hand and feet and genitoanal area during screening	2 weeks[4]	Not allowed[5]
Live vaccinations	6 weeks	Not allowed[6]

[1]If a prohibited treatment of psoriasis was used during the study, the patient must discontinue use of the prohibited treatment if he/she wishes to continue in the study.
[2]In case of undue safety risk for the patient, the patient should discontinue study treatment at the discretion of the investigator.
[3]Including intra-articular or peri-articular injections. Note that inhaled corticosteroids as well as corticosteroid drops in the eye or ear or nasal sprays are permitted.
[4]Mild to moderate topical corticosteroids are allowed only during the screening period if used only on the face, scalp, hands and feet and/or genitoanal area and if not used during at least 12hrs preceding the randomization visit
[5]Topical corticosteroids and other topical treatments will be allowed after Week 12 Visit only if (all must apply): medication was started after the Week 12 visit was completed; medication was used for 14 consecutive calendar days or less; and medication was used for an indication other than psoriasis and not on the area affected with psoriasis.
[6]If the patient received a live vaccination during the study, the patient must discontinue study treatment.
Abbreviations: IL, interleukin; PUVA, psoralen plus ultraviolet A; UVA, ultraviolet A; UVB, ultraviolet B.

B.3.3.2.5 Outcomes specified in the scope

B.3.3.2.5.1 Co-primary endpoint

The primary objective was to demonstrate the superiority of secukinumab (low and high dose) with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared with historical placebo.

B.3.3.2.5.2 Secondary and exploratory outcomes in A2311

Table 14 presents a list of pre-specified secondary and exploratory trial endpoints related to outcomes specified in the scope. Note that psoriasis symptoms on the face, scalp, nails and joints, are not measured outcomes within the secukinumab Phase 3 study.

Table 14: A2311 secondary and exploratory outcomes

Type of outcome	Secondary objectives	Exploratory objectives
Efficacy	• To evaluate the efficacy of secukinumab in paediatric patients with respect to PASI 90 at Week 12, compared with placebo (historical control)	• [redacted]
Relapse/rebound	-	• [redacted]
Adverse effects of treatment	• To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, vital signs, clinical laboratory variables, ECGs, and AE monitoring	• [redacted]
Health-related quality of life.	-	• [redacted]
Not specified	• To evaluate the pharmacokinetics of secukinumab in paediatric patients	• [redacted]

[redacted]

Abbreviations: AE, adverse event; CDLQI, Children's Dermatology Life Quality Index; ECG, electrocardiogram; IGA, Investigator's Global Assessment; IGA mod 2011, Investigator's Global Assessment modified 2011; PASI, Psoriasis Area and Severity Index.

B.3.3.2.6 Baseline participant characteristics

[redacted]

Table 15: A2311 demographics and background characteristics

Characteristic	Secukinumab low dose [redacted]	Secukinumab high dose [redacted]	Total [redacted]
Age group (years), n (%)			
6 – <12	[redacted]	[redacted]	[redacted]
12 – <18	[redacted]	[redacted]	[redacted]
Age (years)			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Vietnamese	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Weight (kg)			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Weight strata (kg), n (%)			
<25	[redacted]	[redacted]	[redacted]
25 - < 50	[redacted]	[redacted]	[redacted]
≥ 50	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation.

[redacted]

Table 16: A2311 disease history and baseline disease characteristics

Background characteristic	Secukinumab low dose [redacted]	Secukinumab high dose [redacted]	Total [redacted]
Baseline PASI score			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]
Baseline PASI, n (%)			
≤ 20	[redacted]	[redacted]	[redacted]
> 20	[redacted]	[redacted]	[redacted]
Baseline total BSA (%)			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]
Baseline IGA mod 2011 score, n (%)			
3 = Moderate disease	[redacted]	[redacted]	[redacted]
4 = Severe disease	[redacted]	[redacted]	[redacted]
Severity of psoriasis (as per randomisation), n (%)			
Moderate†	[redacted]	[redacted]	[redacted]
Severe‡	[redacted]	[redacted]	[redacted]
Severity of psoriasis (as per recalculation¶), n (%)			
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Time since first diagnosis of plaque type psoriasis (years)			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]
Generalised pustular psoriasis, n (%)			
Yes	[redacted]	[redacted]	[redacted]
Palmoplantar pustular psoriasis, n (%)			
Yes	[redacted]	[redacted]	[redacted]
Erythrodermic psoriasis, n (%)			
Yes	[redacted]	[redacted]	[redacted]

Background characteristic	Secukinumab low dose [redacted]	Secukinumab high dose [redacted]	Total [redacted]
Psoriatic arthritis history, n (%)			
Yes	[redacted]	[redacted]	[redacted]
Time since first diagnosis of psoriatic arthritis (years)			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
Previous psoriasis therapies, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]

[†]In A2311 moderate disease was defined as IGA 3 and PASI ≥12 or IGA 4 and PASI ≥12–<20; [‡]In A2311 severe disease was defined as IGA 4 and PASI ≥20; [¶]In one instance the study site incorrectly classified disease severity – the recalculation reflects actual severity at baseline.
Abbreviations: BSA, body surface area; IGA mod 2011, Novartis Investigator's Global Assessment modified 2011; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

B.3.3.3 Comparative summary of trial methodology

Table 17 presents an overview of the methodology of the A2310 and A2311 trials.

Table 17: Comparative summary of trial methodology

Trial number (acronym)	A2310 (NCT02471144)	A2311 (NCT03668613)
Trial design	Multicentre, randomised, double-blind, parallel group, placebo- and active (etanercept)-controlled study	Randomised, open-label, parallel group, two-arm, multicentre study
Eligibility criteria for participants	• Severe plaque psoriasis, defined as a PASI score ≥20, and IGA mod 2011 score of ≥4, and BSA involvement of ≥10%, at randomisation • Failure to respond to or tolerate non-biologic systemic treatment. Detailed eligibility criteria are presented in Table 6.	• Moderate to severe plaque psoriasis, defined as a PASI score ≥12, and IGA mod 2011 score of ≥3, and BSA involvement of ≥10%, at randomisation • Regarded as a candidate for systemic therapy due to: o Inadequate control of symptoms with topical treatment, or o Failure to respond or tolerate previous systemic treatment and/or UV therapy. Detailed eligibility criteria are presented in Table 12.
Settings and locations where the data were collected	Data were collected across 19 countries. One patient was in the UK.	[redacted]
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)	Secukinumab administered subcutaneously at Weeks 0, 1, 2, 3, and 4, and every four weeks thereafter. Dose was based on body weight: <u>Secukinumab low dose (N=40)</u> ≥50 kg: 150 mg 25 to <50 kg: 75 mg <25 mg: 75 mg	[redacted]

Trial number (acronym)	A2310 (NCT02471144)	A2311 (NCT03668613)
Intervention(s) (n=[x]) and comparator(s) (n=[x]) **Permitted and disallowed concomitant medication**	Secukinumab high dose (N=40) ≥50 kg: 300 mg 25 to <50 kg: 150 mg <25 kg: 75 mg Etanercept (N=41) administered subcutaneously every week at 0.8 mg/kg, up to a maximum of 50 mg per dose. Placebo (N=41) administered subcutaneously in 1 ml and 0.5 ml matching the secukinumab prefilled syringes. Placebo was administered at Weeks 0, 1, 2, 3 and 4, and again at Week 8.	[redacted]
Primary outcomes (including scoring methods and timings of assessments)	The primary objective was to demonstrate the superiority of secukinumab (low and high dose) with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared with placebo (A2310) and historical placebo (A2311).	
Pre-planned subgroups	• Patients aged 6 to less than 12 years • Patients aged 12 to less than 18 years	

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 Analysis sets (A2310 and A2311)

The following analysis sets were defined in the trials:

Randomised set: The randomised set was defined as all patients who were randomised. Unless otherwise specified, mis-randomised patients (mis-randomised by the interactive response technology [IRT]) were excluded from the randomised set. Mis-randomised patients are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomisation eligibility and double-blind treatment was not administered to the patient. If patients were re-screened and successfully randomised, they were included in the randomised set according to the treatment assigned in the last randomisation.

Full analysis set (FAS): The FAS comprised all patients from the randomised set to whom study treatment had been assigned. Following the intent-to-treat principle, patients were analysed according to the treatment assigned at randomisation. If the actual stratum (age and weight in A2310; weight and disease severity in A2311) was different to the assigned stratum in IRT (i.e., if the incorrect stratum was inadvertently entered), the actual stratum was used in analyses. Of note, patients excluded from the randomised set were excluded from the FAS.

Safety set: The safety set included all patients who took at least one dose of study treatment during the treatment period. Patients were analysed according to treatment received or actual treatment. The actual treatment or treatment received for summaries of safety data would differ to the treatment assigned at randomisation only if a patient received the wrong treatment during the entire induction period or entire maintenance period.

Analysis of the co-primary and key secondary endpoints was based on the FAS.

B.3.4.2 Sample size and power calculation

B.3.4.2.1 A2310

The plan was to enrol approximately 160 paediatric patients in two subgroups: 6 to less than 12 years of age, and 12 to less than 18 years of age, with stratification by age (<12 years, ≥12 years) and weight (<25 kg, 25–<50 kg and ≥50 kg). At a minimum, 30 patients were to be enrolled in the <12 years subgroup. Enrolment of children aged 6 to less than 12 years proceeded after review of data in the adolescent group.

Two secukinumab dose regimens were tested vs placebo with respect to the co-primary endpoints (PASI 75 response and IGA mod 2011 0 or 1 response at Week 12), so the type-I-error was split to 1.25% one-sided for each comparison. With 40 patients per group and assuming a response rate of 10% for PASI 75 response and IGA mod 2011 0 or 1 response in the placebo group, the power to show a response rate of 65% for PASI 75 response and 45% for IGA mod 2011 0 or 1 response in the secukinumab groups based on Fisher's exact test was approximately 99% for PASI 75 response and approximately 88% for IGA mod 2011 0 or 1 response.

For the secondary endpoint of PASI 90 response at Week 12, assuming a response rate of 8% in the placebo group, the power to show a significant difference between a secukinumab dose and placebo, assuming a response rate of 39% in the secukinumab groups based on Fisher's exact test is approximately 82% for PASI 90 response. The assumed response rates for secukinumab were based on the confirmatory efficacy in severe patients in the adult Phase 3 programme (13). At Week 12, PASI 75 response rates of 11% and PASI 90 response rates of 7% have been reported in the placebo group in Paller et al, 2008 (43) for children and young people aged 4–17 years.

B.3.4.2.2 A2311

The sample size for this study was calculated to ensure an adequate number of subjects for PK analyses and powered efficacy analyses. Approximately 80 patients (at least 60 patients with moderate psoriasis [IGA 3 and PASI ≥12 or IGA 4 and PASI ≥12–<20]) were planned to be enrolled in about 40 centres worldwide. At least five patients were targeted to be in the <25 kg body weight group, and at least 10 patients in each of the other two weight groups (25–<50 kg and ≥50 kg).

Power calculations were performed to support the co-primary endpoints PASI 75 and IGA 0 (clear) or 1 (almost clear) response at Week 12, and secondary endpoint PASI 90 at Week 12, vs placebo (historical control) for the low and high secukinumab dose regimens. The low dose arm with anticipated smaller treatment effect was considered in the power/sample size calculation.

Data from four adult psoriasis placebo-controlled secukinumab trials (ERASURE and FIXTURE (13), FEATURE (41) and JUNCTURE (42)) as well as from two paediatric psoriasis placebo controlled trials with other biologics, etanercept and ustekinumab, (Paller et al 2008 (43), Landells et al 2015 (44)) were used to estimate the historical placebo response rate.

B.3.4.3 Statistical methods used to compare groups for co-primary and secondary outcomes

B.3.4.3.1 A2310

B.3.4.3.1.1 Statistical analysis of co-primary endpoint

The statistical hypotheses for PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12 being tested were that secukinumab (low or high dose) is not superior to placebo in the proportion of patients with PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.

The following hypotheses were to be tested:

- H1: Secukinumab low dose is not superior to placebo with respect to PASI 75 response at Week 12
- H2: secukinumab high dose is not superior to placebo with respect to PASI 75 response at Week 12
- H3: secukinumab low dose is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12
- H4: secukinumab high dose is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12

The co-primary endpoints (PASI 75 and IGA mod 2011 0 or 1 response at Week 12) were evaluated using an exact logistic regression model with treatment group, baseline body weight stratum, age stratum and baseline PASI score as explanatory variables. If convergence was not reached, the covariates could be removed from the model one by one until convergence was reached, by starting with continuous covariates (i.e. baseline PASI) and followed by removing categorical covariates (i.e. age stratum, body weight stratum).

Odds ratios (ORs) were computed for comparisons of secukinumab dose regimens vs placebo utilising the logistic regression model fitted. Confidence intervals (CIs) for risk difference were derived based on the exact method. In case of rates of 0% or 100% in one of the treatment groups, for analyses with multiple imputation, CIs for risk difference and p-values from the t-test for the risk difference comparing to 0 were provided; for analyses with non-responder imputation, Fisher's exact test was to be performed and CIs for risk difference were provided.

B.3.4.3.1.2 Statistical analysis of key secondary endpoint

The secondary variable in the testing strategy was the PASI 90 response at Week 12 (for superiority comparison of secukinumab doses vs placebo). The secondary efficacy variable PASI 90 at Week 12 was tested in the same way as the primary variables. It was analysed using the FAS unless otherwise specified.

The family-wise type I error was set to α=2.5% (one-sided). The graphical approach of Bretz et al, 2009 (45) for sequentially rejective testing procedures was to be used to illustrate the hierarchical testing strategy. The procedure allows the type I error rate associated with a rejected hypothesis to be reallocated according to a set of pre-specified rules. The hypotheses associated to the co-primary and secondary variables are as below.

Co-primary variables:

H1 to H4 (Section B.3.4.3.1.1).

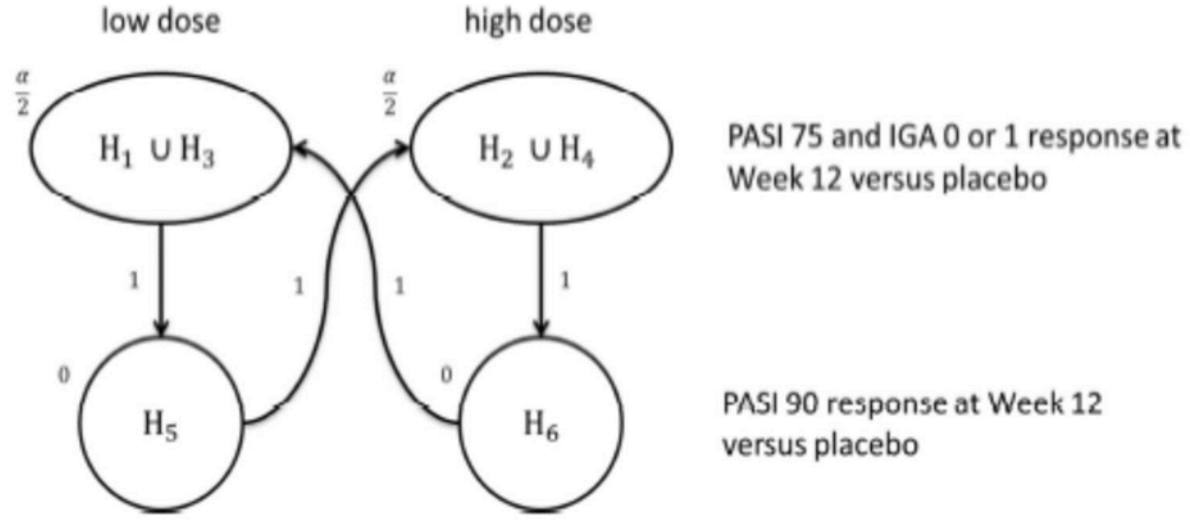
Secondary variable:

H5: secukinumab low dose is not superior to placebo with respect to PASI 90 response at Week 12

H6: secukinumab high dose is not superior to placebo with respect to PASI 90 response at Week 12.

Figure 4 illustrates the approach for sequentially rejective testing procedures.

Figure 4: Testing strategy



Abbreviations: IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index.

One-sided p-values were derived. The family-wise error was set to α=2.5% (one-sided). The hypotheses were mapped into two sets (H1, H3 and H5) or (H2, H4 and H6) such that hypotheses within a set correspond to the same secukinumab dose regimen. The type-I-error probability was to be equally split for both sets of hypotheses and within each set the hypotheses were tested sequentially as follows:

- Within each pair of hypotheses (H1 or H3) and (H2 or H4), each hypothesis was to be tested at α/2 (one-sided). Only if both hypotheses of a pair were rejected, was the testing sequence continued.
- In the next step of the sequence, the null hypotheses corresponding to the PASI 90 comparison of secukinumab vs placebo was to be tested. H5 and H6 were tested at α/2 (one-sided).

- If all hypotheses within a set referring to a secukinumab dose regimen had been rejected, i.e., either (H1, H3 and H5) or (H2, H4 and H6), the corresponding type I error probability could be passed on to the other set of hypotheses, and if needed, hypotheses could be retested at a higher significance level.

B.3.4.3.2 A2311

B.3.4.3.2.1 Statistical analysis of co-primary endpoint

The statistical hypothesis was that secukinumab (high dose/low dose) was not superior to historical placebo with respect to co-primary endpoints. A Bayesian method was chosen to allow the direct incorporation into the analysis of information about placebo response rates from historical data through a meta-analytic-predictive (MAP) prior (46, 47).

A Bayesian logistic regression mixed effects model was fitted to the historical placebo data, including terms study and population (adult or paediatric) to predict efficacy outcomes of a future pediatric trial taking into account between study heterogeneity of the control response rate. The MAP prior was derived on the logit scale, and represented the predicted placebo log odds of the paediatric study, which was used in this study as the comparator. For each endpoint the resulting posterior distributions forming the MAP prior were approximated with a parametric distribution.

A separate logistic regression Bayesian model was fitted for each endpoint on the log odds scale to the secukinumab data from this study with the term treatment (high/low dose). Data from the above models were used to estimate the Bayesian posterior of the log OR between secukinumab high and low dose group over placebo treatment response rate in this study. The median value of the mean log OR as well as the 95% predictive credible interval (CrI) were reported for secukinumab high and low dose. The probability of a positive treatment effect (over placebo) was provided for secukinumab high and low dose groups, which corresponds to the level of evidence for a positive treatment effect. In addition, data were graphically presented in a box-plot; the bar across the box represents the median of the mean prediction, and the box represents the 95% CrI.

B.3.4.3.2.2 Statistical analysis of the secondary endpoint

PASI 90 response at Week 12 endpoint was analysed in exactly the same way as the primary endpoint through a Bayesian logistic regression mixed effects model. The statistical hypothesis was that secukinumab (high dose/low dose) was not superior to placebo with respect to PASI 90 at Week 12.

B.3.4.4 Methods for additional analyses

B.3.4.4.1 Additional data-driven analyses (A2310 only)

In addition to the planned analyses, data-driven (post-hoc) analyses were performed as described below.

B.3.4.4.1.1 Analyses using extended visit window for Week 12

After performing pure non-responder imputation, it was noticed that many Week 12 efficacy assessments were missing and thus patients were counted as non-responders for the analysis at Week 12. Therefore, an additional sensitivity analysis with an extended Week 12 analysis visit window using non-responder imputation and multiple imputation was performed (Week 12 visit window Day 72–102 instead of Day 72–88). Results are presented in the study publication (36).

B.3.4.4.1.2 Analyses by IRT dosing error

As described in Section B.3.3.1.2, 36 patients who were assigned to the secukinumab groups (16 low dose patients and 20 high dose patients) were dispensed active medication at Week 13, 14, 15 visits instead of placebo. This error did not affect the co-primary endpoints or other endpoints measured at Week 12. However, analyses were performed for the below groups of IRT dosing error affected and not-affected patients to understand the impact of overdosing caused due to the error:

- SEC low dose affected (N=16)
- SEC low dose not affected (N=24)
- SEC high dose affected (N=20)
- SEC high dose not affected (N=20).

B.3.4.5 Methods to account for missing data

B.3.4.5.1 A2310

The following imputation methods were applied to the missing data for analysis of PASI and IGA mod 2011 based response variables up to Week 24:

- Response variables based on PASI score and IGA mod 2011 categories were imputed with the multiple imputation method as the primary imputation method. Multiple imputation is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets could then be analysed using standard methods. Within this analysis, the PASI score or IGA mod 2011 categories were imputed, and response variables were derived based on the imputed scores. In the multiple imputation analysis, the response status was imputed based on the individual treatment arm information. For the secukinumab (low or high dose) and etanercept groups, the imputation was performed with the post-baseline values from Week 1 to Week 24; for the placebo group and the placebo-switchers, the post-baseline values from Week 1 to Week 12 and those from Week 13 to Week 24 were used, respectively. Besides the post-baseline values, the imputation included baseline PASI score and additional covariates such as baseline weight and number of previous systemic therapies.

- Pure non-responder imputation was used in sensitivity analysis. Missing values with respect to response variables based on PASI score and IGA mod 2011 categories were imputed with non-response regardless of the reason for missing data (e.g., premature study discontinuation, missed visit, administrative issues). Patients with missing baseline or those with all post-baseline missing were imputed with non-response.

- For CDLQI and CHAQ scores, missing values were to be replaced by last observation carried forward (LOCF). Baseline values were not to be carried forward.

B.3.4.5.2 A2311

The following imputation methods were applied to the missing data for analysis of PASI and IGA mod 2011 based response variables up to Week 24.

Pure non-responder imputation was used as the primary method: Missing values with respect to response variables based on PASI score and IGA mod 2011 categories were to be imputed with non-response regardless to the reason for missing data (e.g., premature study discontinuation, missed visit, administrative issues). Patients with missing baseline or those with all post-baseline missing were to be imputed with non-response.

Response variables based on PASI score and IGA mod 2011 scores were also to be imputed with multiple imputation (Section B.3.4.5.1). Within this analysis, the PASI score or IGA mod 2011 categories were to be imputed and response variables were to be derived based on the imputed scores. In the multiple imputation analysis, the response status was to be imputed based on the individual treatment arm information. CDLQI and the continuous PASI score were imputed with LOCF.

B.3.4.6 Summary of statistical analyses

A summary of statistical analyses performed in A2310 and A2311 is provided in Table 18.

Table 18: Summary of statistical analyses

Trial number (acronym)	A2310 (NCT02471144)	A2311 (NCT03668613)
Hypothesis objective	To demonstrate the superiority of secukinumab (low and high dose) in paediatric patients with severe chronic plaque psoriasis (PASI ≥20) with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared with placebo.	To demonstrate the superiority of secukinumab (low and high dose) in paediatric patients with moderate to severe chronic plaque psoriasis (PASI ≥12) with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared with historical placebo.
Statistical analysis	The co-primary endpoint (PASI 75 and IGA mod 2011 0 or 1 response at Week 12) was evaluated using an exact logistic regression model with treatment group, baseline body weight stratum, age stratum and baseline PASI score as explanatory variables.	A Bayesian logistic regression mixed effects model was fitted to the historical placebo data, including terms study and population (adult or paediatric) to predict efficacy outcomes of a future paediatric trial taking into account between study heterogeneity of the control response rate.
Sample size, power calculation	Planned sample size was 160. Two secukinumab dose regimens were tested vs placebo with respect to the co-primary endpoints (PASI 75 response and IGA mod 2011 0 or 1 response at Week 12), so the type-I-error was split to 1.25% one-sided for each comparison. With 40 patients per group and assuming a response rate of 10% for PASI 75 response and IGA mod 2011 0 or 1 response in the placebo group, the power to show a response rate of 65% for PASI 75 response and 45% for IGA mod 2011 0 or 1 response in the secukinumab groups based on Fisher's exact test was approximately 99% for PASI 75 response and approximately 88% for IGA mod 2011 0 or 1 response.	The sample size for this study was calculated to ensure an adequate number of subjects for PK analyses and powered efficacy analyses. Approximately 80 patients (at least 60 patients with moderate psoriasis [IGA 3 and PASI ≥12 or IGA 4 and PASI ≥12–<20]) were planned to be enrolled. Power calculations were performed to support the co-primary endpoints PASI 75 and IGA 0 (clear) or 1 (almost clear) response at Week 12, and secondary endpoint PASI 90 at Week 12, vs placebo (historical control) for the low and high secukinumab dose regimens. The Low dose arm with smaller treatment effect was considered in the power/sample size calculation.
Data management, patient withdrawals	Response variables based on PASI score and IGA mod 2011 categories were imputed with multiple imputations method as the primary imputation method.	Pure non-responder imputation was used as the primary method: Missing values with respect to response variables based on PASI score and IGA mod 2011 categories were to be imputed with non-response regardless of the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). Patients with missing baseline or those with all post-baseline missing were to be imputed with non-response.

Abbreviations: IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PK, pharmacokinetic.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

A quality assessment of the A2310 RCT is provided in Appendix D.

B.3.6 Clinical effectiveness results of the relevant trials

B.3.6.1 A2310

B.3.6.1.1 Co-primary and key secondary endpoints (Week 12)

Both co-primary endpoints were met; both secukinumab doses (low and high) were superior to placebo with respect to PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.

At Week 12, PASI 75 response was achieved by [redacted] of patients in the secukinumab low dose group and [redacted] of patients in the secukinumab high dose group compared with [redacted] of patients in the placebo group and [redacted] of patients in the etanercept group. IGA mod 2011 0 or 1 response was achieved by [redacted] of patients in the secukinumab low dose group and [redacted] of patients in the secukinumab high dose group compared with [redacted] of patients in the placebo group and [redacted] of patients in the etanercept group. The odds ratio estimates in favour of both secukinumab doses were clinically relevant and statistically significant ($p<0.0001$).

The key secondary endpoint (PASI 90) was also met, with significantly higher responses in the secukinumab groups compared with the placebo and etanercept groups. PASI 90 and 100 are now regarded as clinical treatment goals for paediatric patients with psoriasis, as the aim of therapy is ultimately to achieve clear skin (3).

Co-primary and key secondary endpoint results are presented in Table 19.

Table 19: Logistic regression analysis of IGA mod 2011 0 (clear) or 1 (almost clear), PASI 75, and PASI 90 response at Week 12 (multiple imputation; FAS)

Response criterion	Treatment comparison 'test' vs 'control'	'test' n*/m (%)	'control' n*/m (%)	Odds ratio estimate (95% CI)†	p-value
IGA 0/1	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]

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.
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.

PASI 75, IGA mod 2011 0 or 1 and PASI 90 response rates at Week 12 by treatment group (multiple imputation) are shown in Figure 5.

Figure 5: IGA mod 2011 0 or 1, PASI 75, PASI 90 and PASI 100 response (estimate + 95% CI) at Week 12 (multiple imputation; FAS)

Abbreviations: IGA, Investigator's Global Assessment; m, number of patients evaluable; PASI, Psoriasis Area and Severity Index.

B.3.6.1.2 Sensitivity analysis of co-primary endpoints using non-responder imputation

Sensitivity analyses of the co-primary endpoints were performed using pure non-responder imputation methods instead of multiple imputation for missing values, as described in Section B.3.4.5. The results were consistent with those obtained using the multiple imputation method, confirming the primary analysis results. Results using non-responder imputation were used to inform the NMA (Section B.3.9).

At Week 12, PASI 75 response rates were [redacted] and IGA mod 2011 0 or 1 response rates were [redacted] in the secukinumab low dose group, secukinumab high dose group and placebo group, respectively. Both the secukinumab

doses (low and high) were superior to placebo (p-value <0.0001 for all comparisons). Results are presented in Table 20 and Figure 6.

Table 20: Logistic regression analysis of IGA mod 2011 0 (clear) or 1 (almost clear), PASI 75 and PASI 90 response at Week 12 (pure non-responder imputation; FAS)

Response criterion	Treatment comparison 'test' vs 'control'	'test' n*/m (%)	'control' n*/m (%)	Odds ratio estimate (95% CI)†	p-value
IGA 0/1	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]

†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.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; ETN, etanercept; FAS, full analysis set; m, number of patients evaluable; n*, rounded mean number of responders for 100 imputations; PASI, Psoriasis Area and Severity Index; PLA, placebo; SEC, secukinumab.

Figure 6: IGA mod 2011 0 or 1, PASI 75, PASI 90 and PASI 100 response (estimate + 95% CI) at Week 12 (pure non-responder imputation; FAS)

m = number of patients evaluable
Abbreviations: AIN457, secukinumab; FAS, full analysis set; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index.

B.3.6.1.3 Secondary endpoints

B.3.6.1.3.1 PASI 50 and PASI 100 response at Week 12

At Week 12, PASI 50 response rates in the secukinumab low dose group ( ) and the secukinumab high dose group ( ) were significantly higher compared with the placebo group ( ) ($p<0.0001$) and were similar to response rates in the etanercept group ( ).

PASI 100 response was achieved by of patients in the secukinumab low dose group and of patients in the secukinumab high dose group; by contrast of patients in the etanercept group achieved PASI 100, and no patients in the placebo group did (Table 21).

Table 21: Logistic regression analysis of PASI 50 and PASI 100 response at Week 12 (multiple imputation; FAS)

Response criterion	Treatment comparison 'test' vs 'control'	'test' n*/m (%)	'control' n*/m (%)	Odds ratio estimate (95% CI)†	p-value
PASI 50	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]

m = number of patients evaluable
n* = rounded mean number of responders for 100 imputations
†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.
Abbreviations: CI, confidence interval; ETN, etanercept; FAS, full analysis set; NE, not estimable; PASI, Psoriasis Area and Severity Index; PLA, placebo; SEC, secukinumab.

PASI 100 response rates at Week 12 by treatment group (multiple imputation) are shown in Figure 5.

B.3.6.1.3.2 PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response rates over time

Response rates over time are illustrated in Figure 7 and Figure 8, and tabulated in Appendix I (induction period up to Week 12 and maintenance period up to Week 52).

B.3.6.1.3.2.1 Induction period up to Week 12

Secukinumab responses were observed as early as Week 2 for PASI 75 and PASI 90, Week 3 for IGA mod 2011 0 or 1 and Week 4 for PASI 100. A continuous increase in response rates was observed in both secukinumab dose groups up to Week 12.

Higher PASI 50/75/90/100 and IGA mod 2011 0 or 1 response rates were observed in both secukinumab dose groups than the placebo and the etanercept groups at each visit during the induction period. At Week 12, significantly higher PASI 75/90/100 and

IGA mod 2011 0 or 1 response rates were observed for both secukinumab dose groups than the placebo group. Additionally, significantly higher IGA mod 2011 0 or 1 and PASI 90 response rates were observed at Week 12 in both secukinumab dose groups than the etanercept group ($p<0.05$ for all comparisons), and the PASI 75 response rate was numerically higher than in the etanercept group.

B.3.6.1.3.2.2 Maintenance period up to Week 52

In both secukinumab dose groups, the PASI 75/90/100 and IGA mod 2011 0 or 1 response rates achieved at Week 12 continued to increase further and were then sustained in the maintenance period up to Week 52. Both secukinumab dose groups continued to show higher PASI 50/75/90/100 and IGA mod 2011 0 or 1 response rates compared with the etanercept group at each visit during the maintenance period up to Week 52.

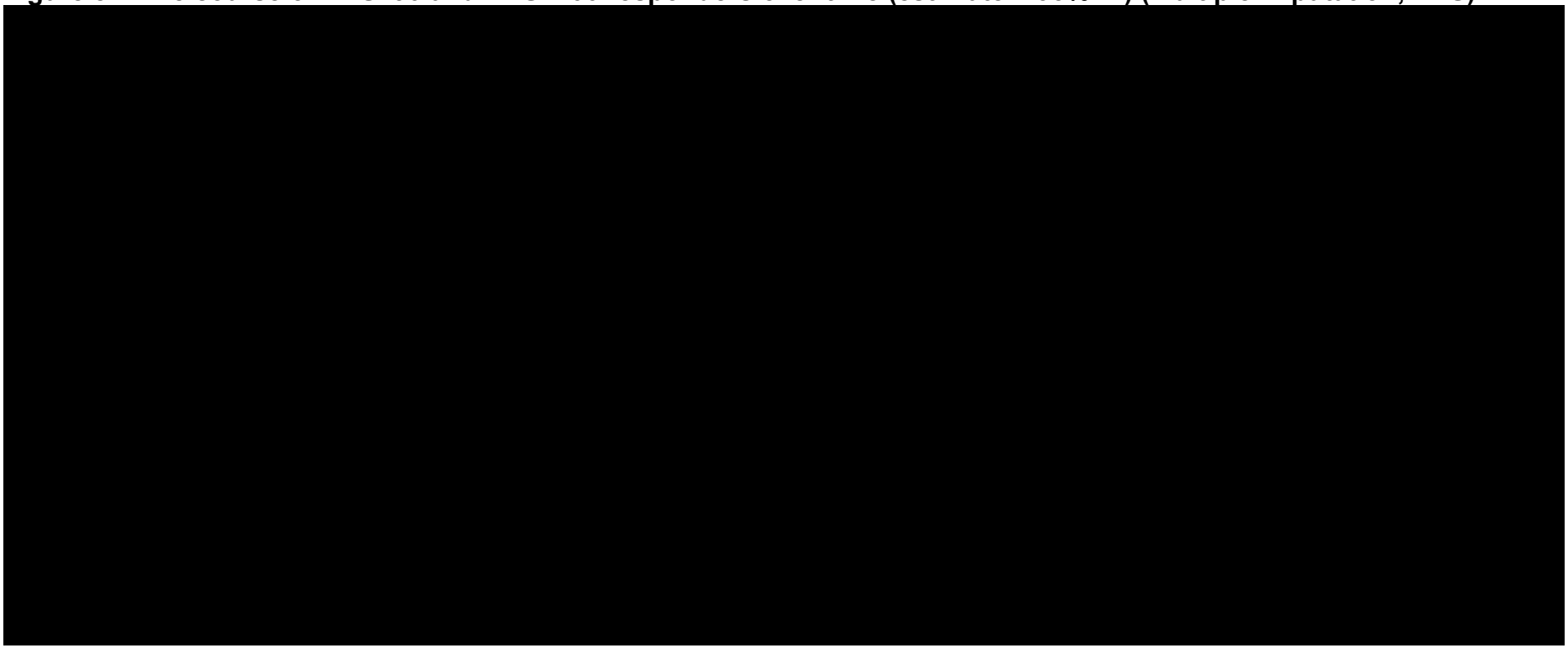
Rapid increases in response were observed for the placebo non-responders who were assigned to secukinumab at Week 12 (placebo - secukinumab low dose and placebo - secukinumab high dose). During the maintenance period, response rates were generally comparable with those in the originally randomised secukinumab groups.

Of note, the results discussed here for the maintenance period include all patients (both those affected and not affected by the IRT dosing error).

Figure 7: Time course of IGA mod 2011 0/1 and PASI 75 responders over time (estimate + 95% CI) (multiple imputation; FAS)

Abbreviations: AIN467, secukinumab; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index.

Figure 8: Time course of PASI 90 and PASI 100 responders over time (estimate + 95% CI) (multiple imputation; FAS)



Abbreviations: AIN467, secukinumab; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index.

B.3.6.1.3.2.3 Analyses by IRT dosing error

As discussed in Section B.3.4.4.1.2, additional analyses were performed for PASI 50/75/90/100 and IGA mod 2011 0 or 1 responses over time up to Week 52 for patients affected and not affect by the IRT dosing error that occurred at Weeks 13, 14 and 15.

Subgroup analysis excluding affected patients

A subgroup analysis of PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 responders over time excluding the IRT dosing error-affected patients demonstrated that responses in both groups were higher compared with the placebo group and the etanercept group throughout the induction period. These continued to be higher than in the etanercept group up to Week 52. These interpretations are aligned with those for the overall population.

B.3.6.1.3.3 Time to PASI 75 and time to PASI 90 response up to Week 12

[redacted] Results are presented in Appendix I.

B.3.6.1.3.4 PASI score over time

B.3.6.1.3.4.1 Induction period up to Week 12

The mean baseline PASI score was ~28 in all the treatment groups. During the induction period, mean PASI scores continuously decreased in all treatment groups, but to a greater extent in the secukinumab groups (low and high dose). At Week 12, the mean PASI scores were decreased (improved) from baseline by 82.9% in the secukinumab low dose group (reaching 5.12) and by 79.9% in the secukinumab high dose group (reaching 5.56) compared with 29.3% in the placebo group (reaching 19.89) and 74.2 % in the etanercept group (reaching 7.50).

B.3.6.1.3.4.2 Maintenance period up to Week 52

During the maintenance period, the mean PASI scores in both secukinumab dose groups (low and high) continued to decrease (improve) further up to Week 52, with similar reductions in both groups. In contrast, the etanercept group showed negligible further reductions in PASI scores after Week 12 up to Week 52. At Week 52, mean PASI scores were decreased from baseline by 92.55% in the secukinumab low dose group (reaching 2.13) and by 91.83% in the secukinumab high dose group (reaching 2.49). In the etanercept arm, mean PASI scores were decreased by 77.67% (reaching 7.24).

The placebo non-responders who were assigned to secukinumab at Week 12 (placebo - secukinumab low dose and placebo - secukinumab high dose) experienced a rapid and continuous decrease in the PASI scores following the switch to active treatment up to Week 52. At Week 24, corresponding to 12 weeks of secukinumab treatment for these patients, mean PASI scores were comparable with those in the originally-randomised secukinumab groups.

Of note, the results discussed here for the maintenance period include all patients, affected and not affected by the IRT dosing error.

Figure 9 presents the time course of percentage change from baseline in PASI score.

Figure 9: Time course of percentage change from baseline in PASI score (mean +/- SE) (multiple imputation; FAS)

N = number of patients in the treatment arm.
Abbreviations: AIN457, secukinumab; FAS, full analysis set; PASI, Psoriasis Area and Severity Index; SE, standard error.

B.3.6.1.3.5 IGA mod 2011 score over time

B.3.6.1.3.5.1 Induction period up to Week 12

[redacted]

B.3.6.1.3.5.2 Maintenance period up to Week 52

[redacted]

Of note, results discussed here for the maintenance period include all patients, affected and not affected by the IRT dosing error.

B.3.6.1.4 Health-related quality of life

B.3.6.1.4.1 Children's Quality of Life Index (CDLQI) 0 or 1 response

The CDLQI total score ranges from 0 to 30, and higher scores indicate greater health-related quality of life (QoL) impairment.

B.3.6.1.4.1.1 Induction period up to Week 12

Throughout the induction period, a higher proportion of patients receiving secukinumab (either dose) achieved a CDLQI 0 or 1 response (indicating no or little QoL impairment) compared with patients receiving placebo or etanercept. At Week 12, the proportions of CDLQI 0 or 1 responders in the secukinumab dose groups (low dose 44.7% and high dose 50%) were significantly higher compared with the placebo group (15%) ($p<0.05$ for both comparisons) and were numerically higher than the etanercept group (36.6%).

B.3.6.1.4.1.2 Maintenance period up to Week 52

Throughout the maintenance period, both secukinumab dose groups had a higher proportion of patients achieving CDLQI 0 or 1 response (indicating no or little impairment) than the etanercept group. At Week 52, the proportion of CDLQI 0 or 1 responders in both secukinumab dose groups (low dose 60.6% and high dose 66.7%) remained numerically higher than the etanercept group (44.4%).

The proportion of patients in each arm with CDLQI 0 or 1 over time is presented in Figure 10.

Figure 10: Time course of CDLQI 0 or 1 achievement over time (estimate + 95% CI) (LOCF; FAS)

N = number of patients in the treatment arm.
Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CI, confidence interval; ETN, etanercept; FAS, full analysis set; LOCF, last observation carried forward; PLA, placebo; SEC, secukinumab.

B.3.6.1.4.1.3 CDLQI score

B.3.6.1.4.1.4 Induction period up to Week 12

B.3.6.1.4.1.5 Maintenance period up to Week 52

[redacted]

B.3.6.2 A2311

B.3.6.2.1 Co-primary and key secondary endpoints

[redacted]

B.3.6.2.2 Exploratory efficacy endpoints

[redacted]

Figure 11: PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 (clear) or 1 (almost clear) response (estimate + 95% CI) at Week 12 (pNRI) (FAS)

Abbreviations: CI, confidence interval; IGA, Investigators Global Assessment; PASI, Psoriasis Area and Severity Index.

Figure 12: PASI 75 response (estimate + 95% CI) by visit (pNRI) to Week 52

Abbreviations: AIN457, secukinumab; CI, confidence interval; FAS, full analysis set; PASI, Psoriasis Area and Severity Index; pNRI, pure non-responder impuation.

Figure 13: PASI 90 response (estimate + 95% CI) by visit (pNRI) to Week 52

Abbreviations: AIN457, secukinumab; CI, confidence interval; FAS, full analysis set; PASI, Psoriasis Area and Severity Index; pNRI, pure non-responder impuation.

Figure 14: PASI 100 response (estimate + 95% CI) by visit (pNRI) to Week 52

Abbreviations: AIN457, secukinumab; CI, confidence interval; FAS, full analysis set; PASI, Psoriasis Area and Severity Index; pNRI, pure non-responder impuation.

Figure 15: IGA mod 2011 0 (clear) or 1 (almost clear) response (estimate + 95% CI) by visit (pNRI) to Week 52

Abbreviations: AIN457, secukinumab; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; pNRI, pure non-responder impuation.

B.3.7 Subgroup analysis

Subgroup analyses are not presented as 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.

B.3.8 Meta-analysis

Pairwise meta-analyses were not conducted as secukinumab was compared directly against etanercept in only one trial (A2310) and was not compared directly against ustekinumab in either A2310 or A2311. Instead, an NMA was conducted (Section B.3.8).

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Overview

A systematic literature review (SLR) was conducted to identify clinical evidence on the efficacy and safety of systemic treatments of paediatric plaque psoriasis (Section B.3.1). A network meta-analysis (NMA) was then conducted to estimate the relative efficacy of secukinumab vs other systemic treatments. Based on the clinical trials included in the SLR, an initial network was created as part of the feasibility assessment. Adalimumab was not connected to this network because the M04-717 trial compared only adalimumab to methotrexate, which was not a comparator in any of the other trials.

Although adult adalimumab data were used in TA455, this solution was adopted because of a need to develop a recommendation for adalimumab in the absence of paediatric data (2). However, it was considered inappropriate and unnecessary to include adult data within this appraisal given that:

- in-scope comparisons vs etanercept and ustekinumab can be made using paediatric data (and remain unaffected by the inclusion of adalimumab in the star-shape network),
- it is appropriate to consider a subset of comparators in a fast-track appraisal if the intervention offers similar or greater benefits at a similar or lower cost (4),

- the inclusion of adult data would increase heterogeneity and could result in a less robust NMA; there were substantial differences in mean age, disease duration and PASI 75 placebo response rates between the adult and paediatric adalimumab trials (48-53).

The base case NMA only included patients with severe disease (PASI ≥20) treated with secukinumab from A2310, so a sensitivity analysis was performed to assess the impact of the inclusion of patients with moderate to severe disease (PASI ≥12) from A2311. This sensitivity analysis also served as the sensitivity analysis including all open-label trials; CADMUS Jr was also identified in the SLR, but it could not be included in the evidence network as it is a single-arm trial with no connection. A2311 could be included as the two secukinumab dosing arms could be connected with the secukinumab arms in A2310.

The intervention of interest was secukinumab low dose as this aligns with the licensed dose (Table 2; note that the marketing authorisation permits escalation to 300 mg in patients with body weight ≥50 kg who may derive additional benefit). However, given that secukinumab high dose was included in the secukinumab RCT, this treatment arm was also considered, with results presented in Appendix D.

Details of dosing for each arm of the NMA are presented in Table 22.

Table 22: Doses considered in the NMA

Treatment arm	Dose	Administration frequency
Secukinumab low dose	• 75 mg for patients <50 kg • 150 mg for patients ≥50 kg	Administered SC at Weeks 0, 1, 2, 3 and 4 followed by monthly maintenance dosing (every 4 weeks).
Secukinumab high dose	• 75 mg for patients <25 kg • 150 mg for patients ≥25 kg and <50 kg • 300 mg for patients ≥50 kg	
Etanercept	• 0.8 mg/kg up to a maximum of 50 mg/dose	• Administered SC once weekly

Treatment arm	Dose	Administration frequency
Ustekinumab standard dose	• 0.75 mg/kg for patients ≤60 kg • 45 mg for patients >60 kg and ≤100 kg • 90 mg for patients >100 kg	Administered SC at Weeks 0 and 4 and every 12 weeks thereafter
Ustekinumab half dose	• 0.375 mg/kg for patients ≤60 kg • 22.5 mg for patients >60 kg and ≤100 kg • 45 mg for patients >100 kg	

Abbreviations: NMA, network meta analysis; SC, subcutaneous.

B.3.9.2 Summary of included trials

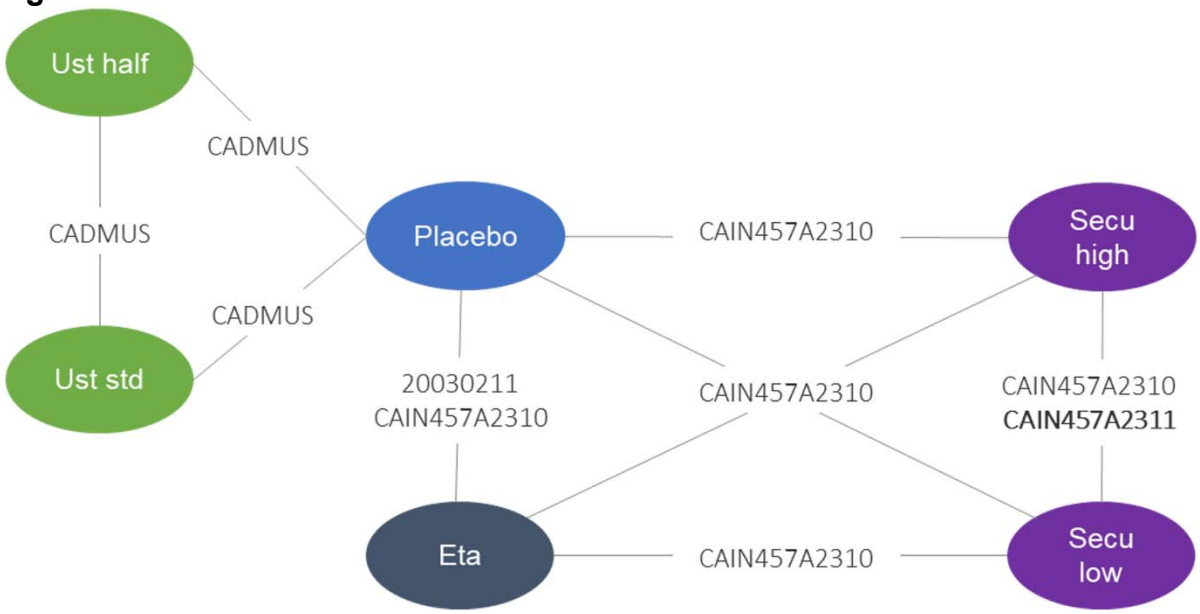
Studies and doses included in the NMA are summarised in Table 1, and the non-outcome-specific network is presented in Figure 16.

Table 23: Studies and doses included in the NMA

Trial (reference)	Secukinumab	Etanercept	Ustekinumab	Placebo
20030211 (43)		✓		✓
CADMUS (44)			✓	✓
A2310 (36)	✓			✓
A2311 (unpublished)†	✓			✓

†Note that A2311 was included in a sensitivity analysis only.
Abbreviations: NMA, network meta-analysis.

Figure 16: NMA evidence network



Abbreviations: NMA, network meta-analysis.

B.3.9.3 Methodology

A brief overview of NMA methodology is presented below. Further details are presented in Appendix D.

The feasibility of performing an NMA on the outcomes of interest was assessed. If a comparator of interest was evaluated against a systemic non-biologic or placebo, the trial was included only if it helped connect the network to another comparator of interest. The feasibility assessment identified potential treatment effect modifiers in paediatric plaque psoriasis and assessed the comparability of the study design characteristics and baseline characteristics.

Outcomes were assessed for feasibility, and those retained in the NMA were PASI response rates (PASI 50, PASI 75, PASI 90, and PASI 100) and mean change in CDLQI from baseline. The endpoints were evaluated at 12 weeks for all trials. The inclusion of Investigator's Global Assessment (IGA)/PGA as an outcome was also considered, however only A2310 reported the proportion of patients achieving a score of 0 or 1 using the 5-point IGA mod 2011 tool. Other studies reported results for the 5-point or 6-point sPGA scale, which is not equivalent regarding the severity of patients in the 0/1 categories.

Direct pairwise comparisons were carried out, and heterogeneity was assessed for each of these comparisons using the Cochran's Q test and the I^2 statistic. In the presence of heterogeneity, potential sources of bias were investigated.

Inconsistency was also evaluated for the closed loop containing 20030211 and A2310 (etanercept vs placebo comparison). Inconsistency would be suspected if the difference of the point estimates obtained from indirect vs direct evidence were significantly different, but these results showed no significant evidence of inconsistency.

The NMA was conducted in line with the Decision Support Unit (DSU) guidelines (54), in a Bayesian framework, and the model (random effects or fixed effects) was to chosen based on the lowest deviance information criterion (DIC). If the DIC of the two models were within three points of each other, the fixed-effects model was to be prioritised, as this can be considered a negligible difference. However, given the small

size of the network and due to convergence issues, it was not possible to use random effects models.

B.3.9.4 Results

B.3.9.4.1 Base-case analysis

This section presents the results of the fixed-effects model of the NMA. The DIC of the fixed-effects model was lower than that of the random-effects model (179 vs 191).

B.3.9.4.1.1 PASI response

Figure 17: Forest plot of the NMA results for the fixed-effects model comparing PASI 50 between secukinumab low dose and each comparator

Abbreviations: CrI, credible interval; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; RR, relative risk.

Figure 18: Forest plot of the NMA results for the fixed-effects model comparing PASI 75 between secukinumab low dose and each comparator

Abbreviations: CrI, credible interval; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; RR, relative risk.

Figure 19: Forest plot of the NMA results for the fixed-effects model comparing PASI 90 between secukinumab low dose and each comparator

Abbreviations: CrI, credible interval; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; RR, relative risk.

Figure 20: Forest plot of the NMA results for the fixed-effects model comparing PASI 100 between secukinumab low dose and each comparator

Abbreviations: CrI, credible interval; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; RR, relative risk.

Table 24: SUCRA values and probabilities for each secukinumab dose to perform better than the comparators for PASI scores

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

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

Figure 21: Rankograms for PASI

Abbreviations: PASI, Psoriasis Area and Severity Index; secukinumab H, secukinumab high dose; secukinumab L secukinumab low dose.

B.3.9.4.1.2 Mean change in CDLQI from baseline

Figure 22: Forest plot of the NMA results for the fixed-effects model comparing mean change in CDLQI between secukinumab low dose and each comparator

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CrI, credible interval; NMA, network meta-analysis; secukinumab H, secukinumab high dose.

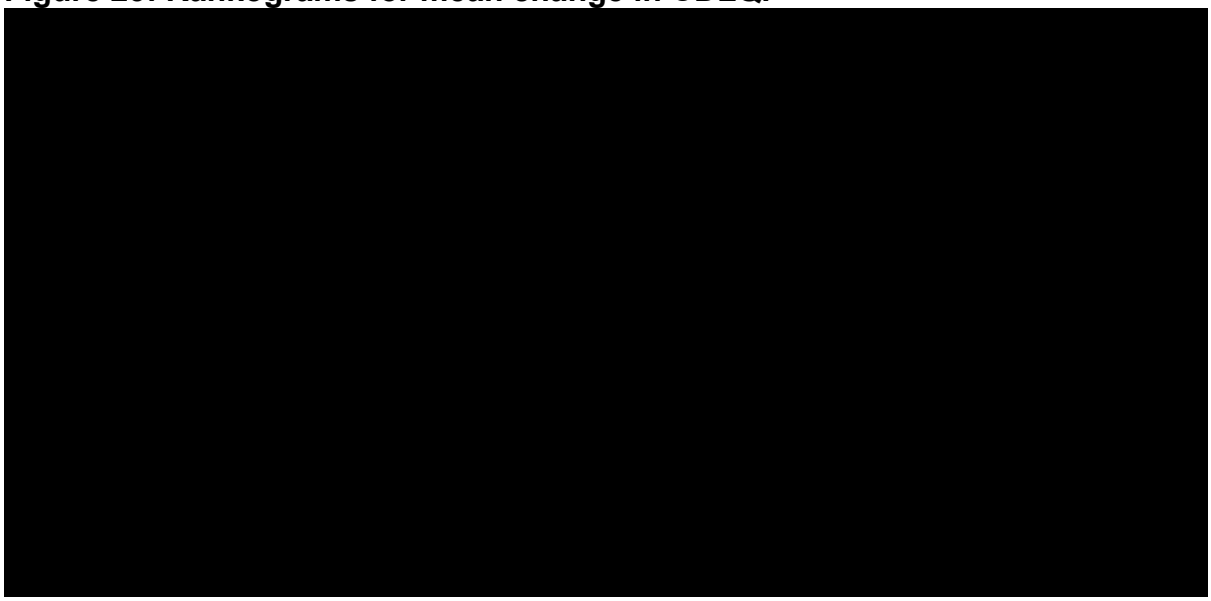
Table 25: SUCRA values and probabilities for each secukinumab dose to perform better than the comparators for mean change in CDLQI

Comparator	SUCRA	Probability of being better	
		Secukinumab low dose	Secukinumab high dose
Ustekinumab standard	[redacted]	[redacted]	[redacted]
Secukinumab low	[redacted]	[redacted]	[redacted]
Ustekinumab half	[redacted]	[redacted]	[redacted]
Secukinumab high	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

Example of interpretation: "Secukinumab low dose has a probability of 70.9% of being better than ustekinumab half dose."

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; SUCRA, surface under the cumulative ranking.

Figure 23: Rankograms for mean change in CDLQI



Abbreviations: CDLQI, Children's Dermatology Life Quality Index.

B.3.9.4.2 Sensitivity analyses

B.3.9.4.2.1 Inclusion of A2311

Similar results were obtained in the sensitivity analysis including A2311, showing that the results are robust to the inclusion of data from a population of patients with more moderate psoriasis treated with secukinumab.

Table 26 compares the SUCRA and probability of secukinumab being better between the base case and sensitivity analyses. Full results for this sensitivity analysis can be found in Appendix D.

Table 26: Comparison of SUCRA and probability of being better between the base case analysis and the sensitivity analysis including A2311 (PASI)

Comparator	SUCRA		Probability of secukinumab low dose being better	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Ustekinumab standard	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab high	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab low	[redacted]	[redacted]	-	-
Ustekinumab half	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]

Comparator	SUCRA		Probability of secukinumab low dose being better	
	Base case analysis	Sensitivity analysis	Base case analysis	Sensitivity analysis
Placebo	[redacted]	[redacted]	[redacted]	[redacted]

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

B.3.9.5 Statistical assessment of heterogeneity

Table 27 displays the results of the inconsistency assessment for the closed loop containing 20030211 and A2310. The results of the direct and indirect comparisons showed no significant evidence of inconsistency. The heterogeneity assessment is reported in Table 28. Based on the Cochran's Q test, no heterogeneity between the two studies was identified. Detailed results of the direct comparisons with trial-level information are reported in Appendix D. Due to the lack of heterogeneity between the trials, the fixed-effects and random-effects results for the direct comparisons are the same.

Table 27: Results from inconsistency assessment for all PASI endpoints available (placebo vs etanercept)

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

Table 28: Heterogeneity assessment for PASI

Comparison	Trials	Outcome	I^2	p-value of the Cochran's Q test
Etanercept vs placebo	20030211 A2310	PASI 50	[redacted]	[redacted]
		PASI 75	[redacted]	[redacted]
		PASI 90	[redacted]	[redacted]

Abbreviations: PASI, Psoriasis Area and Severity Index.

B.3.9.6 Uncertainties in the indirect and mixed treatment comparisons

[redacted]

[redacted]

B.3.9.7 Strengths of the analysis

[redacted]

B.3.9.8 Conclusions

[redacted]

B.3.10 Adverse reactions

B.3.10.1 A2310

B.3.10.1.1 Induction period

Most AEs reported during the induction period were of mild to moderate severity. One patient in each of the secukinumab high dose group and placebo group experienced severe AEs (toxic shock syndrome and blood bilirubin increased, respectively) while two patients in the etanercept group experienced severe AEs (abdominal pain, vomiting, autoimmune pancreatitis, gallbladder polyp).

Treatment-emergent adverse events (TEAEs) observed in the induction period are tabulated by primary SOC in Table 29. Overall, the differences in AE frequencies between treatment groups were marginal.

The most commonly affected SOC was 'infections and infestations' with slightly higher incidence in the secukinumab treatment groups and placebo group compared with the etanercept group. The higher incidence of AEs related to 'infections and infestations' in the secukinumab groups was mainly driven by events of nasopharyngitis and pharyngitis. Gastrointestinal disorders were more frequent in the etanercept group compared with the secukinumab treatment groups and the placebo group and were mainly driven by AEs of abdominal pain, diarrhoea, upper abdominal pain and nausea.

Skin and subcutaneous tissue disorders were more frequent in the secukinumab low dose group than the secukinumab high dose group, placebo group and the etanercept group. The AEs contributing to the higher frequency in the secukinumab low dose group were dry skin (two patients), eczema, diffuse alopecia, psoriasis and urticaria (one patient each).

Table 29: Absolute and relative frequencies for TEAEs, by primary SOC– induction period (safety set)

Primary SOC	SEC low dose N=40	SEC high dose N=40	Any SEC dose N=80	PLA N=41	ETN N=41
	n (%)	n (%)	n (%)	n (%)	n (%)
Any primary SOC	**23 (57.5)**	**25 (62.5)**	**48 (60.0)**	**22 (53.7)**	**25 (61.0)**
Infections and infestations	13 (32.5)	15 (37.5)	28 (35.0)	16 (39.0)	11 (26.8)

Primary SOC	SEC low dose N=40	SEC high dose N=40	Any SEC dose N=80	PLA N=41	ETN N=41
	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders	6 (15.0)	7 (17.5)	13 (16.3)	6 (14.6)	10 (24.4)
General disorders and administration site conditions	4 (10.0)	5 (12.5)	9 (11.3)	3 (7.3)	4 (9.8)
Skin and subcutaneous tissue disorders	5 (12.5)	3 (7.5)	8 (10.0)	3 (7.3)	1 (2.4)
Respiratory, thoracic and 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 and breast disorders	1 (2.5)	2 (5.0)	3 (3.8)	1 (2.4)	2 (4.9)
Blood and lymphatic system disorders	1 (2.5)	1 (2.5)	2 (2.5)	1 (2.4)	0
Eye disorders	0	2 (5.0)	2 (2.5)	1 (2.4)	3 (7.3)
Injury, poisoning and procedural complications	1 (2.5)	1 (2.5)	2 (2.5)	2 (4.9)	0
Musculoskeletal and connective tissue disorders	0	2 (5.0)	2 (2.5)	1 (2.4)	2 (4.9)
Renal and urinary disorders	2 (5.0)	0	2 (2.5)	2 (4.9)	2 (4.9)
Ear and labyrinth disorders	1 (2.5)	0	1 (1.3)	0	2 (4.9)
Metabolism and nutrition disorders	0	1 (2.5)	1 (1.3)	0	1 (2.4)
Cardiac disorders	0	0	0	0	1 (2.4)
Hepatobiliary disorders	0	0	0	0	1 (2.4)
Psychiatric disorders	0	0	0	1 (2.4)	0

Primary system organ classes are sorted in decreasing order of frequency in Any SEC dose group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in the "Any SEC dose".
MedDRA version 22.0 was used for reporting.
Abbreviations: ETN, etanercept; PLA, placebo; SEC, secukinumab; SOC, system organ class.

One patient (2.5%) each in the secukinumab low and high dose groups and four patients (9.8%) in the etanercept group experienced non-fatal SAEs (alanine aminotransferase and toxic shock syndrome in the secukinumab low and high dose groups, respectively, and gastrointestinal toxicity, autoimmune pancreatitis, gallbladder polyp and syncope in etanercept group [one SAE per patient]). One patient

each in the secukinumab high dose group (2.5%), placebo group (2.4%) and etanercept group (2.4%) had AEs leading to discontinuation of the study treatment. The AE leading to discontinuation in the etanercept patient had started during the induction period, however the patient was discontinued later during the maintenance period (Table 30).

Table 30: Deaths, other serious or clinically significant adverse events or related discontinuations – induction period (safety set)

	SEC low dose N=40	SEC high dose N=40	Any SEC dose N=80	PLA N=41	ETN N=41
	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with AEs	23 (57.5)	25 (62.5)	48 (60.0)	22 (53.7)	25 (61.0)
Patients with serious or other significant events					
Death	0	0	0	0	0
Non-fatal SAEs	1 (2.5)	1 (2.5)	2 (2.5)	0	4 (9.8)
Discontinued study treatment due to any AEs	0	1 (2.5)	1 (1.3)	1 (2.4)	1 (2.4)

Abbreviations: AE, adverse event; ETN, etanercept; PLA, placebo; SAE, serious adverse event; SEC, secukinumab.

The overall incidence of AEs possibly related to the study medication was low and was reported for eight patients (20%) in the secukinumab low dose group, six patients (15%) in the secukinumab high dose group, six patients (14.6%) in the placebo group and five patients (12.2%) in the etanercept group.

The most commonly-affected system organ class (SOC) with AEs possibly related to the study drug was 'Infections and infestations' with four patients (10%) in the secukinumab low dose group, three patients (7.5%) in the secukinumab high dose group, five patients (12.2%) in the placebo group and one patient (2.4%) in the etanercept group. The most commonly reported study drug-related AEs in this SOC were nasopharyngitis (two patients [5%] in the secukinumab low dose group, one patient each in the secukinumab high dose group [2.5%], placebo [2.4%] and etanercept groups [2.4%]) and upper respiratory tract infection (two patients [5%] in the secukinumab low dose group and one patient [2.4%] in the placebo group).

B.3.10.1.2 Up to data cut-off (18th September 2019)

Long-term safety includes the safety data until the data cut-off date (18th September 2019). Incidence rates of AEs up to the data cut-off are provided after adjusting for the

exposure (per 100 patient-years [PY]; Table 31) as none of the etanercept patients entered the extension period beyond Week 52.

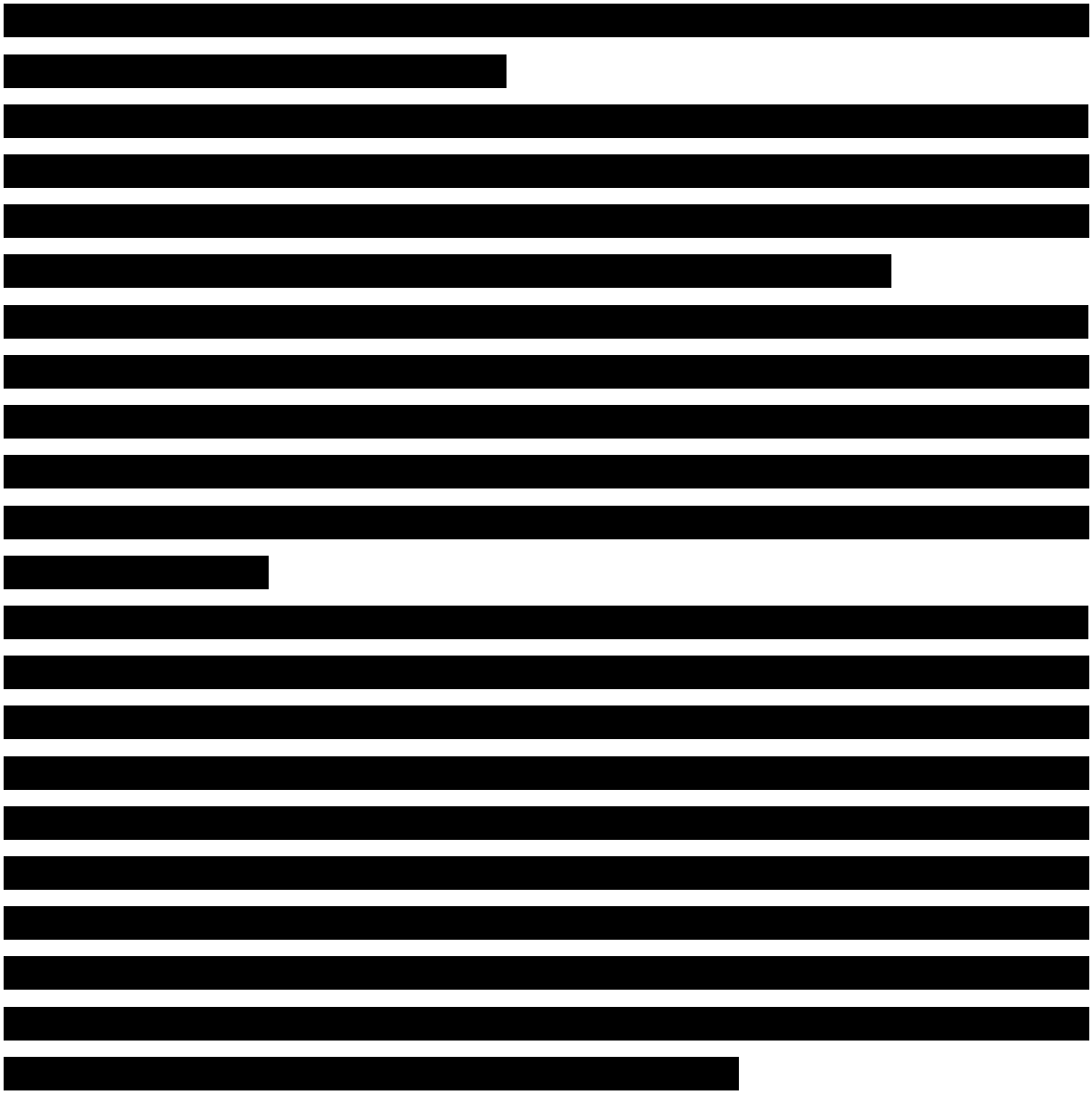


Table 31: Exposure adjusted incidence rates for most frequent TEAEs (≥4.0% or with incidence rate per 100 patient years ≥5.0 in any of the SEC treatment groups for preferred terms), by preferred term – up to the data cut off (18th September 2019; safety set)

Preferred term	Any SEC low dose N=56†	Any SEC high dose N=58†	Any SEC dose N=114†	Etanercept N=41
	n/EX (IR)	n/EX (IR)	n/EX (IR)	n/EX (IR)
Any preferred term	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal infection	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	Any SEC low dose N=56†	Any SEC high dose N=58†	Any SEC dose N=114†	Etanercept N=41
	n/EX (IR)	n/EX (IR)	n/EX (IR)	n/EX (IR)
Seborrhoeic dermatitis	[redacted]	[redacted]	[redacted]	[redacted]
Dysmenorrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngotonsillitis	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]
Eosinophilia	[redacted]	[redacted]	[redacted]	[redacted]
Impetigo	[redacted]	[redacted]	[redacted]	[redacted]

Preferred terms are sorted in decreasing order of IR in Any SEC dose group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
EX = exposure in 100 patient years. IR=incidence rate per 100 patient years.
For patients with event, exposure time is censored at time of first event.
MedDRA version 22.0 was used for reporting.
†After Week 12, the 'any secukinumab dose' group also includes safety data from placebo non-responders who switched to secukinumab.
Abbreviations: ETN, etanercept; PLA, placebo; SEC, secukinumab; TEAE, treatment-emergent adverse event.

[redacted]

Table 32: Exposure adjusted incidence rate for deaths, other serious or clinically significant adverse events or related discontinuations – Up to data cut-off (18th September 2019; safety set)

	Any SEC low dose N=56†	Any SEC high dose N=58†	Any SEC dose N=114†	ETN N=41
	n/EX (IR)	n/EX (IR)	n/EX (IR)	n/EX (IR)
Patients with AEs	[redacted]	[redacted]	[redacted]	[redacted]
Patients with serious or other significant events				
Death	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study treatment due to any AEs	[redacted]	[redacted]	[redacted]	[redacted]

EX=exposure in 100 patient years. IR=incidence rate per 100 patient years.
For patients with event, exposure time is censored at time of first event.
†After Week 12, the 'any secukinumab dose' group also includes safety data from placebo non-responders who switched to secukinumab.
Abbreviations: AE, adverse event; ETN, etanercept; PLA, placebo; SAE, serious adverse event; SEC, secukinumab.

[redacted]

B.3.10.2 A2311

[redacted]

Table 33: Exposure adjusted incidence rates for TEAEs by primary SOC – Entire treatment period (Safety set)

	SEC low dose [redacted]	SEC high dose [redacted]	Any SEC dose [redacted]
	n/EX (IR)	n/EX (IR)	n/EX (IR)
Any primary system organ class	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]

Primary system organ classes were sorted in descending order of IR of AEs in the any SEC dose column. A patient with multiple events within a primary system organ class was counted only once in the total row. For patients with event, exposure time was censored at time of first event. MedDRA version 22.1 has been used for reporting.
EX, exposure in 100 patient years; IR, incidence rate per 100 patient years.
Abbreviations: SEC, secukinumab; SOC, system organ class.

[redacted]

[redacted]

B.3.10.3 Conclusion of the safety of the technology

In paediatric patients with severe (PASI ≥20) and moderate to severe disease (PASI ≥12) in A2310 and A2311, respectively, secukinumab demonstrated a safety profile comparable with the safety profile in adults. Adverse events were mostly mild to moderate in severity, and in the comparison with placebo in the induction period of A2310, differences between secukinumab and placebo were marginal. In both the induction period and entire treatment period of A2310, rates of gastrointestinal disorders were lower in the secukinumab groups compared with the etanercept group.

B.3.11 Conclusions about comparable health benefits and safety

The key clinical outcome on which the NICE assessment of the comparators was based was PASI 75, with PASI 50 and PASI 90 also considered in the NMA (Section B.2). In A2310 (Section B.3.6.1), secukinumab demonstrated superior efficacy versus placebo in PASI 75 response rates (LD [redacted]; HD [redacted], placebo [redacted]), and PASI 75 rates were higher compared with etanercept ([redacted]).

PASI 90 and 100 are now regarded as clinical treatment goals for paediatric patients with psoriasis, as the aim of therapy is ultimately to achieve clear skin (3). Importantly, both secukinumab doses also demonstrated statistically significant efficacy compared with etanercept in IGA 0 (clear)/1 (almost clear) and PASI 90 outcomes (IGA: LD [redacted]; HD [redacted]; etanercept [redacted]. PASI 90: LD [redacted]; HD [redacted]; etanercept [redacted]). Secukinumab also demonstrated numerical improvement vs etanercept in PASI 100 response (LD [redacted]; HD [redacted]; etanercept [redacted])

In A2311 (Section B.3.6.2), secukinumab treatment resulted in high response rates and a safety profile comparable with that observed in A2310.

[redacted]

B.3.9

[redacted]

B.3.12 Ongoing studies

Both A2310 and A2311 are ongoing.

B.4 Cost-comparison analysis

A cost-comparison analysis shows that secukinumab is likely to be cost-saving compared with etanercept and ustekinumab

- A cost-comparison analysis was conducted comparing secukinumab against etanercept and ustekinumab in children and young people (aged 6 years and older) with moderate to severe plaque psoriasis (PASI ≥10)
- The population of interest was aligned with the NICE recommendation for the comparator therapies (patients who have failed to respond to standard systemic therapy, or in whom these treatments are contraindicated or not tolerated)
- The analysis considers costs associated with drug acquisition only, and factors in discontinuation following non-response and subsequent withdrawal from treatment
- In the base-case, secukinumab is shown to result in cost savings of [redacted] and [redacted] compared with etanercept and ustekinumab, respectively
- All considered scenario and sensitivity analyses resulted in substantial cost savings vs both etanercept and ustekinumab

B.4.1 Changes in service provision and management

No changes in service provision and management are anticipated following the introduction of secukinumab. The cost-comparison analysis considers costs associated with drug acquisition only, on the basis that:

- In TA455, costs associated with administration, monitoring and BSC were assumed to be the same for all biologics (2)
- Differences in AE costs between biologics are expected to be minimal.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A cost-comparison analysis was conducted to evaluate the cost to the NHS of using secukinumab instead of etanercept or ustekinumab for treating children and young people (aged 6 years and older) with moderate to severe plaque psoriasis (PASI ≥10) and following failure of standard systemic therapies. Whilst ustekinumab is recommended by NICE only in individuals aged 12 years and older (2), this analysis assumes that ustekinumab is available to individuals aged 6 years and older in line with the marketing authorisation (5). Subgroup analyses present results separately for patients aged 6–11 years and patients aged 12–17 years. A simple economic model was developed in Microsoft Excel to facilitate the comparison. Economic evaluations used in previous NICE appraisals in paediatric psoriasis (2) were used to inform the de novo model's structure, assumptions, and data sources.

A 5-year time horizon is adopted and 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. A 1-year cycle length is used.

Costs were not discounted in the base-case analysis in line with NICE guidance (56). However, the impact of discounting costs at 3.5% was explored in a scenario analysis.

Individuals enter the model receiving treatment with either secukinumab, etanercept or ustekinumab. Response based on PASI 75 is assessed at 12 weeks for

secukinumab and etanercept, and 16 weeks for ustekinumab. Non-responders to etanercept and ustekinumab are assumed to discontinue treatment. For secukinumab patients with weight <50 kg, non-responders are assumed to discontinue treatment. For secukinumab patients with weight ≥50 kg:

- Those who achieve PASI 50–74 at Week 12 transition to the secukinumab high dose (300 mg); response based on PASI 75 is assessed at 24 weeks, with non-responders discontinuing at this time point
- Those who do not achieve PASI 50 at Week 12 discontinue treatment.

Dosing assumptions for secukinumab are in line with the licensed posology.

Response rates for secukinumab are taken from A2310, and relative risks for etanercept and ustekinumab are taken from the NMA (Section B.3.9) and applied to the overall response rate for the secukinumab low dose group in A2310 (80.10%). The resulting response rates are presented in Table 34. Scenarios are considered in which data from A2311 is included in the NMA, and equivalent efficacy is assumed across the comparators (i.e. relative risks of 1). No 24-week PASI 75 data are available in those who:

- weigh ≥50 kg; and
- initially received secukinumab 150 mg, and achieved PASI 50–74 at 12 weeks; and
- received secukinumab 300 mg between weeks 12 and 24.

12-week data in those who weigh ≥50 kg and received secukinumab 300 mg is therefore used as a proxy; this approach assumes that response to the higher dose of secukinumab is uncorrelated with response on the lower dose. In order to explore the impact of this assumption on results, extreme value scenario analyses are performed in which 0% and 100% of patients are assumed to respond at Week 24.

Table 34: Response at 12/16 weeks†

Comparator	Weight	PASI 75 response at 12/16 weeks	PASI 50 response at 12 weeks
Secukinumab (75 mg)	<25 kg	[redacted]	-

	25–50 kg	[redacted]	-
Secukinumab (150 mg)	≥50 kg	[redacted]	[redacted]
Secukinumab (300 mg)	≥50 kg	[redacted]	-
Etanercept	-	[redacted]	-
Ustekinumab	-	[redacted]	-

† Response rates for secukinumab are taken from the clinical study report for A2310 (37); the response rate in patients weighing <25 kg is calculated as the average of the high dose and low dose groups, given that a 75 mg dose was administered to both groups. Response rates for etanercept and ustekinumab are calculated as the product of the relative risk generated from the NMA (Section B.3.9) and the overall response rate for the secukinumab low dose group in A2310.

In those who remain on treatment with each of secukinumab, etanercept and ustekinumab, a 20% withdrawal rate is assumed, in line with the approach taken in TA455 (2). Alternative withdrawal rates of 10% and 30% are tested in scenario analyses.

B.4.2.2 Intervention and comparators' acquisition costs

Table 35 presents a summary of the acquisition costs for secukinumab, etanercept and ustekinumab.

Table 35: Acquisition costs of the intervention and comparator technologies

	Secukinumab	Etanercept	Ustekinumab
Pharmaceutical formulation	150 mg solution for injection†	25 mg powder and solvent for solution for injection	45 mg solution for injection
(Anticipated) care setting	Secondary care		
Acquisition cost (excluding VAT)	List price: £609.39 PAS price: [redacted]	£164.00‡	£2,147.00
Method of administration	Subcutaneous injection		
Doses	For bodyweight <50 kg: 75 mg For bodyweight ≥ 50 kg: low dose 150 mg, high dose 300 mg	0.8 mg/kg up to a maximum of 50 mg	For body weight <60 kg: 0.75 mg/kg For body weight 60–100 kg: 45 mg For body weight ≥100 kg: 90 mg
Dosing frequency	Weeks 0, 1, 2, 3 and 4, then monthly thereafter	Weekly	At weeks 0 and 4, then every 12 weeks thereafter
Dose adjustments	For patients ≥50 kg, all patients begin on the low dose. For non-responders at 12 weeks: • Those achieving PASI 50–74 receive the high dose • Those not achieving PASI 50 discontinue treatment	N/A	N/A

†The cost comparison analysis calculates a cost per mg based on the 150 mg formulation (i.e. the same cost per mg is assumed across all formulations).
‡Cost based on the cheapest available biosimilar (Benepali®).
Abbreviations: N/A, not applicable; PAS, patient access scheme; PASI, Psoriasis Area and Severity Index; VAT, value added tax.

Dosing for each of the treatments is taken from the relevant SPC (5, 6, 57). For each comparator, dosing is determined by weight; modelled dosing is therefore determined by the proportion of individuals at each age between 6 and 17 years (9), and the average weight of individuals at each age (58) (Table 36). This approach is aligned with that taken in TA455.

Table 36: Age distribution and average weight by age (6-17 years)

Age	Proportion of the population†	Average weight (kg)‡
6	9%	21
7	9%	23
8	9%	26
9	9%	29
10	9%	32.5
11	8%	35.5
12	8%	40
13	8%	45
14	8%	50
15	8%	55
16	8%	58.5
17	8%	61.5

†Source: Office for National Statistics (9); ‡Source: Royal College of Paediatrics and Child Health (58)

Vial wastage is included in the model base case (i.e., the number of vials required is rounded up to account for wastage); this is aligned with clinical input provided in TA455. A scenario is considered in which no vial wastage is assumed.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

No costs other than drug acquisition costs are considered (Section B.4.1).

B.4.2.4 Adverse reaction unit costs and resource use

No costs other than drug acquisition costs are considered (Section B.4.1).

B.4.2.5 Miscellaneous unit costs and resource use

No costs other than drug acquisition costs are considered (Section B.4.1).

B.4.2.6 Clinical expert validation

No clinical expert validation was undertaken; however, the approach in this submission is aligned with TA455 which was developed in accordance with clinical expert feedback.

B.4.2.7 Uncertainties in the inputs and assumptions

A summary of the inputs used in the cost-comparison analysis are summarised in Table 37. Key assumptions are presented in Table 38.

Table 37: Summary of model inputs

Description	Input	Reference
Time horizon (years)	5	Assumption
Discount rate	0%	NICE FTA user guide (56)
Withdrawal rate	20%	NICE TA455 (2)
Population distribution: Age 6	9%	Office for National Statistics (9)
Population distribution: Age 7	9%	
Population distribution: Age 8	9%	
Population distribution: Age 9	9%	
Population distribution: Age 10	9%	
Population distribution: Age 11	9%	
Population distribution: Age 12	8%	
Population distribution: Age 13	8%	
Population distribution: Age 14	8%	
Population distribution: Age 15	8%	
Population distribution: Age 16	8%	
Population distribution: Age 17	7%	
Dosing		
Secukinumab <50 kg	75 mg	Proposed usage

Description	Input	Reference
Secukinumab ≥50 kg low dose	150 mg	
Secukinumab ≥50kg high dose	300 mg	
Etanercept <62.5 kg	0.8 mg/kg	British National Formulary (59)
Etanercept ≥62.5 kg	50 mg	
Ustekinumab <60 kg	0.75 mg/kg	
Ustekinumab 60–100 kg	45 mg	
Ustekinumab ≥100 kg	90 mg	
Average weight by age		
Age 6	21 kg	NICE TA455 (2)
Age 7	23 kg	
Age 8	26 kg	
Age 9	29 kg	
Age 10	32.5 kg	
Age 11	35.5 kg	
Age 12	40 kg	
Age 13	45 kg	
Age 14	50 kg	
Age 15	55 kg	
Age 16	58.5 kg	
Age 17	61.5 kg	
Efficacy 12w (secukinumab)		
<25 kg PASI 75	[redacted]	A2310 Clinical Study Report, secukinumab low dose (37)
25–50 kg PASI 75	[redacted]	
>50 kg PASI 75 (150 mg)	[redacted]	
>50 kg PASI 50 (150 mg)	[redacted]	
>50 kg PASI 75 (300 mg)	[redacted]	A2310 Clinical Study Report, secukinumab high dose (37)
Efficacy 12w (etanercept)		
PASI 75	[redacted]	NMA results (Section B.3.9.4)
Efficacy 16w (ustekinumab)		
PASI 75	[redacted]	NMA results (Section B.3.9.4)
Unit costs		
Secukinumab list price (150 mg)	£609.39†	British National Formulary (59)
Secukinumab PAS price (150 mg)	[redacted]	-
Etanercept biosimilar price (50 mg)	£164‡	British National Formulary (60)
Ustekinumab list price (45 mg)	£2,147	British National Formulary (61)

Description	Input	Reference
Mg per unit		
Secukinumab	150 mg	British National Formulary (59-61)
Etanercept	50 mg	
Ustekinumab	45 mg	
Number of doses		
Number of low doses, year 1: secukinumab low dose responders	16	Proposed usage
Number of low doses, year 1: secukinumab low dose partial-responders, high dose responders	6	
Number of high doses, year 1: secukinumab low dose partial-responders, high dose responders	10	
Number of low doses, year 1: secukinumab low dose partial-responders, high dose non-responders	6	
Number of high doses, year 1: secukinumab low dose partial-responders, high dose non-responders	3	
Number of low doses, year 1: secukinumab low dose non-responders	6	
Number of low doses, year 2+: secukinumab low dose responders	12	
Number of low doses, year 2+: secukinumab low dose partial-responders, high dose responders	0	
Number of high doses, year 2+: secukinumab low dose partial-responders, high dose responders	12	
Number of low doses, year 2+: secukinumab low dose partial-responders, high dose non-responders	0	
Number of high doses, year 2+: secukinumab low dose partial-responders, high dose non-responders	0	
Number of low doses, year 2+: secukinumab low dose non-responders	0	
Etanercept responders, year 1	52	British National Formulary (60)
Etanercept non-responders, year 1	52	
Etanercept responders, year 2+	12	
Etanercept non-responders, year 2+	0	
Ustekinumab responders, year 1	5	British National Formulary (61)
Ustekinumab non-responders, year 1	2	
Ustekinumab responders, year 2+	4	
Ustekinumab non-responders, year 2+	0	

† The cost comparison analysis calculates a cost per mg based on the 150 mg formulation (i.e. the same cost per mg is assumed across all formulations); note that the cost per mg is equivalent for the 150 mg and 75 mg formulations, and marginally lower for the 300 mg formulation (Section B.1.2).
‡ Cost based on the cheapest available biosimilar (Benepali®).
Abbreviations: PAS, patient access scheme; PASI, Psoriasis Area and Severity Index.

Table 38: Key assumptions of the analysis

Assumption	Rationale	Sensitivity analysis
Patients are assumed to remain on initial biological treatment until assessment of response.	This assumption is aligned with published NICE technology appraisals for moderate to severe plaque psoriasis, including TA103, TA134, TA146, TA180, TA350, TA442, TA521, TA455, TA596.	N/A
Response is initially assessed at 12 weeks for secukinumab and etanercept and 16 weeks for ustekinumab. Response is assessed again at 24 weeks for secukinumab patients weighing ≥ 50 kg who have moved on to the higher dose.	This is aligned with assumptions in TA455, TA350 and proposed usage of secukinumab.	N/A
The annual probability of discontinuation after the initial assessment of response is 20% for each treatment.	The value is aligned with previous appraisals including TA103, TA134, TA146, TA180, TA350, TA442, TA521, TA455 and TA596.	Alternative discontinuation rates of 10% and 30% are tested.
Vial wastage is included in the analysis	This assumption is aligned with clinical input in TA455	A scenario exploring no wastage is included in the analysis

Abbreviations: N/A, not applicable; NICE, National Institute for Health and Care Excellence.

B.4.3 Base-case results

Base-case results for the full modelled population (6–17 years) are presented in Table 39. Secukinumab is shown to result in cost savings of [redacted] and [redacted] compared with etanercept and ustekinumab, respectively.

Table 39: Base-case results

Technology	Total cost
Secukinumab	[redacted]
Etanercept	[redacted]
Ustekinumab	[redacted]

B.4.4 Sensitivity and scenario analyses

B.4.4.8 Deterministic sensitivity analysis

Parameter uncertainty was tested using deterministic sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range determined by either the 95% CI, or ±15% where no estimates of precision were available. The results of deterministic sensitivity analysis are presented for the comparisons of secukinumab against etanercept and ustekinumab in Figure 24 and Figure 25, respectively. The most influential parameters are shown to be the modelled PASI 75 scores and patient weight; however, secukinumab remains cost-saving for each considered parameter across the full range of plausible values.

Figure 24: Tornado diagram (secukinumab vs etanercept)

Abbreviations: PASI, Psoriasis Area and Severity Index.

Figure 25: Tornado diagram (secukinumab vs ustekinumab)

Abbreviations: PASI, Psoriasis Area and Severity Index.

B.4.4.9 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied, and the results of each analysis reported. The results of scenario analyses are presented for the comparisons of secukinumab against etanercept and ustekinumab in Table 40 and Table 41, respectively.

Table 40: Scenario analyses (secukinumab vs etanercept)

Scenario	Incremental costs
Base case	[redacted]
Time horizon: up to 18 years	[redacted]
Discount rate: 3.5%	[redacted]
NMA including Trial A2311	[redacted]
High dose response: 0% (bookend)	[redacted]
High dose response: 100% (bookend)	[redacted]
Equivalent efficacy across all comparators	[redacted]
Vial wastage excluded	[redacted]
Withdrawal rate: 10%	[redacted]
Withdrawal rate: 30%	[redacted]

Abbreviations: NMA, network meta-analysis.

Table 41: Scenario analyses (secukinumab vs ustekinumab)

Scenario	Incremental costs
Base case	[redacted]
Time horizon: up to 18 years	[redacted]
Discount rate: 3.5%	[redacted]
NMA including Trial A2311	[redacted]
High dose response: 0% (bookend)	[redacted]
High dose response: 100% (bookend)	[redacted]
Equivalent efficacy across all comparators	[redacted]
Vial wastage excluded	[redacted]
Withdrawal rate: 10%	[redacted]
Withdrawal rate: 30%	[redacted]

Abbreviations: NMA, network meta-analysis.

B.4.5 Subgroup analysis

Subgroup analyses for individuals aged 6–11 years and 12–17 years are presented in Table 42. Secukinumab was found to be cost-saving vs etanercept and ustekinumab in both age groups.

Table 42: Subgroup analyses

Technology	Total cost	
	6–11 years	12–17 years
Secukinumab	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]

B.4.6 Interpretation and conclusions of economic evidence

The aim of this analysis was to compare total costs associated with secukinumab, etanercept and ustekinumab in the treatment of children and young people (aged 6 years and older) with moderate to severe plaque psoriasis who are candidates for systemic therapy.

In the base case, secukinumab is shown to result in cost savings of [redacted] and [redacted] compared with etanercept and ustekinumab, respectively. All considered scenario and sensitivity analyses resulted in substantial cost savings vs both etanercept and ustekinumab. Secukinumab is therefore expected to result in substantial savings while providing similar efficacy.

The approach taken in this analysis is aligned with a previous NICE technology appraisal for plaque psoriasis in children and young people (TA455), and is expected to be generalisable to clinical practice in England and Wales.

References

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Appendices

The following appendices are provided as separate documents:

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Checklist of confidential information

Appendix I: Supplementary trial data

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

March 2021

File name	Version	Contains confidential information	Date
ID1669 Secukinumab – clarification response [AIC CIC]	1	Yes	18/03/2021

Section A: Clarification on effectiveness data

Identification and selection of relevant evidence

A1. Appendix D, Section D.1.5, Figure 1; and Section D.1.6, Table 6.

Please clarify the numbers and details of open-label extension (OLE) studies included in the systematic literature review (SLR). Figure 1 in Section D.1.5 shows that 14 records were included in the SLR, while Table 6 in Section D.1.6 lists 12 references as included within the SLR. Please clarify.

The numbers in the PRISMA flow diagram (Figure 1 in Section D.1.5) for OLE studies are correct. However, in the first SLR update the list of included OLE studies was not updated. An updated list is provided in Table 1, with the missing records (n=2) highlighted green.

Table 1: List of open label extension studies and abstracts of already included studies

Study Name	Author_Year	Title and source
M04-717 (Adalimumab)	Papp_2016	Adalimumab long-term safety/efficacy results for pediatric patients with chronic plaque psoriasis from a phase 3, randomized study. Journal of the American Academy of Dermatology. Conference: 74th Annual Meeting of the American Academy of Dermatology. Washington, DC United States. Conference Publication: (var.pagings). 74 (5 SUPPL. 1) (pp AB209), 2016. Date of Publication: May 2016.
	Papp_2016	Efficacy and safety of adalimumab versus methotrexate treatment in pediatric patients with severe chronic plaque psoriasis: Results from the 16-week randomized, double-blind period of a phase 3 study. Journal of Clinical and Aesthetic Dermatology. Conference: Maui Derm 2016. United States. 9 (5 Supplement 1) (pp S11-S12), 2016. Date of Publication: May 2016.
	Papp_2014	Baseline characteristics in pediatric patients with chronic plaque psoriasis from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment. JDDG - Journal of the German Society of Dermatology. Conference: 12th Congress of European Society for Pediatric Dermatology, ESPD 2014. Kiel Germany.

Study Name	Author_Year	Title and source
		Conference Publication: (var.pagings). 12 (SUPPL. 2) (pp 37-38), 2014. Date of Publication: June 2014.
	Papp_2014	Study design and baseline characteristics from a phase 3, randomized, double-blind study of adalimumab versus methotrexate treatment in pediatric patients with chronic plaque psoriasis. Journal of the American Academy of Dermatology. Conference: 72nd Annual Meeting of the American Academy of Dermatology. Denver, CO United States. Conference Publication: (var.pagings). 70 (5 SUPPL. 1) (pp AB190), 2014. Date of Publication: May 2014.
CADMUS (Ustekinumab)	Landells_2015	Safety and efficacy of ustekinumab in adolescent patients with moderate to severe plaque psoriasis: Results through 1 year of the phase 3 CADMUS trial. Journal of the American Academy of Dermatology. Conference: 73rd Annual Meeting of the American Academy of Dermatology. San Francisco, CA United States. Conference Publication: (var.pagings). 72 (5 SUPPL. 1) (pp AB202), 2015. Date of Publication: May 2015.
	Phillpp_2020	Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients (>= 6 to < 12 years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study. British Journal of Dermatology 2020. 183(4):664-672. Doi: 10.1111/bjd.19018. Date of Publication: May 2020
	Phillpp_2019	Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in pediatric patients (>6 to <12 year of age): Results from CADMUS Jr. Journal of the European Academy of Dermatology and Venereology. Conference: 6th Congress of the Skin Inflammation and Psoriasis International Network. France. 33 (SUPPL. 3) (pp 18), 2019. Date of Publication: April 2019.
20030211 (Etanercept)	Langley_2018	Pharmacokinetics, Immunogenicity, and Efficacy of Etanercept in pediatric Patients With Moderate to Severe Plaque Psoriasis. Journal of Clinical Pharmacology. 58 (3) (pp 340-346), 2018. Date of Publication: March 2018.
	Varni_2012	Health-related quality of life of pediatric patients with moderate to severe plaque psoriasis: Comparisons to four common chronic diseases. European Journal of

Study Name	Author_Year	Title and source
		Pediatrics. 171 (3) (pp 485-492), 2012. Date of Publication: March 2012.
	Siegfried_2010	Intermittent etanercept therapy in pediatric patients with psoriasis. Journal of the American Academy of Dermatology. 63 (5) (pp 769-774), 2010. Date of Publication: November 2010.
	Paller_2010	Long-term etanercept in pediatric patients with plaque psoriasis. Journal of the American Academy of Dermatology. 63 (5) (pp 762-768), 2010. Date of Publication: November 2010.
	Paller_2016	Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis. Journal of the American Academy of Dermatology. 74 (2) (pp 280-287.e3), 2016. Date of Publication: 01 Feb 2016.
	Paller_2016	Five-year open-label extension study of safety and efficacy of etanercept in children and adolescents with moderate to severe plaque psoriasis. Journal of the American Academy of Dermatology. Conference: 74th Annual Meeting of the American Academy of Dermatology. Washington, DC United States. Conference Publication: (var.pagings). 74 (5 SUPPL. 1) (pp AB251), 2016. Date of Publication: May 2016.
	Paller_2010	Safety and efficacy of etanercept treatment in children and adolescents with plaque psoriasis: 96-week results of open-label extension study. Journal of the American Academy of Dermatology. Conference: 68th Annual Meeting of the American Academy of Dermatology, AAD. Miami, FL United States. Conference Publication: (var.pagings). 62 (3 SUPPL. 1) (pp AB11), 2010. Date of Publication: March 2010.

Methods used to assess the clinical effectiveness evidence

A2. Appendix D, Section D.1.8, Table 16.

Table 16 presents the company's quality assessment of 4 studies including M04-717 (adalimumab), CADMUS (ustekinumab), 20030211 (etanercept) and Bodemer 2020 (secukinumab) but does not seem to include the A2311 study. Please clarify whether quality assessment was conducted for the A2311 study, and provide the results of the assessment, if available.

Quality appraisal was conducted only for randomised controlled trials (RCTs) in the SLR; A2311 is an open label trial.

A2310 trial - primary and secondary outcomes

A3. Document B, Section B.1.1, Table 1, pages 10-13.

The outcome: 'Duration of response' is listed among the outcomes considered in the CS. However, Figures 7 and 8 on pages 81-82 of Section B.3.6.1.3.2.2 (PASI response rates over time), Figure 9 on page 84 of Section B.3.6.1.3.4.2 (PASI score over time), and Figures 12-15 on pages 90-91 of Section B.3.6.2.2 (IGA and PASI response rates over time), appear to be the only data on duration of response reported in the submission. Please clarify whether other numerical data (including survival curves) are available. If available, please, provide them.

Table 2 provides cross-references to sections of the A2310 and A2311 clinical study reports (CSRs) reporting numerical data on duration of response. Some of these numerical data are linked to figures presented in Document B. Survival curves are not available.

Table 2: Numerical duration of response data in clinical study reports

Response measure	Corresponding section in Document B	CSR reference
A2310 – Week 52 CSR (1)		
PASI response rates over time	Figures 7–8	Table 11-1 (page 100)
PASI score over time	Figure 9	Table 14.2-4.1.3 (page 521)
IGA score over time	Section B.3.6.1.3.5.2	Table 14.2-4.3.3 (page 542)
CDLQI 0/1 over time	Figure 10	Table 11-4 (page 108)
A2311 – Week 52 CSR (2)		
IGA and PASI response rates over time	Figures 12–15	Table 11-1 (page 83)
PASI score over time	NA	Table 14.2-3.1 (page 225) Figure 14.2-2.1 (page 322)
IGA score over time	NA	Table 14.2-4.1 (page 232)
CDLQI score over time	NA	Section 11.4.1 (page 93)

Abbreviations: CDLQI, children's dermatology life quality index; CSR, clinical study report; IGA, investigator's global assessment; NA, not applicable; PASI, psoriasis area and severity index.

A4. Document B, Section B.1.1, Table 1, pages 10-13.

The outcome: 'Relapse rate' is listed among the outcomes considered in the CS. However, the results for relapse rates are not explicitly presented and discussed in the submission. Please clarify whether data on relapse rate are available (including survival curves) and explain why they have not been included in the submission. If available, please, provide them.

Data on relapse rates were omitted from the submission in error; information is provided below. Please note that relapse was defined as "when the achieved maximal PASI improvement from baseline is reduced by >50%".

A2310

[redacted]

A2311

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

A2310

[redacted]

[redacted]

A2311

[redacted]

Clinical effectiveness results

A5. Document A, Section A.7.1.1, Table 4, page 17.

Please clarify which method has been used for multiple imputation. Document B reference 43 provides the following information: "For efficacy analyses at week 12, missing post-baseline data and all efficacy measurements taken after patients entered the escape group were imputed as nonresponses. For binary end points, missing data were imputed as nonresponses; for continuous end points, missing data were imputed to have the baseline values." Please clarify whether the same approach was used for the analyses reported in Table 4. Please clarify also the extent of missingness.

Response variables based on psoriasis area and severity index (PASI) score and investigator's global assessment (IGA) mod 2011 categories were imputed with the multiple imputation method as the primary imputation method in trial A2310. This approach was described in Document A, Table 4 and Document B, Table 19 for trial A2310. Pure non-responder imputation was performed on response variables based on PASI score and IGA mod 2011 categories in sensitivity analysis in A2310. This approach was presented in Document B, Table 20 and Figure 6, and are described

in Section B.3.6.1.2. Methods to account for missing data in A2310 was further described in Document B, Section B.3.4.5.1. Non-responder imputation was used to analyse missing data in Document B, reference 43 (Paller et al.) (3).

Methods for imputation of missing data were considered when assessing the comparability of endpoints across trials for the NMA. As reported in Table 3, results using NRI were available for all trials for the proportions of patients achieving a specific PASI response. This imputation means that patients who did not have a value recorded for the PASI score at Week 12 were considered as having not achieved the specific PASI threshold. Therefore, while the base-case statistical method in A2310 was based on multiple imputation, we maintained consistency with other trials by using NRI in the NMA base case.

Table 3: Approaches used to handle missing data for the different outcomes of interest

Trial	Treatment arms	PASI responses	Change in CDLQI
20030211†	Etanercept Placebo	NRI	Missing values considered to have 0% improvement from baseline
CADMUS	Ustekinumab standard dose Placebo	NRI	No imputation
CAIN457A2310	Secukinumab low dose Secukinumab high dose Etanercept Placebo	NRI	LOCF

†Refers to the trial in reference 43 of Document B (3).
Abbreviations: CDLQI, Children's Dermatology Life Quality Index; NRI, non-responder imputation; PASI, psoriasis area and severity index; LOCF, last observation carried forward.

Pages 250–268 of the A2310 Week 52 CSR provide data on the number of missing patients at each timepoint for the outcomes PASI 50, PASI 75, PASI 90, PASI 100, and IGA 0 or 1 response (1).

A6. PRIORITY. Document B, Section B.1.1.2.

The company has not included adalimumab as a relevant comparator despite it being listed in the NICE final scope. Reasons provided in the CS include:

because it doesn't fit in the NMA (Section A, page 11) and because there are no trials in children (Section B, page 9). The ERG believes that adalimumab should be included in the network. Please clarify whether it is possible to link to the network through adalimumab by finding a trial comparing methotrexate to placebo, secukinumab or etanercept. If this is not possible, please present a summary for adalimumab versus methotrexate. Please note that in TA455 adalimumab was connected to the network using all available adult evidence. The ERG would consider this approach appropriate (see also question B1 on this issue).

It is not possible to link adalimumab to the NMA as there are no trials comparing methotrexate with placebo, secukinumab or etanercept. Methotrexate was only a comparator in the adalimumab M04-717 trial.

Although adult adalimumab data were used in TA455, this solution was adopted because of a need to develop a recommendation for adalimumab in the absence of paediatric data (4). However, it was considered inappropriate and unnecessary to include adult data within this appraisal given that:

- in-scope comparisons vs etanercept and ustekinumab can be made using paediatric data (and remain unaffected by the inclusion of adalimumab in the star-shape network),
- it is appropriate to consider a subset of comparators in a fast-track appraisal if the intervention offers similar or greater benefits at a similar or lower cost – there is precedence for this from TA521 (5),
- the inclusion of adult data would increase heterogeneity and could result in a less robust NMA; there were substantial differences in mean age, disease duration and PASI 75 placebo response rates between the adult and paediatric adalimumab trials (6-11).

As per the recommendation in TA455, it is expected that clinicians will prescribe biologics for paediatric psoriasis responsibly, given the guidance wording to use the least expensive option if more than one treatment is suitable. The NHS can be

reassured clinicians will prescribe responsibly and use the least expensive clinically appropriate option when choosing treatments.

A7. Document A, Section A.6 Table 3, page 14.

Trial A2311 compares secukinumab at low and high dose versus placebo; however, there is mention of an historical placebo group. Please provide more details of the historical placebo data and explain their relevance. Since the high dose is not part of the current assessment, please justify its use.

A historical placebo control based on data from qualifying trials was used as the comparator for the primary and key secondary endpoint analysis. This was in line with guidance from and discussions with health authorities including FDA and EMA, which suggested reducing placebo exposure as well as overall clinical trial burden for the paediatric population.

Historical placebo data included in this study were based on clinical appropriateness and alignment of definitions (endpoints, clinical disease population and time point of assessment). Integrated in the analysis were placebo data from Novartis-reported secukinumab adult placebo-controlled studies (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and paediatric placebo-controlled study CAIN457A2310. In addition, paediatric placebo-controlled study data from literature on other biologics (etanercept, ustekinumab) were utilised (3, 12).

The historical placebo control in A2311 allowed for the inclusion of the trial in an NMA sensitivity analysis, to assess the efficacy of secukinumab in patients with less severe disease (PASI ≥12 rather than PASI ≥20).

High dose secukinumab is relevant and part of this assessment for patients >50 kg. The secukinumab summary of product characteristics (SmPC) states that for patients >50 kg, some patients may derive additional benefit from the higher dose (300 mg), which is equivalent to the high dose for patients >50 kg in A2310 and A2311.

A8. <u>PRIORITY.</u> Document B, Section B.3.3.1.7.

Please provide baseline characteristics for all studies included in the NMA (2003002, CADMUS, A2310 and A2311). This could be similar to the information given in Table 10 Section B.3.3.1.7, page 47.

A summary of baseline characteristics for all studies included in the NMA is presented in Table 4.

Table 4: Summary of baseline characteristics reported across the studies

Study Name		CADMUS				20030211†		CAIN457A2310				CAIN457A2311	
Author, year		Landells 2015 (12)				Paller 2008 (3)		Bodemer 2020 (13)				Novartis data on file (14)	
Treatment arm		UST std. dose‡	UST half dose¶	UST both doses	PLA	ETN	PLA	SEC LD	SEC HD	ETN	PLA	SEC LD	SEC HD
Randomised		36	37	73	37	106	105	40	40	41	41	[redacted]	[redacted]
Age (Years)	Mean	14.8	15.1	14.9	15.6	14†	13†	13.7	13.2	13.5	13.7	[redacted]	[redacted]
	SD	1.7	1.7	1.7	1.5	4–17†	4–17†	2.9	3.2	2.9	3.3	[redacted]	[redacted]
Gender	Male (%)	44.4	48.6	46.6	54.1	52	50	32.5	42.5	39	46.3	[redacted]	[redacted]
	Female (%)	55.6	51.4	53.4	45.9	48	50	67.5	57.5	61	53.7	[redacted]	[redacted]
Weight (kg)	Mean	62	68.2	65.1	64.7	59.6†	59.8†	52.6	53.6	51.9	55.6	[redacted]	[redacted]
	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]
Race (%)	White/ Caucasian	94.4	81.1	87.7	91.9	78	71	85	85	73.2	87.8	[redacted]	[redacted]
	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]
PASI (0-72)	Mean	21.7	21	21.3	20.8	16.7†	16.4†	27.6	28	28.4	28	[redacted]	[redacted]
	SD	10.4	8.5	9.4	8	12–51.6†	12–56.7†	6.9	8.7	9	8.1	[redacted]	[redacted]
BSA (%)	Mean	31.9	33.6	32.7	27.4	21†	20†	37.6	40.3	43.1	40	[redacted]	[redacted]

Study Name		CADMUS				20030211†		CAIN457A2310				CAIN457A2311	
Author, year		Landells 2015 (12)				Paller 2008 (3)		Bodemer 2020 (13)				Novartis data on file (14)	
Treatment arm		UST std. dose‡	UST half dose¶	UST both doses	PLA	ETN	PLA	SEC LD	SEC HD	ETN	PLA	SEC LD	SEC HD
	SD	23.2	21.4	22.1	16.4	10–90†	10-95†	13.9	17.6	19.6	17.7	[redacted]	[redacted]
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]
	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]
Diagnosis of PsA	%	NR	NR	NR	NR	5	13	12.5	7.5	7.3	7.3	[redacted]	[redacted]
Prior systemic conventional therapy	%	47.2	37.8	42.5	43.2	58††	62††	65	52.5	46.3	48.8	[redacted]	[redacted]
Prior biologic therapy	%	8.3	10.8	9.6	13.5	0	0	7.5	0	2.4	0	[redacted]	[redacted]

†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.
Abbreviations: BSA, body surface area; ETN, etanercept; HD, high dose; kg, kilogram; mg, milligram; LD, low dose; PASI, psoriasis area and severity index; PLA, placebo; PsA, psoriatic arthritis; PsO, psoriasis; SD, standard deviation; SEC, secukinumab; std., standard; UST, ustekinumab.

A9. PRIORITY. Document B, Section B.3.6.1.2.

For all studies in the NMA please provide in one table for comparison, the treatment effect sizes (and CIs) for all the outcomes; the ERG would like to be in the position to replicate the NMA. This could be similar to Tables 20/21 Section B.3.6.1.2, pages 77-79. The ERG has concerns regarding the confidence intervals and p-values presented in Table 20 (Section B.3.6.1.2, page 77). Please check these results.

Inputs for the NMA are provided in Table 5 and Table 6.

Table 5: NMA inputs – PASI scores

Treatment	Reported in trial				Recalculated for multinomial NMA			
	PASI 50 n/N	PASI 75 n/N	PASI 90 n/N	PASI 100 n/N	PASI 0-50 n/N	PASI 50-75 n/N	PASI 75-90 n/N	PASI 90-99 n/N
CADMUS study (12)								
Ustekinumab standard dose	32/36	29/36	22/36	14/36	4/36	3/32	7/29	8/22
Ustekinumab half dose	30/37	29/37	20/37	8/37	7/37	1/30	9/29	12/20
Placebo	11/37	4/37	2/37	1/37	26/37	7/11	2/4	1/2
20030211 study (3)								
Etanercept	79/106	60/106	29/106	NA	27/106	19/79	31/60	NA
Placebo	24/105	12/105	7/105	NA	81/105	12/24	5/12	NA
CAIN457A2310 study								
Secukinumab high dose	[redacted]							
Secukinumab low dose	[redacted]							
Etanercept	[redacted]							
Placebo	[redacted]							
CAIN457A2311 study								
Secukinumab high dose	[redacted]							
Secukinumab low dose	[redacted]							

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

Table 6: NMA inputs – CDLQI scores

Endpoint	Treatment comparison	'test'		'control'		Mean difference (95% CI)
	'test' vs 'control'	N	Mean CFB (SE)	N	Mean CFB (SE)	
CADMUS study						
CDLQI – change from baseline (CFB)	Ustekinumab standard dose vs Placebo	32	–6.7 (0.9899)	32	–1.5 (0.5657)	–5.2 (–7.43, –2.97)
	Ustekinumab half dose vs Placebo	35	–5.6 (1.0818)	32	–1.5 (0.5657)	–4.1 (–6.49, –1.71)
20030211 study						
CDLQI – change from baseline (CFB)	Etanercept vs Placebo	106	–5.4 (0.5439)	105	–3.1 (0.4977)	–2.3 (–3.75, –0.85)

Abbreviations: CFB, change from baseline; CI, confidence interval; SE, standard error.

There was initially a programming error in the calculation of the odds ratio estimates and their 95% CIs for logistic regression analysis (pure NRI), and we apologise that an outdated source was used for Document B. Table 7 is a corrected version of Table 20 in Document B. Please note that the NMA incorporated the updated, corrected version of Table 20 therefore NMA results submitted are not affected.

Table 7: Logistic regression analysis of IGA mod 2011 0 (clear) or 1 (almost clear), PASI 75 and PASI 90 response at Week 12 (pure non-responder imputation; FAS)

Response criterion	Treatment comparison	'test'	'control'	Odds ratio estimate (95% CI)†	p-value
	'test' vs 'control'	n*/m (%)	n*/m (%)		
IGA 0/1	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]

Response criterion	Treatment comparison	'test'	'control'	Odds ratio estimate (95% CI)†	p-value
	'test' vs 'control'	n*/m (%)	n*/m (%)		
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]

†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.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; ETN, etanercept; FAS, full analysis set; m, number of patients evaluable; n*, rounded mean number of responders for 100 imputations; PASI, Psoriasis Area and Severity Index; PLA, placebo; SEC, secukinumab.

A10. Document B, Section B.3.9.6, page 104.

Random effect models would be preferable in this instance especially since the NMA links are not all well populated and there is heterogeneity between included studies. The ERG recognises that small networks may pose problems with regard to the fitting of random-effects models, but would like further commentary on the limitations of using fixed effect models.

The NMA was conducted in line with the DSU guidelines (15, 16) in a Bayesian framework, and the choice of model (random effects [RE] or fixed effects [FE]) was planned to be based on the lowest Deviance Information Criterion (DIC), if both models converged. The FE and RE models were developed and convergence was checked for both models before considering the comparison of DIC values.

In the analysis conducted, the RE model did not converge using vague prior distributions. The non-convergence of the RE model was expected based on the low amount of data included in the network. Indeed, direct comparisons between two treatments in the network were informed by only one trial, except for the comparison between placebo and etanercept (for which two trials provided data). Several publications have highlighted that when networks contain a small number of studies, estimating the between-study variance becomes difficult (17, 18).

The use of an FE model rather than an RE model therefore led to the assumption that no heterogeneity exists between studies. Therefore, studies were considered to

inform on the same unknown treatment effect. On the contrary, RE models would have considered unexplained heterogeneity between studies and would have allowed treatment effect to vary between studies (the latter being a more reasonable assumption when considering the populations and study characteristics at baseline). The use of the FE model therefore led to considering only one common effect size, when the RE model would consider the distribution of treatment effects. The results obtained through FE NMAs are therefore less generalisable to wider populations compared to RE models, and the credible intervals obtained through the NMAs could be underestimated.

Given the small size of the network and due to convergence issues, it was not possible to use a RE model. Therefore, the FE model was prioritised.

A11. PRIORITY. Section B.3.3.1.1.2, page 37.

Please provide clarification on the treatment received by participants in the placebo group of trial A2310. Please clarify whether they only receive placebo for the first 12 weeks before receiving either a low or a high dose of secukinumab. Other medical treatments have a rule whereby if there is no or poor response the treatment is stopped. Please clarify whether such a rule applies to secukinumab.

Treatment received by participants in the placebo group

Trial A2310 was double-blind for the secukinumab and placebo arms. Double-dummy treatment administration ensured neither patients nor investigators were aware of treatment assignment between Weeks 0 and 12 (the etanercept arm was single blind).

Participants in the placebo group of trial A2310 only received placebo for the first 12 weeks. Placebo patients not achieving PASI 75 at Week 12 were switched to secukinumab at the pre-assigned dose level. Placebo patients who achieved a PASI 75 response at Week 12 did not progress into the maintenance period. All secukinumab and etanercept patients continued the same treatment as received from Weeks 0–8 during the maintenance period from Week 12 onwards.

Stopping rules

The secukinumab SmPC states that for all indications (including paediatric plaque psoriasis) ‘a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks' (19).

In clinical practice, it is anticipated that the stopping rule for secukinumab in paediatric plaque psoriasis will align with the rule in the NICE recommendation for adult plaque psoriasis. TA350 states: “it is recommended that secukinumab treatment is stopped after 12 weeks if patients do not achieve either PASI 75, or PASI 50 with a 5-point reduction in DLQI” (20).

A12. PRIORITY. Document B, Section B.1.3.2.2, pages 22-24.

Please explain your understanding of the market shares of each NICE-recommended treatment option for plaque psoriasis in children and young people (adalimumab, etanercept and ustekinumab).

It is not possible to obtain indication-level prescribing data for England or the UK from standard data sources such as IQVIA, as the data do not distinguish between treatment use across different indications. In the absence of market share data, assumptions were made based on clinical expert opinion. Adalimumab is estimated to have a 50% market share, including biosimilars; etanercept and ustekinumab are estimated to have a 25% market share each (Novartis estimate).

Section B: Clarification on cost-comparison data

B1. PRIORITY. Document B, Table 1, page 11.

The ERG notes that adalimumab is not included as a comparator in the cost comparison analysis. The ERG considers adalimumab to be a relevant and important comparator for the cost comparison because:

- **Adalimumab was included in TA455, and connected to the network using all available adult evidence, with the committee concluding that**

this was appropriate and that ustekinumab and adalimumab had similar effectiveness.

- **The view of the ERG's clinical expert is that adalimumab is an appropriate comparator for secukinumab as it is routinely used in clinical practice and would be preferred to etanercept.**
- **The company's budget impact analysis assumes adalimumab consumes 50% of market share (see Cell "E31", sheet: "budget impact" on the submitted economic model) and is therefore an important comparator.**
- **Adalimumab is particularly relevant for patients under the age of 12, where ustekinumab does not currently have NICE approval, and the only other available comparators are etanercept and adalimumab.**

Whilst the ERG's preference would be for the company to re-run the NMA using all available adult data, and use the corresponding response rates and relative risks in the cost-comparison model, the ERG would also consider it acceptable to include adalimumab in the cost-comparison model on the basis of equal efficacy to ustekinumab, given the findings of TA455. Please provide:

- **A full set of cost comparator analyses, including updated parameter tables, results tables and figures with the inclusion of adalimumab as a comparator.**
- **A fully executable cost comparison model excel file with these changes implemented and the functionality to re-run all scenario analyses.**

It is not possible to link adalimumab to the NMA, and the inclusion of adult adalimumab data is considered inappropriate and unnecessary for the reasons provided in the response to Question A6. However, a scenario is considered in which adalimumab is assumed to have equivalent efficacy to ustekinumab.

A table of acquisition costs, updated to include adalimumab at the lowest nationally available cost as specified in the letter from NHS England (2019) (21), is presented in the Appendix, and the results of the scenario in which adalimumab is included as a comparator are presented in Table 8.

[redacted]

A fully executable cost-comparison model (Excel) is provided with these changes implemented and including the functionality to re-run all scenario analyses.

Table 8: Scenario analysis including adalimumab as a comparator

	Secukinumab	Etanercept	Ustekinumab	Adalimumab
Base-case	[redacted]	[redacted]	[redacted]	[redacted]

B2. Document B, Table 34, page 117.

The table provides PASI-75 response rates for the comparators at 12 and 16 weeks respectively. Please:

- **Clarify how the overall response rate for secukinumab low dose group ([redacted] from study A2310 is calculated.**
- **Provide a clinical explanation as to why the PASI-75 response is dependent on patient weight for secukinumab but not for etanercept or ustekinumab.**
- **Clarify why it is appropriate to assume that the relative risk of response for etanercept and ustekinumab compared to secukinumab applied in the cost-comparison model is constant across all weight groups (<25KG, 25-50KG and >50KG).**
- **If clinically appropriate, and if sufficient data are available from the trials, please provide a scenario analysis that uses relative risks of response that vary across the weight categories.**

The overall response rate for secukinumab is the rate of achievement of PASI 75 response amongst the secukinumab low dose group at Week 12 in study A2310 (Table 11-1 in the clinical study report for study A2310 (22)). Primary statistical analyses were performed using multiple imputation for missing data. At Week 12, PASI 75 response was achieved by [redacted] of patients in the secukinumab low dose group compared with [redacted] of patients in the placebo group.

[redacted]. Please note that in this multiple imputation analysis, [redacted] is a rounded mean number of responders for 100 imputations.

Clinical advice and the SmPCs for etanercept and ustekinumab suggest that the dose should be weight-based (based on pharmacokinetics), although weight thresholds vary between treatments.

Unfortunately, we do not have access to data on the efficacy endpoints including PASI 75 for etanercept or ustekinumab stratified by weight, so we are unable to provide the analysis requested. Efficacy is assumed to be consistent across weight categories for ustekinumab and etanercept in the absence of efficacy by weight categories for specific doses from the relevant clinical trials.

A scenario is presented in Table 9 in which equivalent efficacy is assumed across all weight categories for secukinumab (i.e., a response rate of [redacted]);

[redacted]

Table 9: Scenario analysis assuming equivalent efficacy across all weight categories

	Secukinumab	Etanercept	Ustekinumab
Base-case	[redacted]	[redacted]	[redacted]
Assuming equivalent efficacy across all weight categories	[redacted]	[redacted]	[redacted]

B3. <u>PRIORITY</u>. Document B, Table 37, page 121.

The number of secukinumab dosages, and dose increases at 12 weeks for partial responders, used in the model is described as "proposed usage". Please provide a table that compares the proposed usage of secukinumab, in terms of number of doses and assumptions about dose increase to 300mg at 12 weeks, with treatment usage data from the clinical trials. If trial usage is different to the proposed usage, please provide a cost comparison scenario analysis using the dosages from the trials to calculate treatment acquisition costs.

In study A2310, secukinumab low dose and secukinumab high dose represented alternative arms of the clinical trial; it was not possible to transition from secukinumab low dose to secukinumab high dose based on initial response to the low dose. A scenario is therefore presented in Table 10 in which no patients transition to the higher dose following response assessment (i.e., all patients who do not respond to secukinumab at 12 weeks are assumed to discontinue treatment).

[redacted]

Table 10: Scenario analysis in which no patients transition to the higher dose

	Secukinumab	Etanercept	Ustekinumab
Base-case	[redacted]	[redacted]	[redacted]
No patients transition to higher dose	[redacted]	[redacted]	[redacted]

B4. PRIORITY. Document B, page 118.

The ERG note that the cost comparison model assumes a 20% all-cause withdrawal rate applied to all comparators. Please provide:

- **Tabulated data describing all available treatment withdrawal data from the trials.**
- **Further clinical justification for the assumption that the withdrawal rate can be considered similar across all treatments.**
- **If possible, a cost-comparison scenario analysis that utilises treatment specific withdrawal rates.**

Withdrawal data from the trials are presented in Table 11.

Table 11: Treatment withdrawals across the RCT studies

Study Name	Author, year	Time point (weeks)	Treatment arm	Randomised	Treatment Withdrawals		
					Due to any cause, n	Due to lack of efficacy, n	Due to AE, n
CADMUS (Ustekinumab)	Landells 2015 (12)	12	Ustekinumab Standard dose	36	NR	NR	NR
			Ustekinumab Half standard dose	37	NR	NR	NR
			Combined dose	73	NR	NR	NR
			Placebo	37	NR	NR	NR
20030211 (Etanercept)	Paller 2008 (3)	12	Etanercept	106	NR	NR	1
			Placebo	105	2	NR	NR
CAIN457A2310 (Secukinumab)	Novartis Data on File (22)	12	Secukinumab Low dose	[redacted]	[redacted]	[redacted]	[redacted]
			Secukinumab High dose	[redacted]	[redacted]	[redacted]	[redacted]
			Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
			Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Bodemer_2020 (13)	12-52	Secukinumab Low dose	39	1	NA	1
			Secukinumab High dose	38	1	1	0
			Placebo - Secukinumab Low dose†	16	1	NA	1
			Placebo - Secukinumab High dose†	18	2	NA	NA
			Etanercept	40	6	3	1

†5 patients in the placebo group who were PASI 75 responders at Week 12 did not proceed into the maintenance period as defined in the protocol.
Abbreviations: AE, adverse event; NA, not applicable; NR, not reported; RCT, randomised controlled trial.

In the absence of head-to-head RCT data, a flat assumption across all comparators is the fairest way to make an assessment. In trial A2310, the etanercept withdrawal rate is higher than secukinumab withdrawal rate. Both treatments have low and similar withdrawal rates in Weeks 1–12; in the maintenance period (Weeks 12–52) [redacted] etanercept patients withdrew compared with [redacted] secukinumab patients.

A 20% withdrawal rate is assumed in the base case analysis which is in line with the approach taken in TA455 (4).

A cost-comparison scenario analysis using treatment specific discontinuation rates is not possible since no discontinuation rate specific to ustekinumab is available.

B5. Document B, page 20 and Table 36, page 120.

The company indicate that paediatric psoriasis is associated with an increased risk of obesity. However, the data included in the economic model to inform treatment dosages are based on ONS data, which the ERG assumes are general population average weights by age. Please provide a scenario analysis and commentary describing the potential impact of a higher than average age-specific weight on the results of the cost-comparison analysis. This might include, for example, a scenario where all patients in the 12-17 age subgroup receive treatment dosages assuming an average weight of ≥50kg.

In order to explore the impact of higher weight in paediatric psoriasis patients on the cost-comparison analysis, scenario analyses are presented in Table 12 in which:

- All patients aged 12-17 years are assumed to weigh at least 50kg,
- The weight of all patients is assumed to be increased by 20%.

[redacted]

Table 12: Scenario analyses considering higher patient weight

	Secukinumab	Etanercept	Ustekinumab
Base-case	[redacted]	[redacted]	[redacted]
All patients aged 12-17 weigh ≥50 kg	[redacted]	[redacted]	[redacted]

	Secukinumab	Etanercept	Ustekinumab
All patient weights increased by 20%	[redacted]	[redacted]	[redacted]

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21. NHS England and NHS Improvement. Reference Prices for Adalimumab. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/04/reference-prices-for-adalimumab-letter.pdf (last accessed 17th March 2021). 2019.
22. Novartis. Data on file: A2310 Week 24 CSR.

Appendix

Drug acquisition costs for secukinumab and comparators were obtained from the British National Formulary for Children (BNFc). The only exception to this is the cost for adalimumab biosimilar, which was assumed to be the interim national reference price set by the NHS England tendering process.

Table 13: Acquisition costs of the intervention and comparator technologies

	Secukinumab	Etanercept	Ustekinumab	Adalimumab
Pharmaceutical formulation	150 mg solution for injection†	25 mg powder and solvent for solution for injection	45 mg solution for injection	20 mg solution for injection
(Anticipated) care setting	Secondary care			
Acquisition cost (excluding VAT)	List price: £609.39 PAS price: [redacted]	£164.00‡	£2,147.00	£68.27
Method of administration	Subcutaneous injection			
Doses	For body weight <50 kg: 75 mg For body weight ≥ 50 kg: low dose 150 mg, high dose 300 mg	0.8 mg/kg up to a maximum of 50 mg	For body weight <60 kg: 0.75 mg/kg For body weight 60–100 kg: 45 mg For body weight ≥100 kg: 90 mg	For body weight <30 kg: 20 mg For body weight ≥ 30 kg: 40 mg
Dosing frequency	Weeks 0, 1, 2, 3 and 4, then monthly thereafter	Weekly	At weeks 0 and 4, then every 12 weeks thereafter	At weeks 0 and 1, then every 2 weeks thereafter
Dose adjustments	For patients ≥50 kg, all patients begin on the low	N/A	N/A	N/A

	Secukinumab	Etanercept	Ustekinumab	Adalimumab
	dose. For non-responders at 12 weeks: • Those achieving PASI 50–74 receive the high dose • Those not achieving PASI 50 discontinue treatment			

†The cost comparison analysis calculates a cost per mg based on the 150 mg formulation for secukinumab and the 20 mg formulation for adalimumab (i.e. the same cost per mg is assumed across all formulations).
‡Cost based on the cheapest available biosimilar (Benepali®).
Abbreviations: N/A, not applicable; PAS, patient access scheme; PASI, Psoriasis Area and Severity Index; VAT, value added tax.

The co-primary endpoints (PASI 75 and IGA mod 0 or 1 response) and the key secondary endpoint (PASI 90) are reported in Tables 19 and 20 (Document B, pages 75 and 77 of the company submission) in terms of "rounded mean number of responders for 100 imputations/number of patients evaluable". The secondary endpoints (PASI 50 and PASI 100) are reported in Table 21 (Document B, page 79) in a similar format. The ERG is unable to locate actual observed counts of participants achieving these endpoints in the submission. Please either indicate where these data are presented in the submission or provide the actual observed counts of participants achieving the co-primary (PASI 75 and IGA mod 0 or 1 response). If possible, please provide also the observed counts for people achieving the secondary endpoints (PASI 90, PASI 50, PASI 100).

Table 20, Document B presents logistic regression analysis of IGA mod 0 or 1, PASI 75 and PASI 90 response at week 12 using pure non-responder imputation. Using this imputation approach, missing values with respect to response variables based on PASI score and IGA mod 0 or 1 were imputed with non-response regardless of the reason for missing data. Therefore, only actual observed counts of participants achieving these endpoints were considered in the analysis. There was a typographic error in the footnote for Table 20 of Document B and the footnote for Table 7 of clarification response, for which we apologise. Instead of "n* is the rounded mean number of responders for 100 imputations", 'n' should read number of subjects observed achieving the endpoint (i.e. responders). The actual observed counts of participants achieving IGA mod 0 or 1, PASI 75 and PASI 90 response at Week 12 correspond to 'n', number of subjects observed achieving the endpoint (i.e. responders) in Table 1 where the non-responder imputation approach was undertaken.

The corrected version of Table 20 (Document B) and Table 7 (clarification response) is reproduced in Table 1 below:

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

Table 1: Logistic regression analysis of IGA mod 2011 0 (clear) or 1 (almost clear), PASI 75 and PASI 90 response at Week 12 (pure non-responder imputation; FAS)

Response criterion	Treatment comparison	'test'	'control'	Odds ratio estimate (95% CI)†	p-value
	'test' vs 'control'	n/m (%)	n/m (%)		
IGA 0/1	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]

†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.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; ETN, etanercept; FAS, full analysis set; m, number of patients evaluable; n, number of subjects observed achieving the endpoint (i.e. responders); PASI, Psoriasis Area and Severity Index; PLA, placebo; SEC, secukinumab.

Table 19, Document B presents logistic regression analysis of IGA mod 0 or 1, PASI 75 and PASI 90 response at week 12 using multiple imputation. With this simulation based approach, missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. Therefore, the rounded mean number of responders for 100 imputations were reported in Table 19.

Table 21, Document B presents logistic regression analysis of PASI 50 and PASI 100 response at Week 12 using multiple imputation. As logistic regression analysis of PASI 50 and PASI 100 response at Week 12 using non-responder imputation was not

Clarification questions

provided previously in Document B, the results are presented in Table 2. As above, using non-responder imputation for missing data, the n numbers represent observed counts of participants achieving PASI 50 and PASI 100 at Week 12.

Table 2: Logistic regression analysis of PASI 50 and PASI 100 response at Week 12 (pure non-responder imputation; FAS)

Response criterion	Treatment comparison 'test' vs 'control'	'test' n/m (%)	'control' n/m (%)	Odds ratio estimate (95% CI)†	p-value
PASI 50	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	SEC low dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs PLA	[redacted]	[redacted]	[redacted]	[redacted]
	SEC low dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]
	SEC high dose vs ETN	[redacted]	[redacted]	[redacted]	[redacted]

†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.
Abbreviations: CI, confidence interval; ETN, etanercept; FAS, full analysis set; NE, not estimable; PASI, Psoriasis Area and Severity Index; PLA, placebo; SEC, secukinumab; m, number of patients evaluable; n, number of subjects observed achieving the endpoint (i.e. responders)

Please note that while the base-case statistical method in A2310 was based on multiple imputation, we maintained consistency with other trials by using non-responder imputation in the NMA base case. This consistency is intended to avoid any potential heterogeneity induced by distinct statistical methods used to manage missing data.

Clarification questions

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]**, on behalf of the British Association of Dermatologists' Therapy & Guidelines sub-committee**
2. Name of organisation	**British Association of Dermatologists**

3. Job title or position	**Adult and Paediatric Consultant Dermatologists**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with moderate to severe plaque psoriasis? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training and research of Dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of Dermatology services across all service settings. It is funded by the activities of its Members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	The BAD is a registered charity and owns various companies. The British Association of Dermatologists Biologic Interventions Register (BADBIR) is the national psoriasis biologic and systemic treatment registry (and an NIHR portfolio study) run by the BAD as a non-profit-making limited company. This company receives funding from most manufacturers of biological drugs for psoriasis on the registry to collect pharmacovigilance data. The BAD does not receive any funding from BADBIR.

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Secukinumab would be used as a systemic treatment to: • control psoriasis with the aim of a 'clear' or 'nearly clear' by Physician's Global Assessment rating • reduce the impact of the disease on quality of life. It might also treat any associated arthritis.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Prior NICE TA455 has defined an adequate response as a 75% reduction in the PASI score from the start of treatment. Additionally, significant reduction in age-appropriate dermatology quality of life scores (e.g. CDLQI or TQol).

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – for some patients with moderate-to-severe psoriasis where other approved medications are contraindicated or lack efficacy. Psoriasis begins in childhood in approximately 1/3 of cases and is likely to be a life-long condition. Psoriasis in childhood and adolescence has been shown to have a large impact on quality of life and associated comorbidities including potential impact on physical and mental health both short and long term: 1. Psoriasis: Is the impairment to a patient's life cumulative? 2. Risks of developing psychiatric disorders in pediatric patients with psoriasis 3. Psychological differences between early and late onset psoriasis: A study of personality traits, anxiety and depression in psoriasis 4. A retrospective cohort study to evaluate the development of comorbidities, including psychiatric comorbidities, among a pediatric psoriasis population In real-world practice, not all patients with psoriasis who fulfil NICE criteria for biologic therapy respond to existing biologic therapies; secondary failure is also common. This is largely data from adult cohorts, but the same issues are recognised to be relevant for paediatric patients by practicing paediatric dermatologists (Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017 May;176(5):1297-1307. doi: 10.1111/bjd.15027. Epub 2017 Mar 20. PubMed PMID:27589476; 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 Nov;135(11):2632-2640. doi: 10.1038/jid.2015.208. Epub 2015 Jun 8.

	PubMed PMID:26053050; Differential Drug Survival of Second-Line Biologic Therapies in Patients with Psoriasis, J Invest Dermatol. 2018 Apr;138(4):775-784. doi: 10.1016/j.jid.2017.09.044. Epub 2017 Dec 6.)
	
	N.B. Additional reference:
	
	Biologics may be less effective in the real world, cf. to trial data due to use of biologic therapies. Comparison of Drug Discontinuation, Effectiveness, and Safety Between Clinical Trial Eligible and Ineligible Patients in BADBIR JAMA Dermatol. 2018 May 1;154(5):581-588. doi: 10.1001/jamadermatol.2018.0183.
	
	Use of biologic therapy in the UK for all ages is currently limited to those with severe disease as defined by a PASI 10. This excludes use of highly effective biologic therapy (within the licensed indication – i.e. moderate or severe) where the disease is associated with a severe impact on their QoL, physical, social or psychological function. Specifically, adults with moderate disease and those with severe disease but of limited extent – i.e. high-need areas such as the face, hands, feet, flexural/genital sites. Adults in these two groups will not have a PASI score of 10 but nevertheless will suffer major impact from their disease. Options for these patients are profoundly limited if methotrexate is not effective or cannot be tolerated. Newer small molecule drugs (e.g. dimethyl fumarate and apremilast) are not approved by NICE for patients with a PASI <10 either. Therefore, we would strongly suggest that the NICE CG153 criteria used for non-biologic systemic therapy be generalised to biologic therapy, i.e. psoriasis that cannot be controlled with topical therapy, and:
	
	• has a significant impact on physical, psychological or social wellbeing, and
	• one or more of the following:
	  o psoriasis is extensive or
	  o psoriasis is localised and associated with significant functional impairment and/or high levels of distress or
	  o phototherapy has been ineffective, cannot be used or has resulted in rapid relapse.
	
	Including these indications with the NICE criteria would still be entirely consistent with the licensed indications for these treatments (moderate-to-severe psoriasis).

What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Treatment is matched to disease extent and severity and the impact it has on the child or young person. If the patient has associated psoriatic arthritis this also influences therapy. Standard systemic agents such as ciclosporin or methotrexate are used 'off-license' but in line with consensus guidelines for the treatment of psoriasis in individuals aged 16 years and under. Licensed systemic agents include etanercept, adalimumab and ustekinumab. Topical treatments initially (many psoriasis treatments are off-licence for children) can be used but are difficult to apply if the psoriasis is extensive. Phototherapy is used for disease flares but not as maintenance therapy as this only increases the risk of future skin cancers. 1. Efficacy and safety of treatments for childhood psoriasis: a systematic literature review 2. Systemic treatments in paediatric psoriasis: a systematic evidence-based update 3. S2k guidelines for the treatment of psoriasis in children and adolescents 2019 4. Management of Pediatric Plaque Psoriasis using Biologics 5. Biologics in pediatric psoriasis - efficacy and safety
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: 1. BAD guideline for biologic therapy for psoriasis 2020 2. S2k guidelines for the treatment of psoriasis in children and adolescents 2019 3. NICE CG153 2017 4. Systemic treatments in paediatric psoriasis: a systematic evidence-based update
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Severe psoriasis in children is uncommon and treatment pathways may vary across the UK. There is recent evidence that although topical treatments can control psoriasis, in many paediatric patients 60% will have inadequate control. Progression to systemics and biologics for 25% of patients (Bruins *et al.*) may take some time and there is a concern that living with moderate to severe psoriasis at this age can have a large impact on quality of life and life outcomes (Kimball *et al*.). For more widespread disease, systemic treatments may have an important role including off-licence medications and licensed biological therapies. Ongoing research and registry data (BADBIR) into efficacy and safety of medications, short- and long-term, is needed to define pathways more clearly. Children and young people with severe psoriasis would generally be seen or discussed with centres with expertise in paediatric dermatology and systemic medications. More formal pathways are currently being established to manage

	paediatric patients with severe psoriasis and future role of personalised biomarkers predicting response to systemic medications may become more relevant. 1. Bruins FM *et al*. Treatment persistence in paediatric and adolescent psoriasis patients followed into young adulthood: from topical to systemic treatment – a prospective, longitudinal, observational cohort study of 448 patients 2. Kimball et al. Risks of developing psychiatric disorders in pediatric patients with psoriasis 3. What determines the treatment persistence in paediatric psoriasis? 4. Can Etanercept and Ustekinumab be Considered a First-Line Systemic Therapy for Pediatric/Adolescents in Moderate to Severe Psoriasis? A Systematic Review
• What impact would the technology have on the current pathway of care?	Secukinumab is an anti-IL-17 agent. It would be the first biologic in its class to specifically target the IL-17 pathway in children and young people which provide a therapeutic option for these individuals where other treatment options are ineffective, lacking efficacy, or contraindicated. More agents within the same 'market' may provide motivation to drive down the NHS price for other biological drugs in psoriasis, reducing overall NHS costs. A novel mode of action offers the opportunity to further study and clarify personalised treatment for psoriasis in the future.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – biologic therapy is a well-established intervention for psoriasis.
• How does healthcare resource use differ between the technology and current care?	Current licensed biologic medications include anti-TNF and anti-IL12/23. This is an anti-IL-17 which is a different target may have specific indications for certain phenotypes of psoriasis and associated morbidities (for example axial arthritis). There would not be any expected differences in health resource use compared to existing NICE-approved agents aside from drug acquisition costs.
• In what clinical setting should the technology be used? (For example,	Secondary care – specialist paediatric dermatology services.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment or specific facilities would be required. Paediatric dermatology centres already familiar with using biological therapies to treat children and young people with psoriasis would be able to prescribe these therapies without additional training.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	N/A
• Do you expect the technology to increase health-related quality of life more than current care?	Potentially yes for some selected patients, by providing an additional treatment option for this major, chronic debilitating disease.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who have had a poor response to currently prescribed therapies and those with associated sub-types of arthritis.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No practical implications beyond current biological medicines available. The injections are monthly which might suit some children with associated psoriasis rather than weekly or fortnightly injections.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Baseline disease severity and impact of disease – these are assessed routinely in clinic. Baseline bloods which are in line with current tests for any systemic medication. Prior NICE TA455 has recommended that adalimumab, etanercept and ustekinumab are recommended in children and young people (different licensed ages) with psoriasis if the disease is severe (PASI of 10 or more) and has not responded to standard systemic therapies, or these options are contraindicated or not tolerated. Treatment should be stopped if the psoriasis has not responded adequately (defined as a 75% reduction in the PASI score from the start of treatment). No additional testing from what is already recommended for biologics.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes – for selected patients.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes – it would be the first IL-17 licensed for use in children and young people.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – patients who have not responded, poorly responded or contraindicated to existing treatments and have specific co-morbidities.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In adults, secukinumab can cause worsening of inflammatory bowel disease, therefore consider avoiding if there is co-existent inflammatory bowel disease (e.g. Crohns, ulcerative colitis). Certainly for discussion with gastroenterology. There may also be an increased risk of candida infection and therefore contraindicated in individuals with inherited susceptibility to mucocutaneous candidiasis.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	**The following outcomes were reported in the trials:** PASI100, PASI90, PASI75, PASI50, IGA clear/almost clear, change in CDLQI and number of individuals achieving CDLQI score of 0 or 1, composite clinical safety and tolerability (assessed by growth, weight gain, tolerability of s/c injections, vital signs, clinical laboratory variables, ECGs and adverse events), percentage of individuals with clinically important reduction in disability as evaluated by CHAQ questionnaire. All these outcomes are important and relevant. Other outcomes that may not have been reported but are highly relevant include: • **Psoriasis improvement on the face, scalp, nails:** Plus, other high-need sites, i.e. hands and feet, flexural/genital psoriasis. • **Response rate:** Over what time period? It would be important to include longer treatment outcomes. • **Relapse rate:** over what time period? It would be important to include longer treatment outcomes.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See notes above.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is very limited information about use of the technology outside clinical trials. It would be extremely important for all people with psoriasis who meet the eligibility criteria to be enrolled in BADBIR when prescribed this agent to ensure capture of high-quality pharmacovigilance data and to allow relevant comparisons with other biologic agents (N.B. around 20,000 patients now registered – please see www.badbir.org). We suggest featuring a future research recommendation in the final guidance, along the lines of that featured in the ustekinumab STA (TA180):

	"The collection of data on the use of ustekinumab and other biological therapies as part of the British Association of Dermatologists' Biologics Intervention Register (BADBIR)."
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No; however, it is worth pointing to the living systematic review and network meta-analyses by the Cochrane Skin Group: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA455?	No, but licensed biological therapies in children may be future comparators such as adalimumab, ustekinumab and etanercept. N.B. Ciclosporin cannot be used for > 1 year and is therefore a less relevant comparator for this STA. Similarly, PUVA is associated with increased risk of skin cancer and can only be used in the shorter term.
21. How do data on real-world experience compare with the trial data?	Real-world and trial data are more likely to converge in children due to generally fewer comorbidities and usual exclusion criteria such as pregnancy and neoplasia.
Equality	
22a. Are there any potential equality issues that should be	No.

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Secukinumab targets an additional cytokine pathway from the current biological medications licensed in childhood psoriasis and therefore increases therapeutic options
- Secukinumab would be useful option in certain patients with psoriasis; existing therapies, while effective for many, do not work for *all* those requiring treatment
- Trial data supports the use of secukinumab in children with psoriasis
- There is more than 5 years of accrued data for the use of secukinumab in adults showing efficacy and safety

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis Association
3. Job title or position	Patient Advocacy and Communications Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Psoriasis Association is the leading national charity and membership organisation for people affected by psoriasis in the UK. The Association has three main aims: to provide information, advice and support to those whose lives are affected by psoriasis; to raise awareness of psoriasis; and to promote and fund research into the causes, nature and care of psoriasis, and to publish and disseminate the results of that research. The Psoriasis Association receives no funding from Government or the Department of Health. The Association is funded primarily by its members and supporters via a number of different means, including membership fees, donations, fundraising and legacies. The Psoriasis Association currently has around 2,000 'traditional members' however in addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by psoriasis or psoriatic arthritis to communicate with one another via online forums on their own websites (~14,000 registered users), and Social Media (~6,500 registered users on closed Facebook group). The main Psoriasis Association website averages 45,000 visits per month. Of particular note and of relevance for this assessment is the 'sister' website run by the Psoriasis Association - www.psoteen.org.uk for teenagers and young people with psoriasis. Other social media channels used by the Psoriasis Association that lend themselves more to "raising awareness" include Twitter (~12,000 followers) and Instagram (~7,250 followers), along with a YouTube channel offering further information.
4b. Has the organisation received any funding from the manufacturer(s) of the	**Funding received from pharmaceutical companies in the last 12 months:-** Novartis - £3,630, consultancy services Abbvie - £1,500 corporate membership, £6,500 core funding, £5,000 emergency COVID-19 support, £180 honorarium Almirall – £1,500 corporate membership, £5,000 emergency COVID-19 support

technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Amgen – £1,500 corporate membership, £8,500 emergency COVID-19 support, £4,500 sponsored project, £345 honorarium Eli Lilly – £1,500 corporate membership, £5,000 emergency COVID-19 support Janssen – £412.50 honorarium, £5,000 emergency COVID-19 support, £15,000 core funding LEO Pharma – £1,500 corporate membership, £5,000 emergency COVID-19 support UCB – £1,500 corporate membership, £2,500 emergency COVID-19 support, £2,193.91 matched fundraising The Psoriasis Association has a policy that no more than 15% of income can come from the pharmaceutical industry
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information was gathered through monitoring discussion and feedback through the Psoriasis Association's helpline, website forums and social media channels.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Psoriasis is a chronic condition which can have a significant impact on an individual's quality of life. The physical symptoms, which can include persistent itching and skin which cracks and bleeds, can be debilitating for some people. However, the full life impact of psoriasis can go far beyond the physical symptoms, affecting everything from mental health and self-esteem to work life, hobbies, relationships, choice of clothing and quality of sleep. People with psoriasis are more likely to suffer from depression and anxiety than the general population. Social withdrawal and isolation are also common amongst people with psoriasis - a reaction to stigmatisation and insensitive comments from others, which can also lead to entrenched feelings of shame and embarrassment. The visible nature of the condition can be particularly difficult to deal with, especially when psoriasis is present in areas which are always visible, and difficult to cover, such as the scalp, face and hands. Psoriasis on the hands and feet can be particularly debilitating and, in severe cases, can prevent an individual from working or being able to complete day-to-day tasks around the house. In the case of parents of children who are living with psoriasis, we know that this group commonly experiences feelings of frustration, guilt, helplessness and exasperation when it comes to their child's psoriasis, and the quest to find an effective treatment. It can be extremely upsetting to watch your child suffer painful and debilitating physical symptoms of the condition, and, sadly, often experience stigmatisation, name-calling and bullying from other children their age who do not understand the condition too. On top of this, there is the added frustration of the trial and error approach to finding an effective treatment, often leaving parents with the 'false dawn' of witnessing their child experiencing temporary relief from their psoriasis before the devastating blow of their symptoms returning and that feeling of being back at square one. As such, the emotional impact on parents and carers of children with psoriasis can be significant. In addition, the time taken by parents and carers to help their child apply their treatments (particularly topical treatments) should not be underestimated.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	While there is a recognition amongst psoriasis patients that treatment options have improved in recent years, there is still a huge sense of frustration at the trial and error approach to finding an effective treatment, and a perception that patients must 'jump through the hoops' of trying and treatments which are cheaper (and often perceived to be ineffective/less effective) before getting access to a treatment which will be more successful in the longer term. We know that many patients find topical treatments messy and time-consuming to apply on a regular basis. There is also a feeling amongst people with psoriasis that topical treatments may be helpful for temporary relief, but that they are not a suitable long term solution as they do not address the underlying cause of psoriasis. Patient experiences of UVB and PUVA therapy are mixed. Many people do experience positive results with these treatments, but the relief from symptoms of psoriasis is often only temporary and there is dismay when symptoms do return, sometimes only a few weeks after the end of a course of UVB or PUVA treatment. The requirement of travelling to hospital two or three times a week for up to ten weeks at a time to receive this type of treatment is also reported to be inconvenient for many people with psoriasis, particularly those who work full time or have young children. The general feeling amongst patients seems to be that systemic and biologic treatments for psoriasis are more effective and provide a greater chance of longer term relief from symptoms. On many occasions, patients have described to us their experiences of these treatments as being 'life-changing', and the addition of biologic treatments in particular has been very much welcomed by patients. However we note that many patients do seem to be particularly concerned about the potential side-effects of these treatments, and are especially apprehensive when first offered a systemic or biologic treatment. Discussion on our forums and social media channels suggests that many people read the list of potential side effects of a systemic or biologic treatment and assume that they will experience all of them severely, and that this perception may be feeding apprehension about these treatments.

	In terms of care, unfortunately we read all too often about patients' frustrations with their GPs' lack of knowledge of psoriasis, and many people feel that their concerns about their condition are not taken seriously until they have seen a dermatologist. Unfortunately, the current waiting time to see a dermatologist after referral in many parts of the country is another source of frustration for patients. We feel that patients' experiences in secondary care are generally much better than in primary care due to a number of factors, including the increased range of treatment options available, and the specialist knowledge of the healthcare professionals they are seeing. However, one area in which care is consistently falling short at present is in the provision of specialist care to help with the psychosocial impact of living with psoriasis.
8. Is there an unmet need for patients with this condition?	Yes, most definitely. As alluded to in previous answers, we believe that the biggest unmet need at present is the psychosocial support required by many people who are living with psoriasis. At present, for the vast majority of people with psoriasis, adequate psychosocial support is simply not available to help deal with the various ways in which psoriasis can impact on different aspects of day-to-day life. In addition to the unmet need for psychosocial support, while the range of treatment options for psoriasis has improved considerably in recent years, there is still an unmet need for many people with psoriasis in terms of access to an effective treatment. Too many people are having to suffer without access to such a treatment, for too long. The longer a person with psoriasis is left to cope without an effective treatment, the more entrenched unhealthy coping behaviours can become, which can lead to long term psychological issues for which support may still be required beyond the point where an effective treatment is finally made available to that individual.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The main advantages for patients and carers are efficacy and convenience. In terms of efficacy, we know anecdotally from the patients in our communities that those who are taking Secukinumab and other biologics have, more often than not, experienced very positive improvements in their psoriasis symptoms. We know that improvements such as clear/clearer skin, lack of pain, discomfort and itching are extremely important to people with psoriasis, and that an improvement in physical symptoms goes hand-in-hand with psychosocial factors, such as feeling more confident, feeling more inclined to take part in hobbies and social activities, and wearing preferred items of clothing. In terms of convenience, we know that patients generally find taking their treatment via injection at monthly intervals (as is recommended for adults taking Secukinumab for plaque psoriasis) vastly more convenient than other existing treatments for psoriasis, such as topical treatments and UVB light treatment. This dosing and method of administration has far less impact on patients' day-to-day lives than having to apply messy and greasy creams several times a day, or taking time out of work to arrange regular hospital appointments. This, in turn, helps to reduce the overall impact of psoriasis on people's lives (of which the treatment of the condition is a bit part).
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As mentioned above, one of the potential disadvantages of Secukinumab (and other systemic and biologic drugs for the treatment of psoriasis) is some patients' apprehension about potential side-effects. This is particularly important in the period before a patient starts Secukinumab but has not yet had the chance to experience the treatment for themselves, as we know that some patients read the list of side-effects on the patient information and assume that they will experience them all, or ask for other people's experiences of receiving the treatment and then dwell disproportionately on negative experiences as compared with positive experiences. This issue may provide something of a barrier to some people deciding to start Secukinumab (or other systemic or biologic drugs) in the first place.

	Another potential disadvantage for some patients is the method of administration. We know that some people struggle with injections, particularly when they are self-administered. This could be a barrier to using Secukinumab (and other systemic or biologic treatments which are administered via either per-filled syringe or pre-filled 'pen device').
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Younger people may potentially benefit more from Secukinumab than other groups. One reason for this is that, with psoriasis, early-onset disease has been shown to be significantly more associated with anxiety and depression than late-onset disease. As such, if an effective treatment such as secukinumab can be offered early, it could help to reduce the chances of long term psychological issues associated with living with psoriasis, as it could help to address unhealthy coping mechanisms before these patterns of behaviour become too entrenched. A changed life: the life experiences of patients with psoriasis receiving biological treatment - Maruthappu - 2021 - British Journal of Dermatology - Wiley Online Library As psoriasis cannot be cured, there is strong support that "management should aim to minimise physical and psychological harm by treating patients early in the disease process" - https://doi.org/10.1016/S0140-6736(20)32549-6
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Secukinumab would be a welcome addition to the treatments available for plaque psoriasis in children and young people.
- Access to timely, effective treatments early in the life course of psoriasis could help prevent or lessen future psychological comorbidities associated with living with psoriasis from a young age.
- The impact of living with a highly visible skin condition should not be underestimated at any stage of life, however the implications for the age cohort this appraisal is looking at of living with moderate to severe skin disease should not be overlooked or dismissed.
- The pain, itch and unsightliness of moderate – severe psoriasis can impact not only on young people's self-esteem and confidence, but on their ability to concentrate in educational settings, and achieve their life potential.
- The frequency of appointments required for alternative therapies (particularly phototherapy) would require many periods of absence from school / college / university settings. Once the treatment and monitoring regimes of secukinumab are established it is not a time consuming treatment. The frequency of doses would also allow the patient flexibility in attending school / extra-curricular events for example overnight school trips, Duke of Edinburgh Award expeditions etc.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance
3. Job title or position	Chief Executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	A patient-centred charity that exists to support people affected by psoriasis and psoriatic arthritis. Activities include information both in print and via a comprehensive website. Telephone support offering help, advice and a sign-posting service to other resources is also available. The organisation also supports research via a small grants scheme. Health care professionals continued professional development is promoted and supported with an accredited online training resource (free to NHS staff). There is no formal membership of the organisation, but subscriptions are available to receive a bi-annual journal, all other patient resource and support are free and can be accessed anonymously. Access to the website is also free, with limited sign-up details needed to enter the PAPAA Knowledge Bank and online subscriber's area. Use of social media is also part of the organisation's activities, but with a strict policy of only publishing evidenced-based and reliably sourced content. Funding is via donations, journal subscriptions, online shop sales, fundraising activities and an ethical investment portfolio. No funds are currently accepted from commercial organisations (including the pharmaceutical industry) or third party agents representing or supporting those sectors.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	No

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	PAPAA also has a continuing data gathering process. For this submission we have used information and testimonials from people submitted via the 'share your story' section of our website. The information is anonymised, but reflects real people with a lived experience of psoriasis.
Living with the condition	
6. What is it like to live with the condition? What do carers	For many people psoriasis can be very mild and not affect them or interfere with their daily lives, but the story of how people are seen and how that impacts on them, particularly at a young age, can be very shocking. It needs to be noted that for young people, how their psoriasis affects them can vary, but on the whole experiences are very similar, and influence the rest of

experience when caring for someone with the condition?	their lives. Whether that is education, employment and relationships, the psychological effects of being diagnosed, the treatment and how those around them see the skin manifestations should not be underestimated. The following are quotes from people who have been diagnosed with psoriasis at a young and reflect the overall views of what and how the condition affects their education, work, social life and relationships *"I have had psoriasis since the age of 12; it changed my life from going out socially to becoming home bound never having the confidence to go out in the daytime, only in the dark hours."* *"I was diagnosed with psoriasis when I was 5-years old after I got my ears pierced. I found out that my father had it as well and I inherited it through him. Throughout the years I would have outbreaks during times when I would get strep throat sometimes when I would get sick in general and in my later years when I went drinking excessive alcohol."* "*I have had psoriasis since I was 14. I am 22 now and it has always been the same. I believe it is a disease, when people only associate you as 'psoriasis' rather than a person."* *"My first attack was when I was 15, I was covered in lesions and I was in care. I was picked on and staff accused me of having scabies! I had another attack at age 17 and then at 30 and now I have chest pains and severe pain in right hip and knee; my nails are pitted..."* *"I have suffered with psoriasis since birth. My psoriasis has flared up and down over the years and it's just something I've learnt to live with. I am now 39. I know it's something that will eventually disappear and move to another area. I have had just about every area, apart from my face affected over the years,*

	including bad scalp plaque psoriasis, hands, feet, all creases of my body, spots (tiny fluid filled ones all over my legs), these now appear in different areas depending on the weather and my stress levels!" *"I developed psoriasis at 11. Clearly, there was a strong genetic link as my father had severe psoriasis. My mother's reaction was very negative in that she said no one would ever want to marry me with this! Not a great thing for a young adolescent to hear. I spent weeks in hospital having bed rest and tar baths as a teenager."* *"I've had patches of psoriasis on my head and body since I was about 10 years old. Steroid creams are useless [for me]. Then joint pain and arthritis symptoms started when I was 26 and they all came on really quickly affecting every joint in my body from the jaw down."* *"When I was 12 I was diagnosed with psoriasis. I remember the day it just appeared. My mum and I thought it was just poison ivy, but then it kept getting worse. Every day at school from that point until I graduated high school people kept looking at me and making fun of me."* From these few honest reflections of people who have been affected by psoriasis from a young age, it is clear that it can have a heavy burden on the individuals and those around them. Managing psoriasis well in young people has the potential to provide a more positive view of the condition and give hope that over a lifetime, it will be managed effectively with little impact.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is an increased positivity towards newer therapies, but access is often frustrating to patients, with the feeling that they are not being offered the best therapies or are being offered less effective lower costing therapies. There is also a concern that given psoriasis is life-long that once therapies begin to fail that there won't be sufficient alternative treatments going forward. For the younger age group there are fewer licenced treatments, so choice and alternatives can make management harder.
8. Is there an unmet need for patients with this condition?	The need to have options as therapies begin to fail or stop working is always a fear and will continue to be an unmet need. Choice, accessibility and options are a particular concern of patients with psoriasis.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Adding an alternate to the existing treatment range and therapy that provides a different target if similar class therapies fail in this groups is particularly important.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There doesn't appear to be any obvious disadvantages versus other similar class therapies.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who have both psoriasis and psoriatic arthritis might benefit from a therapy that is beneficial in both conditions.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware.

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Psychological impact should not be underestimated • Life-long condition with no cure • Treatments often fail, therefore wide choice needed • Psoriasis causes significant negative impact on quality of life • Impact on education on younger age group •

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

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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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).

[redacted].

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 pediatric population that would allow connection to the NMA and 3) data in the pediatric 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, consumes a significant market share (50%), and is likely to be at least as effective as another comparator (etanercept). 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.
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 patient,

- 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

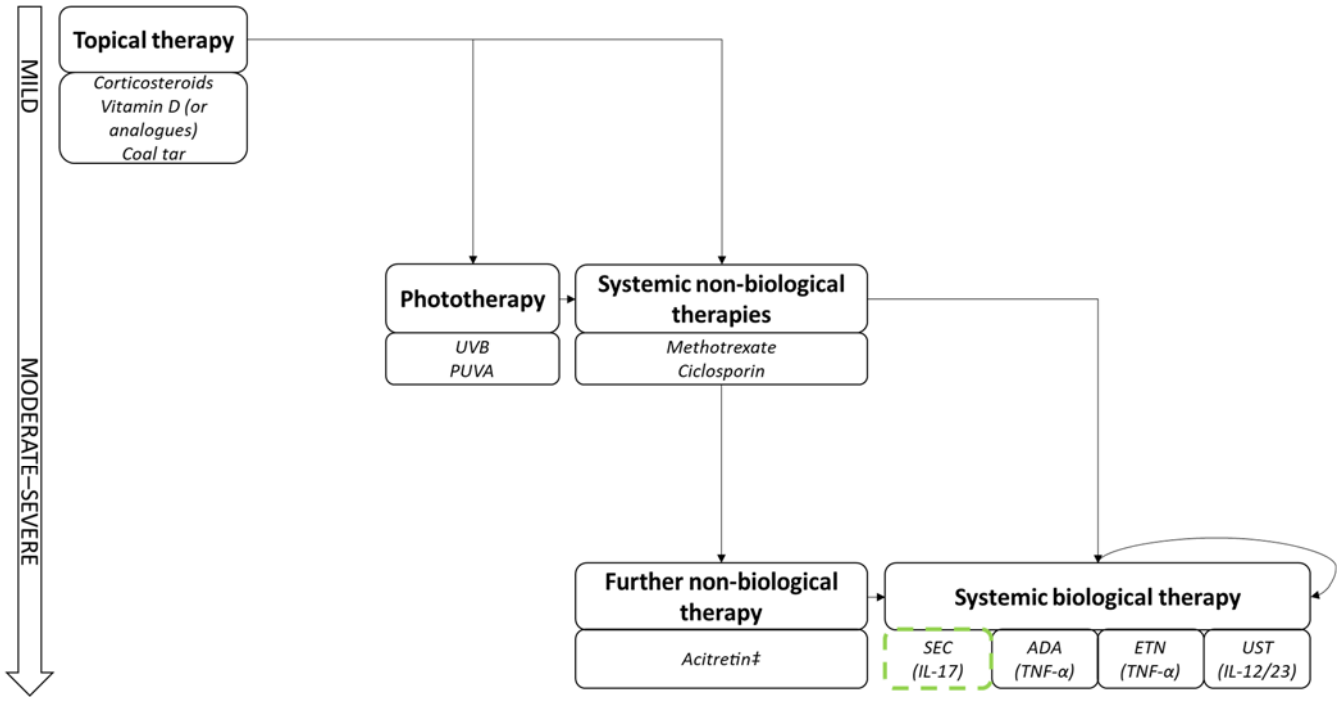
Treatment	Mechanism of action	Age range	Disease status	Dosage and schedules	Treatment pathway
Adalimumab	TNFα inhibitor	4 years and older	Severe chronic plaque psoriasis	0.8 mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	Where topical therapy and phototherapies are inadequate 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	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, respectively. The direct

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				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] Secukinumab does not currently have a UK marketing authorisation for treating moderate to severe plaque psoriasis in children and young people.[26] 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 summary of product characteristics (SmPC) to increase the dosage to 150 mg for patients <50 kg.[27]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				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. o Etanercept and ustekinumab are considered relevant comparators as head-to-head trial data are	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	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			available for secukinumab vs etanercept, [redacted]. o 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	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, because PASI outcomes do not capture symptoms in difficult-to-treat body locations such as scalp, face and nails. 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

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				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 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	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	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]

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 [redacted] 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] (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 PGA 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 PGA 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			
Median								
Min–Max								
Psoriasis history, n (%)								

	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**
Generalised pustular psoriasis								
Palmoplantar pustular psoriasis								
Erythrodermic psoriasis								
Diagnosis of psoriatic arthritis, n (%)								
Yes	5 (12.5)	3 (7.5)	3 (7.3)	3 (7.3)	14 (8.6)			
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								
Mean								
SD								
Median								
Min–Max								
Previous psoriasis therapies, n (%)								
Yes	40 (100.0)	40 (100.0)	41 (100.0)	41 (100.0)	162 (100.0)			
No	0	0	0	0	0			

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**	**Secukinumab high dose**	**Total**
Sex, n (%)								
Male	13 (32.5)	17 (42.5)	19 (46.3)	16 (39.0)	65 (40.1)			
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)			
≥12	32 (80.0)	31 (77.5)	31 (75.6)	31 (75.6)	125 (77.2)			
Age (years)								
N	40	40	41	41	162			
Mean	13.7	13.2	13.7	13.5	13.5			
SD	2.92	3.21	3.27	2.94	3.06			
Median								
Min–Max								
Weight (kg)								
N	40	40	41	41	162			
Mean	52.60	53.61	55.68	51.96	53.47			
SD	15.263	20.179	22.280	19.430	19.345			
Median								
Min–Max								
Weight strata (kg), n (%)								
<25	2 (5.0)	3 (7.5)	3 (7.3)	4 (9.8)	12 (7.4)			
25 to <50	17 (42.5)	15 (37.5)	17 (41.5)	16 (39.0)	65 (40.1)			
≥50	21 (52.5)	22 (55.0)	21 (51.2)	21 (51.2)	85 (52.5)			
Race, n (%)								
Caucasian (or White)	34 (85.0)	34 (85.0)	36 (87.8)	30 (73.2)	134 (82.7)			

	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**
Black (or African American)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vietnamese						[redacted]	[redacted]	[redacted]
Native American (American Indian or Alaska Native)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	1 (2.5)	0	1 (2.4)	0	2 (1.2)			
Ethnicity, n (%)								
Hispanic/Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
East Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Southeast Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
South Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
West Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Russian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Mixed ethnicity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Child-bearing status, n (%)								
Pre-menarche	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

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]
	NRI $£	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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 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. “actual observed counts of participants/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	[redacted]							

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, in general, were achieved by similar proportions of the low and high dose secukinumab groups. In the etanercept group, a similar proportion to the secukinumab group achieved PASI 50 but the proportions achieving PASI 90 and PASI 100 were lower. Few of the placebo group achieved PASI 90 or PASI 100, but around one-quarter achieved PASI 50.

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. "actual observed counts of participants/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	[redacted]							
PASI 100	[redacted]							

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. Up to week 52, adverse events described as “severe” were experienced by one participant (2.5%) in the low dose secukinumab group (bronchitis), three participants (7.5%) in the high dose secukinumab group (lymphadenopathy, tinea pedis, enterocolitis bacterial, and toxic shock syndrome), four participants (9.8%) in the etanercept group (vomiting, autoimmune pancreatitis, gallbladder polyp, pharyngitis, ectopic pregnancy, erythodermic psoriasis and abdominal pain), two participants in the placebo-low dose secukinumab group (gastrointestinal infection, nasal septum deviation and pharyngitis) and two in the placebo-high dose secukinumab group (therapy non-responder, lung abscess, pneumonia, thrombophlebitis, infectious pleural effusion and venous thrombosis limb). Considering the entire treatment period, further severe AEs were experienced by two participants in the any secukinumab high dose group (photoelectric conjunctivitis and abdominal hernia) and one participant (1.8%) in the any secukinumab low dose group (multiple injuries).

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 (n=40)**	**High dose secukinumab (n=40)**	**Any dose secukinumab (n=114)**	**Any low dose (n=56)/ Any high dose (n=58)**	**Etanercept (n=41)**

Any TEAE	**34 (85.0)**	**34 (85.0)**	**92 (80.7%)**	**45 (80.4)/47 (81.0)**	**34 (82.9)**
Infections & infestations	30 (75.0)	27 (67.5)	75 (65.8)	39 (69.6)/36 (62.1)	27 (65.9)
Gastrointestinal disorders	12 (30.0)	13 (32.5)	31 (27.2)	14 (25.0)/17 (29.3)	14 (34.1)
Skin & subcutaneous tissue disorders	12 (30.0)	12 (30.0)	31 (27.2)	14 (25.0)/17 (29.3)	10 (24.4)
General disorders & administration site conditions	9 (22.5)	9 (22.5)	22 (19.3)	9 (16.1)/13 (22.4)	8 (19.5)
Respiratory, thoracic & mediastinal disorders	6 (15.0)	10 (25.0)	21 (18.4)	8 (14.3)/13 (22.4)	4 (9.8)
Nervous system disorders	6 (15.0)	6 (15.0)	18 (15.8)	9 (16.1)/9 (15.5)	4 (9.8)
Musculoskeletal & connective tissue disorders	1 (2.5)	3 (7.5)	11 (9.6)	4 (7.1)/7 (12.1)	5 (12.2)
Injury, poisoning & procedural complications	4 (10.0)	4 (10.0)	10 (8.8)	4 (7.1)/6 (10.3)	1 (2.4)
Reproductive system & breast disorders	3 (7.5)	5 (12.5)	10 (8.8)	4 (7.1)/6 (10.3)	3 (7.3)
Blood & lymphatic system disorders	6 (15.0)	2 (5.0)	9 (7.9)	6 (10.7)/3 (5.2)	2 (4.9)
Investigations	5 (12.5)	2 (5.0)	9 (7.9)	5 (8.9)/4 (6.9)	6 (14.6)
Eye disorders	2 (5.0)	4 (10.0)	6 (5.3)	2 (3.6)/4 (6.9)	3 (7.3)
Psychiatric disorders	2 (5.0)	0 (0.0)	4 (3.5)	3 (5.4)/1 (1.7)	1 (2.4)
Renal & urinary disorders	2 (5.0)	2 (5.0)	4 (3.5)	2 (3.6)/2 (3.4)	3 (7.3)
Vascular disorders	1 (2.5)	2 (5.0)	4 (3.5)	1 (1.8)/3 (5.2)	1 (2.4)

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%. Table 18 below, backs up PASI 50-100 category results shown in Document B Figures 17-20, also showing that the secukinumab low dose being ranked (3rd) has a possible non-significant disadvantage compared to the ustekinumab standard dose (ie being ranked 1st) and the secukinumab high dose (ranked 2nd), whilst is marginally better, again non-significantly, to the half dose ustekinumab. Placebo is inferior to all of the active treatments. 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.

The results show that like the PASI category results, those on ustekinumab standard dose had improved QoL by 12 weeks marginally (non-significantly) more so than secukinumab low dose. However, for QoL, the next best was ustekinumab half dose, then secukinumab high dose with etanercept and placebo being far less effective. The CS also reports for CDLQI , sensitivity analyses that include A2311 into the NMA which. All are summarised in Table 21 below.

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

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

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

.

The safety of secukinumab for the pediatric 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 ≥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, consumes a significant market share (50%), is likely to be at least as effective as the other comparators.

   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 "NICE Fast track appraisals – guiding notes" states the following: *"The criteria for comparator choice are to avoid companies comparing with the most expensive and least effective treatment…"*. The ERG believes that, in this case, the comparators chosen are comparing secukinumab with the most expensive (ustekinumab) and least effective (etanercept) treatment options which overestimates 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. Furthermore, the ERG notes that the 'NICE Fast Track Appraisals – guiding notes' do not explicitly require an NMA to support the choice of comparator (page 3).Therefore, the rationale for the non-inclusion of adalimumab due to the inability to connect it to the NMA network is not 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. This was deemed appropriate as the committee 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).[40] The ERG, therefore, 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, 50kg, 75kg

and 100kg) to illustrate the impact of weight-based dosing on results. For all weight categories considered, 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	Etanercept	Ustekinumab	Adalimumab
Unit cost	[redacted]	£82.00	£2,147.00	£68.27
Per x mg	*150*	*25*	*45*	*20*
Dosage (25 kg)	75	20	19	20
Dosage (50 kg)	150	40	38	40
Dosage (75 kg)	150	50	45	40
Dosage (100 kg)	150	50	90[B]	40
Cost per dose (25 kg), with wastage	[redacted]	£82.00	£2,147.00	£68.27
Cost per dose (50 kg), with wastage	[redacted]	£164.00	£2,147.00	£136.54
Cost per dose (75 kg), with wastage	[redacted]	£164.00	£2,147.00	£136.54
Cost per dose (100 kg), with wastage	[redacted]	£164.00	£2,147.00	£136.54
Doses per year	16[A]	52	5	27
Acquisition cost for 1 year (25 kg)	[redacted]	£4,264.00	£10,735.00	£1,775.00
Acquisition cost for 1 year (50 kg)	[redacted]	£8,528.00	£10,735.00	£3,550.00
Acquisition cost for 1 year (75 kg)	[redacted]	£8,528.00	£10,735.00	£3,550.00
Acquisition cost for 1 year (100 kg)	[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 pediatric 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 pediatric 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 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 provide 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 pediatric 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 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 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).

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

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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

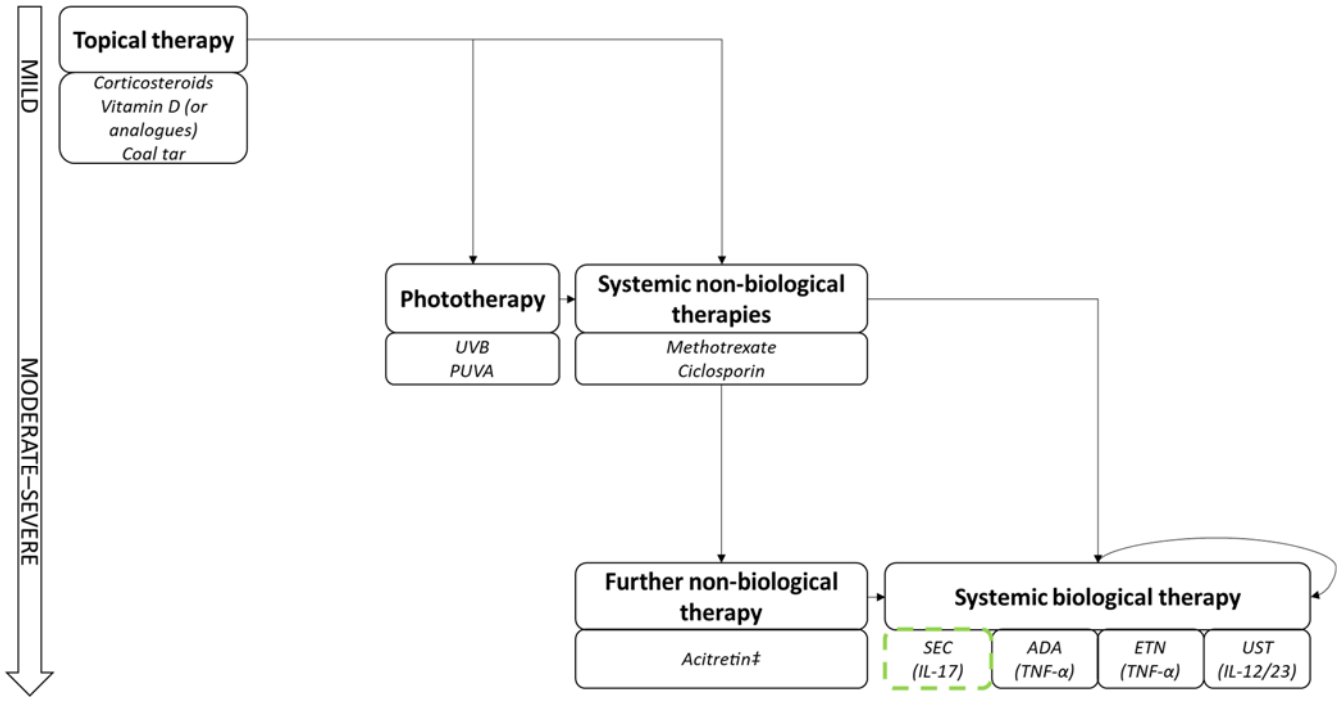
Treatment	Mechanism of action	Age range	Disease status	Dosage and schedules	Treatment pathway
Adalimumab	TNFα inhibitor	4 years and older	Severe chronic plaque psoriasis	0.8 mg/kg up to a maximum of 40 mg at weeks 0 and 1, then every 2 weeks thereafter	Where topical therapy and phototherapies are inadequate 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, respectively. The direct

	Final scope issued by NICE[26]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				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]

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] (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			
Median								
Min–Max								
Psoriasis history, n (%)								

	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**
Generalised pustular psoriasis								
Palmoplantar pustular psoriasis								
Erythrodermic psoriasis								
Diagnosis of psoriatic arthritis, n (%)								
Yes	5 (12.5)	3 (7.5)	3 (7.3)	3 (7.3)	14 (8.6)			
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								
Mean								
SD								
Median								
Min–Max								
Previous psoriasis therapies, n (%)								
Yes	40 (100.0)	40 (100.0)	41 (100.0)	41 (100.0)	162 (100.0)			
No	0	0	0	0	0			

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 (%)								
Caucasian (or White)	34 (85.0)	34 (85.0)	36 (87.8)	30 (73.2)	134 (82.7)	[redacted]	[redacted]	[redacted]

	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**
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]
	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	[redacted]							

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	[redacted]							
PASI 100	[redacted]							

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]

[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]

[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])/ Any high dose ([redacted])**	**Etanercept ([redacted])**

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).

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NICE National Institute for Health and Care Excellence

Secukinumab for treating moderate to severe plaque psoriasis in children and young people

Technical briefing

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

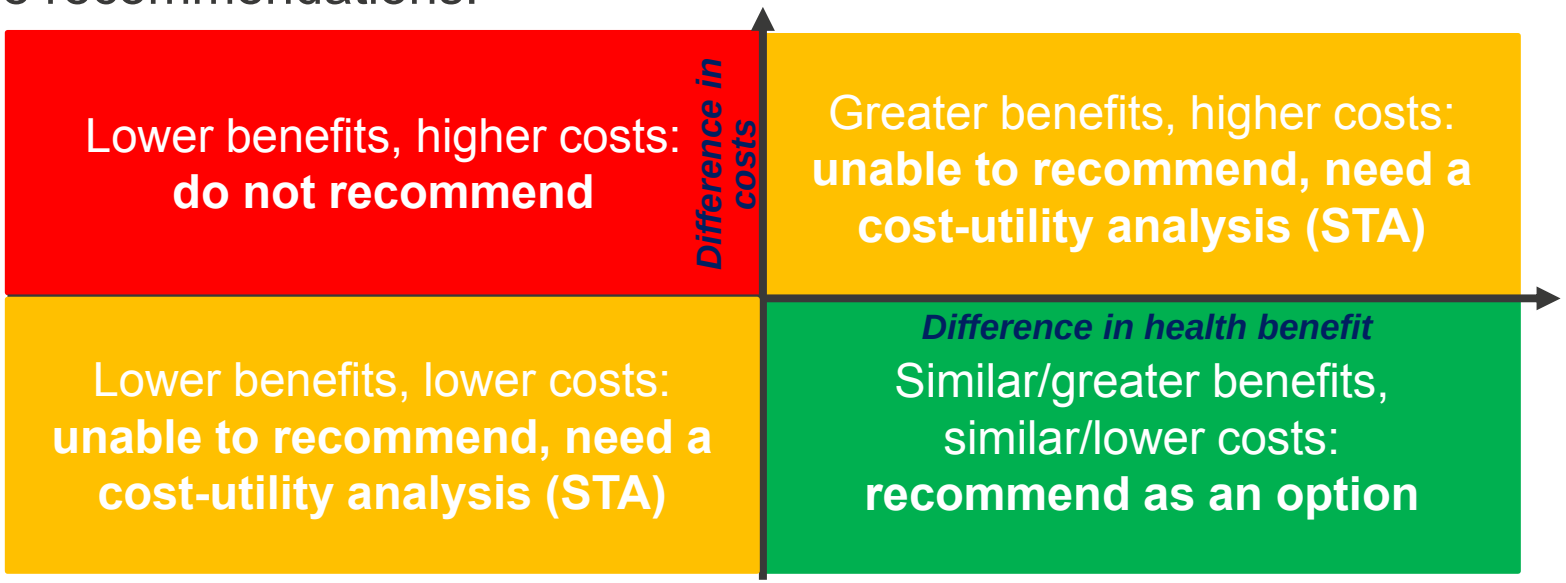
Authors: Henry Edwards

Fast Track Appraisals: Cost comparison

This topic is proposed as an FTA using cost comparison methods

- FTAs are appraisals in which less-detailed discussion is sufficient
  - Cost comparison FTA considered if the technology provides **similar/greater benefits** at **similar/lower cost** vs a **NICE-recommended** comparator

- Possible recommendations:



  - If a technology is recommended through cost comparison, guidance states:
    - ***"If patients and their clinicians consider both the technology and comparators to be suitable treatments, the least costly should be used"***

Key issues

Company has proposed this appraisal follows the FTA process based on secukinumab having similar health benefits and costs to etanercept, ustekinumab (TA455).

- Are the company's chosen comparators relevant comparators?
- Are the health benefits and safety of secukinumab and the company's chosen comparators similar?
- Are the costs of secukinumab and the company's chosen comparators similar?

Abbreviations: FTA: fast track appraisal, TA: technology appraisal

Plaque psoriasis - disease background

- Chronic inflammatory condition characterised by flaky, scaly, itchy and red plaques on skin
- Varies in severity and distribution ranging from small patches on the elbows and knees to almost complete body coverage
- Unpredictable, relapsing and remitting course
- Associated with comorbidities such as depression, anxiety, arthritis, cardiovascular disease
- Graded as mild, moderate or severe (based on location, area affected, severity of lesions and impact on individual)
- Population:

NICE

Patient and clinical perspective

Chronic, distressing and debilitating, need for a range of highly effective convenient treatments with minimal adverse reactions and impact on lifestyle

Impact of psoriasis

psoriasis is a relapsing/remitting life-long disease with varying degree of severity; impact sleep and social interactions

not always visible to others, itch causes great distress to patients and should be considered as an outcome

People would like

Consideration of high-impact and difficult-to-treat sites such as palms, soles, flexures, genitals – do not produce a high PASI score

Consideration to people who have received all biological therapies and then had treatment failure: choice, accessibility and options

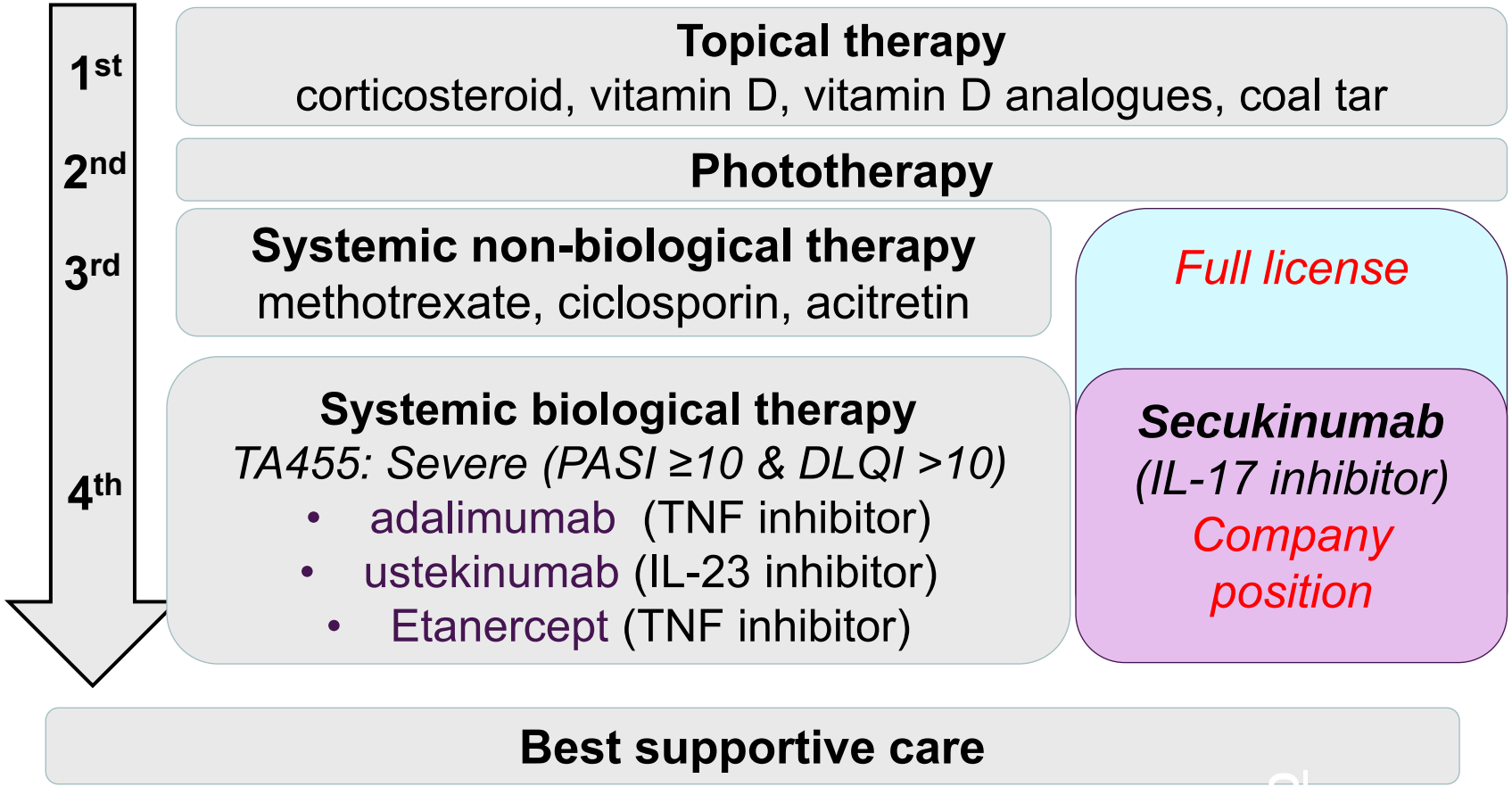
Secukinumab

High-affinity, fully human monoclonal anti-human interleukin-17A (IL-17A) antibody of the IgG1/kappa isotype to inhibit its interaction with the IL-17 receptor.

NICE

Source: British Association of Dermatologists [BAD], Psoriasis and Psoriatic Arthritis Alliance [PAPAA], Psoriasis Association.

Decision problem: population and positioning



Abbreviations: DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index TA: technology appraisal

Decision problem: population and positioning

NICE scope: "Children and young people with severe plaque psoriasis "

Trials: "moderate to severe plaque psoriasis in children aged 6-17 who are candidates for systemic therapy"

Company's position: Children and young people with moderate to severe plaque psoriasis who have failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated.

In line with comparators

The proposed position in the treatment pathway is narrower than the marketing authorisation:

- It is inline with the NICE recommended comparator (TA455).
- In line with secukinumab's recommendation in adults (TA350)
- Expected to be used here in clinical practice

ERG: reasonable and in line with current clinical practice in the UK.

Abbreviation: TA: technology appraisal

Decision problem: Comparators

Failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated

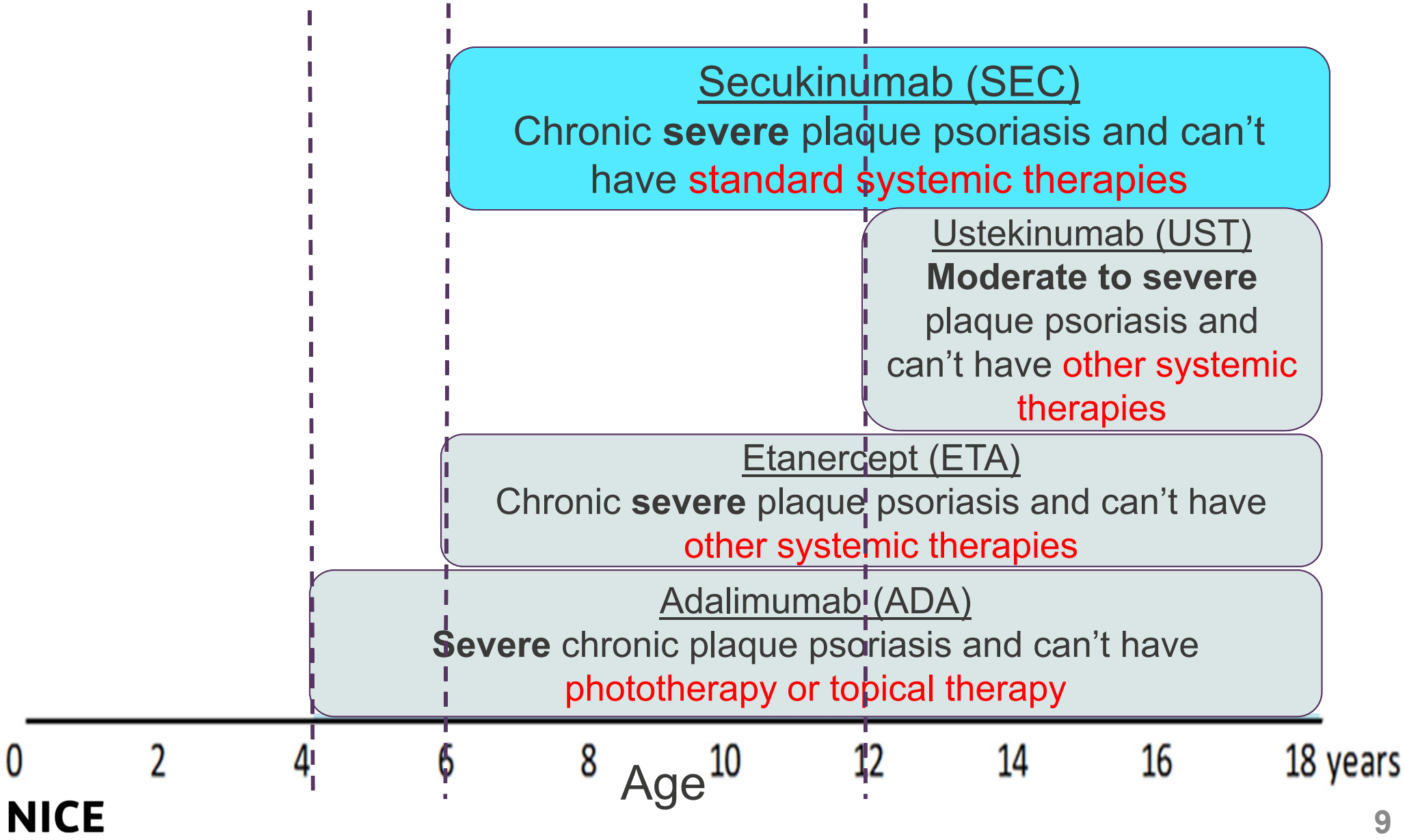
NICE scope	Company position	Company rationale
• adalimumab • etanercept • ustekinumab • best supportive care.	• ~~adalimumab~~ • etanercept • ustekinumab • ~~best supportive care.~~	• FTA process has allows for only 1 comparison to be made i.e. not all comparator are needed • Adalimumab is not included 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.

ERG

- Adalimumab should be included because:
  - It is the most likely treatment to be displaced by secukinumab in UK clinical practice
  - It composes a substantial proportion of the market share
  - It was included in TA455, and connected to the NMA using adult data
    - Acknowledge that no trial evidence for them and some assumptions would need to be made
  - Particularly relevant as a comparator in the under 12 age group

Abbreviations: FTA: fast track appraisal, NMA: network meta-analysis, TA: technology appraisal

Comparators by age



The technologies

	Secukinumab	Ustekinumab	Etanercept	Adalimumab (not included by company)
Mode of action	Anti-IL-17A	IL-12/IL-23	TNF-alpha	TNF-alpha
NICE recommendation	Anticipated to be the same	• Disease is severe • has not responded to standard systemic therapy or these options are contraindicated or not tolerated.		
Safety	Similar to other biologicals	Similar to other biologicals	Similar to other biologicals	Similar to other biologicals
Current market share (anticipated @y3)	XXXX	XXXX	XXXX	XXXX
Cost effectiveness	-	Between £13,368 and £26,253 £/QALY	Between dominance and £29,177 £/QALY	Between £10,624 and £25,657 £/QALY
Key out come	PASI 75	PASI 75 (PASI 50 and PASI 90 were also considered)	PASI 75 (PASI 50 and PASI 90 were also considered)	PASI 75 (PASI 50 and PASI 90 were also considered)

NICE

Abbreviations: IL: interleukin; PASI: Psoriasis Area and Severity Index, QALY: quality-adjusted life year, TNF: tumor necrosis factor.
Market share data taken from budget impact assessment

FTA choice of comparator (2)

ERG

- Omission of best supportive care, non-biological treatment and phototherapy acceptable in line with expected use
- Ustekinumab, etanercept and **adalimumab** are relevant comparators
- Adalimumab should be included because:
  - It is the most likely treatment to be displaced by secukinumab in UK clinical practice
  - It composes a substantial proportion of the market share
  - It was included in TA455, and connected to the NMA using adult data
    - Acknowledge that no trial evidence for them and some assumptions would need to be made
  - Particularly relevant as a comparator in the under 12 age group (ustekinumab not available)

Technical team

- Agree that adalimumab is a relevant comparator
  - ***"If patients and their clinicians consider both the technology and comparators to be suitable treatments, the least costly should be used"***

Abbreviations: FTA: fast track appraisal, NMA: network meta-analysis, TA: technology appraisal

FTA choice of comparator (3)

	Scrutiny assessment
Is the technology pharmacologically similar to the comparator(s)?	✓
Does the company's decision problem cover: a) all (decreasing risk) or only part (increasing risk) of the technology's marketing authorisation for this indication? b) all (decreasing risk) or only part (increasing risk) of the population for whom the comparator has been recommended by NICE?	a) Increasing risk, but in line with expected use b) Decreasing risk
Has the company made a comparison to a relevant NICE-recommended comparator?	✓
Are there any risks in making a case against this NICE-recommended comparator?	Adalimumab should be included

Clinical effectiveness

Clinical effectiveness evidence

Study	A2310 (n=162)	A2311 (n=84)
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: • ≥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	• Secukinumab low dose **(licensed dose)** • Secukinumab high dose	• Secukinumab low dose (licensed dose) • Secukinumab high dose
Comparator	Placebo: Two SC injections at each dose, except for patients <25 kg who received one SC injection. Etanercept: Weekly SC dose of 0.8 mg/kg (up to a maximum of 50 mg).	Results for secukinumab low/high dose were compared with placebo response rates from historical data.
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

Clinical effectiveness evidence

	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 [redacted]	Secukinumab high dose [redacted]	Total [redacted]
Baseline PASI score								
N	40	40	41	41	162	[redacted]	[redacted]	[redacted]
Mean	27.6	28.0	28.0	28.4	28.0	[redacted]	[redacted]	[redacted]
SD	6.89	8.67	8.09	9.05	8.15	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI, n (%)								
≤ 20	0	1 (2.5)	0	0	1 (0.6)	[redacted]	[redacted]	[redacted]
> 20	40 (100.0)	39 (97.5)	41 (100.0)	41 (100.0)	161 (99.4)	[redacted]	[redacted]	[redacted]
Age (years)								
N	40	40	41	41	162	[redacted]	[redacted]	[redacted]
Age <12, n (%)	8 (20.0)	9 (22.5)	10 (24.4)	10 (24.4)	37 (22.8)	[redacted]	[redacted]	[redacted]
Age ≥12, n (%)	32 (80.0)	31 (77.5)	31 (75.6)	31 (75.6)	125 (77.2)	[redacted]	[redacted]	[redacted]
Mean (SD)	13.7 (2.92)	13.2 (3.21)	13.7 (3.27)	13.5 (2.94)	13.5(3.06)	[redacted]	[redacted]	[redacted]
Baseline IGA mod 2011 score, n (%)								
3 = Moderate disease	0	1 (2.5)	0	0	1 (0.6)	[redacted]	[redacted]	[redacted]
4 = Severe disease	40 (100.0)	39 (97.5)	41 (100.0)	41 (100.0)	161 (99.4)	[redacted]	[redacted]	[redacted]

ERG: 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.

NICE: Definitions of severe differ from TA455

IGA, PASI 75 and PASI 90 results

- At Week 12, PASI 75 response was achieved by XXXX of patients in the secukinumab low dose group compared with XXXX of patients in the placebo group and XXXX of patients in the etanercept group

Response criterion	SEC n*/m (%)	Placebo n*/m (%)	Vs Placebo Odds ratio estimate (95% CI)†; p	ETN n*/m (%)	Vs ETN Odds ratio estimate (95% CI)†; p
IGA 0/1	XXXX	XXXX	XXXX	XXXX	XXXX
PASI 50	XXXX	XXXX	XXXX	XXXX	XXXX
PASI 75	XXXX	XXXX	XXXX	XXXX	XXXX
PASI 90	XXXX	XXXX	XXXX	XXXX	XXXX

Abbreviations: ETN, etanercept; IGA, Investigator's Global Assessment; LD, low dose (secukinumab) PASI, Psoriasis Area and Severity Index; SEC, secukinumab.

NICE

n* = rounded mean number of responders for 100 imputations
m = number of patients evaluable
Source: company submission table 19 p.75

Trial results: Week 12 and week 52

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

Abbreviations: IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index

a Placebo group switching to low dose secukinumab at week 12.
b Placebo switching to high dose secukinumab at week 12
n* = rounded mean number of responders for 100 imputations
m = number of patients evaluable
Source: company submission table 19 p.75

NICE

Safety profile

- Secukinumab showed a safety profile in paediatric patients with severe (PASI ≥20) and moderate to severe disease (PASI ≥12) comparable with the safety profile in adults.
- Adverse events were mostly mild to moderate in severity.
- Adverse events possibly related to study medication were generally low, up to week 52: 11/40 (27.5) in the low dose secukinumab group and 13/40 (32.5%) in the high dose secukinumab group.
- The majority of these were infections and infestations [redacted]

[redacted]

ERG:
The ERG's clinical advisor believes that the safety of secukinumab for the pediatric population is as would be expected and similar to the safety profile in adults.

NICE

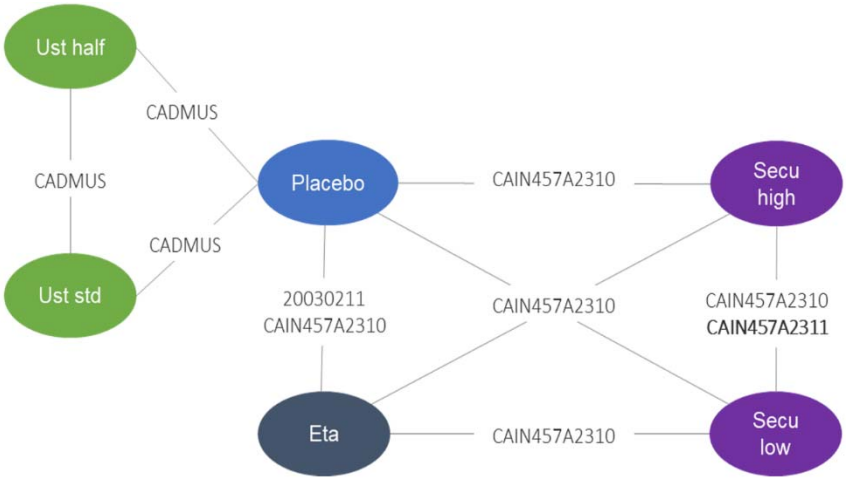
Abbreviations: PASI: Psoriasis Area and Severity Index

.

Company's network meta-analysis (NMA)

- Included following outcomes:
  - PASI (PASI 50, 75, 90, 100), and mean change in CDLQI from baseline
- Timepoint: 12 weeks
- 4 trials included in the network CADMUS, 20030211, A2311 and CAIN457A2310)
- A fixed effect model was used because of the size of the network and convergence issues

Trial	Secukinumab	Etanercept	Ustekinumab	Placebo
20030211		✓		✓
CADMUS			✓	✓
A2310	✓			✓
A2311	✓			✓



ERG
- Company did not include M04-717 study (adalimumab v methotrexate in paediatric patients) study – not connectable to the network
- ERG acknowledges that it is difficult to included into the NMA since there are no common treatment arms to link with the other three studies.
- NMA methodology was appropriate

Abbreviations: CDLQI: Children's Dermatology Life Quality Index; NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index; NMA: network meta-analysis. Source: company submission, figure 16 p.94

Company NMA results for efficacy

- [redacted]

Forest plot of the NMA results for the fixed-effects model comparing PASI 50 between secukinumab low dose and each comparator

Forest plot of the NMA results for the fixed-effects model comparing PASI 75 between secukinumab low dose and each comparator

Source: company submission figures 17&18 p. 97&98. Abbreviations**:** NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

Children's Dermatology Life Quality Index

NMA results demonstrate similar benefit

Forest plot of the NMA results for the fixed-effects model comparing mean change in CDLQI between secukinumab low dose and each comparator

Source: company submission figure 22 p. 101. Abbreviations: CDLQI, Children's Dermatology Life Quality Index; NMA: network meta-analysis

SUCRA scores and performance probabilities

Comparator	SUCRA	Probability for secukinumab to perform better	
		Secukinumab low dose	Secukinumab high dose
PASI scores			
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]
Mean change in CDLQI			
Ustekinumab standard	[redacted]	[redacted]	[redacted]
Secukinumab low	[redacted]	[redacted]	[redacted]
Ustekinumab half	[redacted]	[redacted]	[redacted]
Secukinumab high	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

Source: company submission tables 24 & 25
Abbreviations: CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; SUCRA, surface under the cumulative ranking.

Adalimumab

Company

- Presented no comparative clinical data for adalimumab.
- Adalimumab could not be connected to the evidence network due to the lack of adalimumab trial data on children and/or young people
- Included a scenario in which adalimumab is assumed to have equivalent efficacy to ustekinumab in response to clarification

ERG

- Paucity of data for adalimumab in the paediatric population – Adult adalimumab data were used in TA455
- Company scenario is a simplification but is consistent with conclusions for TA455

  "*the results for PASI 75 showed that the effectiveness of ustekinumab and adalimumab were similar, and that ustekinumab and adalimumab were more effective than etanercept*"
- Preferred to use a naïve indirect comparison from study M04-717 (Adalimumab vs. Methotrexate)

PASI 75 responses used in the economic model

PASI 75 responses	Secukinumab			Etanercept	Ustekinumab	Adalimumab
	<25 kg	25-50kg	≥50kg			
Company preferred	[redacted]	[redacted]	[redacted]	64.6%	87.1%	-
Company base case (with adalimumab included)	[redacted]	[redacted]	[redacted]	64.6%	87.1%	87.1%[A]
ERG preferred	[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.

[B] Taken from a naïve indirect comparison of adalimumab from study M04-717 which was not placebo controlled and therefore may provide inconsistent results

NICE Source: ERG report Table 24

FTA clinical effectiveness

	Scrutiny assessment
Has the company presented evidence using the same outcome measures as those used in the cost-effectiveness model for the NICE-recommended comparator?	✓
Does the technology have similar (or improved) efficacy to the comparator?	✓*
Is the adverse event profile of the technology similar to that of the NICE-recommended comparator?	✓
Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	✓

ERG
*Adalimumab is a notable exclusion from NMA

NICE

*Adalimumab not used as a comparator in clinical efficacy comparisons.

Cost comparison

Company cost-comparison model

Model approach & assumptions

- 5-year time horizon
- 12 to 16-week initial phase (aligned with licenses)
- PASI 75 response rate after initial phase taken from company NMA
- Patients receiving secukinumab who weigh ≥50kg that achieve PASI 50-74 transition to high dose secukinumab and are reassessed for PASI-75 response at week 24
- Non-responders after the initial phase are assumed to discontinue treatment
- Discontinuation rate from the second year on assumed to be 20% per year
- Patients who discontinue treatment for any reason are assumed to have no further treatment acquisition costs

ERG:

- Preference for a time horizon of 12 years from age 6-17 to capture all relevant costs
- Model assumes no treatment costs incurred following treatment discontinuation.
  - Does not reflect clinical practice and means treatments with lower PASI-75 response rates are more likely to be cost saving.
- Uniform 20% withdrawal rate may be an overestimation for secukinumab and ustekinumab which tend to have lower withdrawal rates than etanercept or adalimumab

NICE Abbreviations: NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

Company cost-comparison model

Resource use assumptions

- Healthcare resource costs assumed to be similar to other biologics and excluded from the cost comparison
  - Similar monitoring
  - Comparable safety profile
  - Similar treatment administration
- **Therefore company model considers only acquisition costs**

ERG:
- Unlikely to be a differences in monitoring costs and it is reasonable to assume similar healthcare resource use across the comparators.
- Assumption of no differences in AE costs between treatment arms to be reasonable and is also consistent with the approach taken in TA455.

Abbreviations: AE: adverse events; TA: technology appraisal

.

Acquisition cost

Results include confidential prices for:

- Secukinumab
- Etanercept
- Ustekinumab
- Adalimumab

	Secukinumab	Etanercept	Ustekinumab	Adalimumab
Doses per year	16	52	5	27
Acquisition cost for 1 year (25 kg)	[redacted]	[redacted]	[redacted]	[redacted]
Acquisition cost for 1 year (≥50 kg)	[redacted]	[redacted]	[redacted]	[redacted]

Cost comparison results – company

Deterministic results

	Incremental costs (secukinumab vs. etanercept)	Incremental costs (secukinumab vs. ustekinumab)	Incremental costs** (secukinumab vs. adalimumab)
Base case	XXXX	XXXX	XXXX
Scenarios			
Age 6-11 subgroup	XXXX	XXXX	XXXX
Age 12-17 subgroup	XXXX	XXXX	XXXX
Time horizon: up to 18 years	XXXX	XXXX	XXXX
NMA including Trial A2311 (open label trial)	XXXX	XXXX	XXXX
Equal efficacy of all comparators (PASI-75 response at XXXX)	XXXX	XXXX	XXXX

*Analysis in response to clarification queries
** Replicated by the ERG
Abbreviations: NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

Cost comparison results – ERG (6-17)

- The ERG base case includes a number of preferred assumptions. The ERG also provides further scenario analysis applied to the ERG base case.

Preferred assumption	Incremental costs vs. etanercept	Incremental costs vs. ustekinumab	Incremental costs vs. adalimumab
Company base case	XXXX	XXXX	XXXX
Adalimumab PASI-75 from M04-717 study	XXXX	XXXX	XXXX
12- year time horizon	XXXX	XXXX	XXXX
ERG preferred base case	XXXX	XXXX	XXXX
Additional scenario analyses applied to ERG preferred base case			
0% all cause annual withdrawal	XXXX	XXXX	XXXX
Withdrawal rates from trials	XXXX	XXXX	XXXX
PASI-75 equal to 100%	XXXX	XXXX	XXXX
Inclusion of subsequent lines of biologic treatment	XXXX	XXXX	XXXX

Abbreviations: NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

NICE

Cost comparison results – ERG (6-11)

Preferred assumption	Incremental costs vs. etanercept	Incremental costs vs. ustekinumab	Incremental costs vs. adalimumab
Base case	XXXX	XXXX	XXXX
Adalimumab PASI-75 from M04-717 study	XXXX	XXXX	XXXX
12- year time horizon	XXXX	XXXX	XXXX
ERG preferred base case	XXXX	XXXX	XXXX
Additional scenario analyses applied to ERG preferred base case			
0% all cause annual withdrawal	XXXX	XXXX	XXXX
Withdrawal rates from trials	XXXX	XXXX	XXXX
PASI-75 equal to 100%	XXXX	XXXX	XXXX
Inclusion of subsequent lines of biologic treatment	XXXX	XXXX	XXXX

NICE Abbreviations: NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

Cost comparison results – ERG (12-17)

Preferred assumption	Incremental costs vs. etanercept	Incremental costs vs. ustekinumab	Incremental costs vs. adalimumab
Base case	XXXX	XXXX	XXXX
Adalimumab PASI-75 from M04-717 study	XXXX	XXXX	XXXX
12- year time horizon	XXXX	XXXX	XXXX
ERG preferred base case	XXXX	XXXX	XXXX
Additional scenario analyses applied to ERG preferred base case			
0% all cause annual withdrawal	XXXX	XXXX	XXXX
Withdrawal rates from trials	XXXX	XXXX	XXXX
PASI-75 equal to 100%	XXXX	XXXX	XXXX
Inclusion of subsequent lines of biologic treatment	XXXX	XXXX	XXXX

NICE Abbreviations: NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

Innovation

Consultee comments:

- **Psoriasis and Psoriatic Arthritis Alliance:** Not particularly, given other similar agents are also available in this age group.
- **Novartis:** Secukinumab offers a novel mechanism of action for the treatment of plaque psoriasis in children and adolescents.
- **Novartis:** Secukinumab can be considered a step-change in the management of paediatric psoriasis

Equality

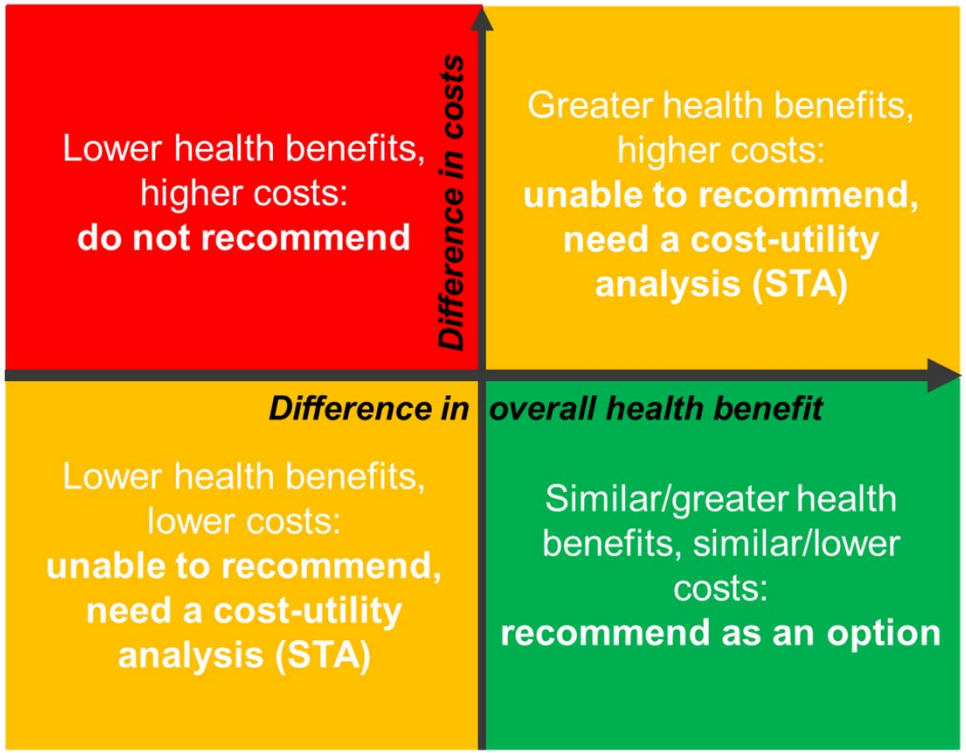
Consultee comments:

- PASI may underestimate disease severity in people with darker skin as redness may be less evident (a component of PASI)
- DLQI will underestimate impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression

NICE

Sources: British Association of Dermatologists [BAD], Psoriasis and Psoriatic Arthritis Alliance [PAPAA], Psoriasis Association.

Potential recommendations: cost comparison



What is the committee view on:

- the choice of comparators
- Specifically the inclusion/exclusion of adalimumab
- the similarity of health benefits and safety of secukinumab and comparators
- the similarity of costs of secukinumab and comparators
- is it reasonable to recommend secukinumab in the same way as TA455?

Part 1 for screen

NICE National Institute for Health and Care Excellence

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

Lead team presentation

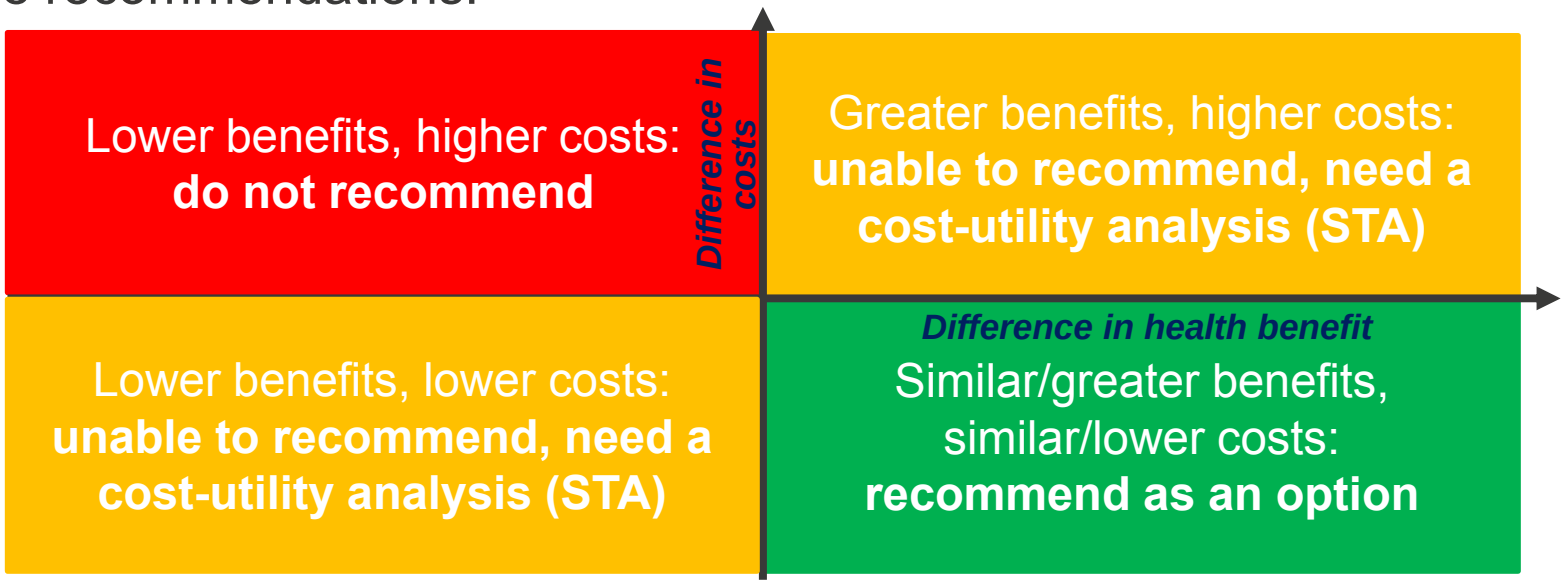
Vice Chair: Sanjeev Patel
Technology Appraisal Committee B
Lead team: Stephen Smith (clinical), Laura Bojke (cost), Tony Wootton (lay)
ERG: University of Aberdeen HTA Group
Technical team: Henry Edwards, George Millington
Company: Novartis
1st committee meeting 4 August 2021 virtual

Fast Track Appraisals: Cost comparison

This topic is proposed as an FTA using cost comparison methods

- FTAs are appraisals in which less-detailed discussion is sufficient
  - Cost comparison FTA considered if the technology provides **similar/greater benefits** at **similar/lower cost** vs a **NICE-recommended** comparator

- Possible recommendations:



  - If a technology is recommended through cost comparison, guidance states:
    - ***"If patients and their clinicians consider both the technology and comparators to be suitable treatments, the least costly should be used"***

Key issues

Company has proposed this appraisal follows the FTA process based on secukinumab having similar health benefits and costs to etanercept and ustekinumab (TA455).

- Are the company's chosen comparators relevant?
  - Is it appropriate not to include adalimumab as a comparator?
- Are the health benefits and safety profiles of secukinumab and the company's chosen comparators similar?
- Are the costs of secukinumab and the company's chosen comparators similar?

Abbreviations: FTA: fast track appraisal, TA: technology appraisal

Plaque psoriasis - disease background

- Chronic inflammatory condition characterised by flaky, scaly, itchy and red plaques on skin
- Varies in severity and distribution ranging from small patches on the elbows and knees to almost complete body coverage
- Unpredictable, relapsing and remitting course
- Associated with comorbidities such as depression, anxiety, arthritis, cardiovascular disease
- Graded as mild, moderate or severe (based on location, area affected, severity of lesions and impact on individual)
- Population:

NICE

*Figure for adult population

Patient and clinical perspective

Chronic, distressing and debilitating, need for a range of highly effective convenient treatments with minimal adverse reactions and impact on lifestyle

Psoriasis

psoriasis is a relapsing/remitting life-long disease with varying degree of severity; impact sleep and social interactions

not always visible to others, itch causes great distress to patients and should be considered as an outcome

People would like

Consideration of high-impact and difficult-to-treat sites such as palms, soles, flexures, genitals – do not produce a high PASI score

Consideration to people who have received all biological therapies and then had treatment failure: choice, accessibility and options

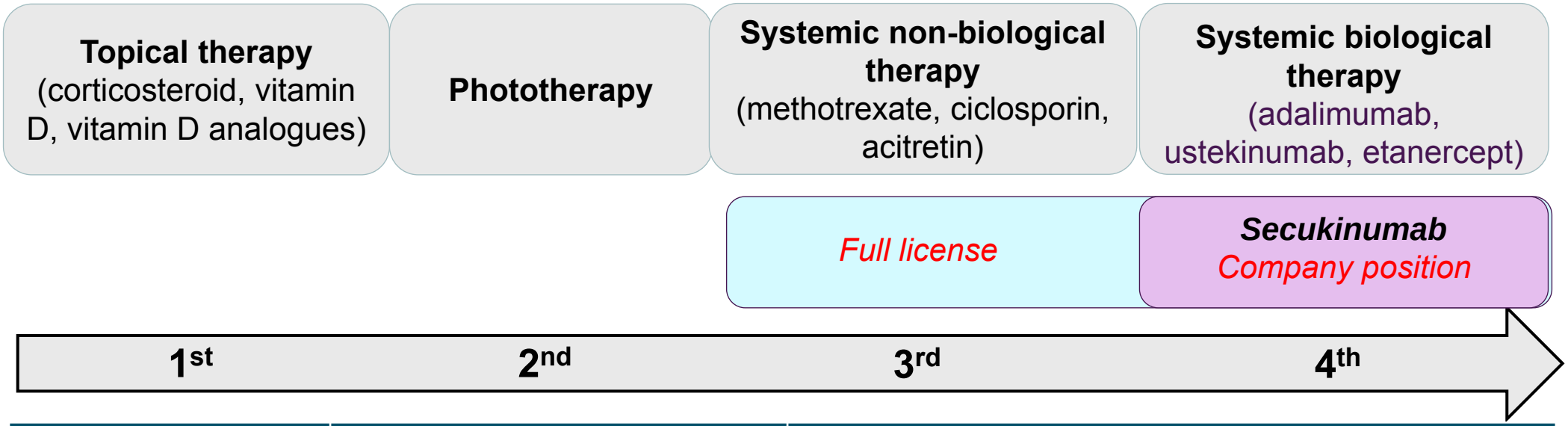
Secukinumab

High-affinity, fully human monoclonal anti-human interleukin-17A (IL-17A) antibody of the IgG1/kappa isotype to inhibit its interaction with the IL-17 receptor.

Lead team: recognise that patients and clinicals would benefit from another treatment option

Source: British Association of Dermatologists [BAD], Psoriasis and Psoriatic Arthritis Alliance [PAPAA], Psoriasis Association.

Decision problem: population and positioning



NICE scope	Trials	Company's position
Children and young people with severe plaque psoriasis	Moderate to severe plaque psoriasis in children aged 6-17 who are candidates for systemic therapy	Children and young people with moderate to severe plaque psoriasis who have failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated.

ERG: The proposed position in the treatment pathway is narrower than the marketing authorisation:

- In line with the NICE recommended comparators (TA455*: Severe PASI ≥10 & DLQI >10*)
- In line with secukinumab's recommendation in adults (TA350)
- Reasonable and expected to be used there in clinical practice

Lead team: In line with anticipated use in clinical practice

Abbreviation**:** TA: technology appraisal

Decision problem: Comparators

Failed to respond to standard systemic therapies, or in whom these treatments are contraindicated or not tolerated

NICE scope	Company position	Company rationale
• adalimumab • etanercept • ustekinumab • best supportive care.	• ~~adalimumab~~ • etanercept • ustekinumab • ~~best supportive care.~~	• FTA process has allows for only 1 comparison to be made i.e. not all comparator are needed • 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.

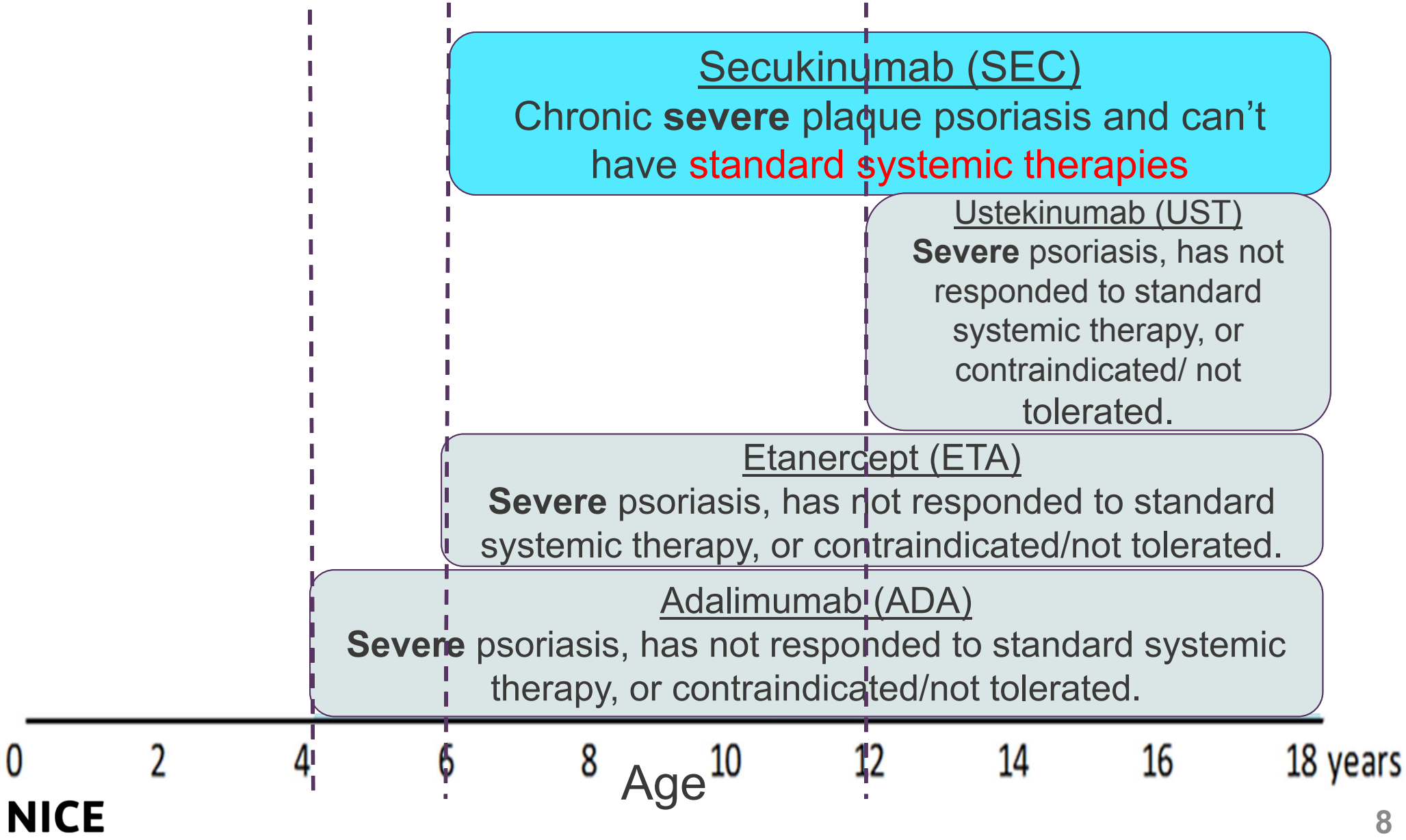
ERG

- Adalimumab should be included because:
  - It is the most likely treatment to be displaced by secukinumab in UK clinical practice
  - It composes a substantial proportion of the market share due to low cost generic biologics
  - It was included in TA455, and connected to the NMA using adult data
    - Acknowledge that no trial evidence for children and some assumptions would need to be made
  - Particularly relevant as a comparator in the under 12 age group

Abbreviations: FTA: fast track appraisal, NMA: network meta-analysis, TA: technology appraisal

Differences by age

Recommendations from TA455



The technologies

	Ustekinumab	Etanercept	Adalimumab (not included by company)	Secukinumab
Mode of action	IL-12/IL-23	TNF-alpha	TNF-alpha	Anti-IL-17A
NICE recommendation	• Disease is severe • has not responded to standard systemic therapy or these options are contraindicated or not tolerated.			Positioned to be the same
Safety	Similar to other biologicals	Similar to other biologicals	Similar to other biologicals	Similar to other biologicals
Current market share (anticipated @y3)	XXX XXX	XXX XXX	XXX XXX	XXX XXX
Cost effectiveness Vs best supportive care	Between £13,368 and £26,253 £/QALY	Between dominance and £29,177 £/QALY	Between £10,624 and £25,657 £/QALY	-
Key out come	PASI 75 (PASI 50 and PASI 90 were also considered)	PASI 75 (PASI 50 and PASI 90 were also considered)	PASI 75 (PASI 50 and PASI 90 were also considered)	PASI 75

Abbreviations: IL: interleukin; PASI: Psoriasis Area and Severity Index, QALY: quality-adjusted life year, TNF: tumor necrosis factor.
Source :Market share data taken from budget impact assessment

FTA choice of comparator

Adalimumab is a relevant comparator

ERG

- Omission of best supportive care, non-biological treatment and phototherapy acceptable in line with expected use
- Ustekinumab, etanercept and **adalimumab** are relevant comparators
- Adalimumab should be included because:
  - It is the most likely treatment to be displaced by secukinumab in UK clinical practice
  - It composes a substantial proportion of the market share
  - It was included in TA455, and connected to the NMA using adult data
    - Acknowledge that no trial evidence for children, including placebo comparator, and some assumptions would need to be made
  - Particularly relevant as a comparator in the under 12 age group (ustekinumab not available)

Lead team

- Agree that adalimumab is a relevant comparator

Clinical effectiveness

Clinical effectiveness evidence

Study	A2310 (n=162)	A2311 (n=84)
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: • ≥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	• Secukinumab low dose **(licensed dose)** • Secukinumab high dose	• Secukinumab low dose (licensed dose) • Secukinumab high dose
Comparator	Placebo: Two SC injections at each dose, except for patients <25 kg who received one SC injection. Etanercept: Weekly SC dose of 0.8 mg/kg (up to a maximum of 50 mg).	Results for secukinumab low/high dose were compared with placebo response rates from historical data.
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

Baseline characteristics (1)

Potentially more severe

	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 [redacted]	Secukinumab high dose [redacted]	Total [redacted]
Baseline PASI score								
N	40	40	41	41	162	[redacted]	[redacted]	[redacted]
Mean	28	28	28	28	28	[redacted]	[redacted]	[redacted]
SD	7	9	8	9	8	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI, n (%)								
≤ 20	0	1 (2)	0	0	1 (1)	[redacted]	[redacted]	[redacted]
> 20	40 (100)	39 (98)	41 (100)	41 (100)	161 (99)	[redacted]	[redacted]	[redacted]
Baseline IGA mod 2011 score, n (%)								
3 = Moderate disease	0	1 (3)	0	0	1 (1)	[redacted]	[redacted]	[redacted]
4 = Severe disease	40 (100)	39 (97)	41 (100)	41 (100)	161 (99)	[redacted]	[redacted]	[redacted]

Baseline characteristics (2)

Notable age split

	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 [redacted]	Secukinumab high dose [redacted]	Total [redacted]
Age (years)								
N	40	40	41	41	162	[redacted]	[redacted]	[redacted]
Age <12, n (%)	8 (20)	9 (23)	10 (24)	10 (24)	37 (23)	[redacted]	[redacted]	[redacted]
Age ≥12, n (%)	32 (80)	31 (78)	31 (76)	31 (76)	125 (77)	[redacted]	[redacted]	[redacted]
Mean	14	13	14	14	14	[redacted]	[redacted]	[redacted]
Weight strata (kg), n (%)								
<25	2 (5)	3 (8)	3 (8)	4 (10)	12 (7)	[redacted]	[redacted]	[redacted]
25 to <50	17 (43)	15 (37)	17 (42)	16 (39)	65 (40)	[redacted]	[redacted]	[redacted]
≥50	21 (52)	22 (55)	21 (51)	21 (51)	85 (53)	[redacted]	[redacted]	[redacted]
Mean	53	54	56	52	53	[redacted]	[redacted]	[redacted]

ERG: 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.

NICE: Definitions of severe differ from TA455

IGA, PASI 75 and PASI 90 results from A2310

Clinical benefit compared with etanercept and placebo

- At Week 12, PASI 75 response was achieved by [redacted] of patients in the secukinumab low dose group compared with [redacted] of patients in the placebo group and [redacted] of patients in the etanercept group

Response criterion	SEC n*/m (%)	Placebo n*/m (%)	Vs Placebo Odds ratio estimate (95% CI)†; p	ETN n*/m (%)	Vs ETN Odds ratio estimate (95% CI)†; p
IGA 0/1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ETN, etanercept; IGA, Investigator's Global Assessment; LD, low dose (secukinumab) PASI, Psoriasis Area and Severity Index; SEC, secukinumab.
n* = rounded mean number of responders for 100 imputations
m = number of patients evaluable
Source: company submission table 19 p.75

NICE

Trial results: Week 12 and week 52

Clinical benefit is sustained to week 52

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

Abbreviations: IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index

a Placebo group switching to low dose secukinumab at week 12.
b Placebo switching to high dose secukinumab at week 12
n* = rounded mean number of responders for 100 imputations
m = number of patients evaluable
Source: company submission table 19 p.75

NICE

Safety profile

Company

- Secukinumab showed a safety profile in paediatric patients with severe (PASI ≥20) and moderate to severe disease (PASI ≥12) comparable with the safety profile in adults.
- Adverse events were mostly mild to moderate in severity.
- Adverse events possibly related to study medication were generally low, up to week 52: 11/40 (27.5) in the low dose secukinumab group and 13/40 (32.5%) in the high dose secukinumab group.
- The majority of these were infections and infestations [redacted]

- **ERG: C**linical advisor believes that the safety of secukinumab for the pediatric population is as would be expected and similar to the safety profile in adults.

NICE

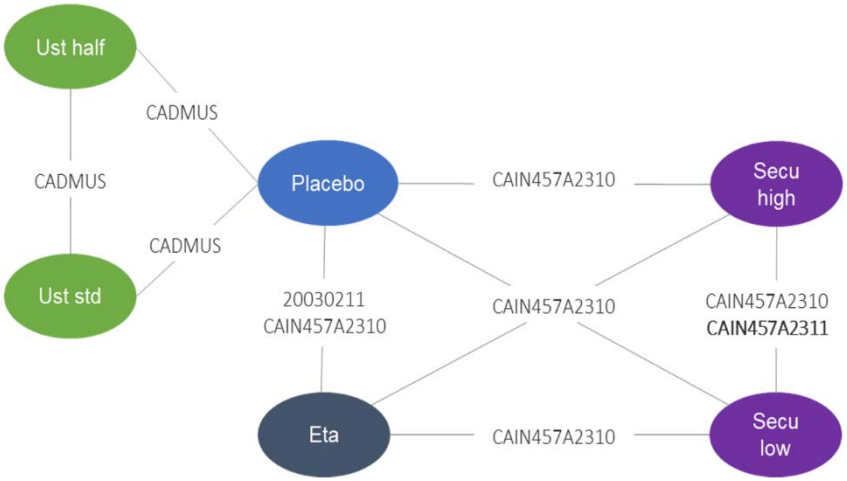
Abbreviations: PASI: Psoriasis Area and Severity Index

.

Company's network meta-analysis (NMA)

- Included following outcomes:
  - PASI (PASI 50, 75, 90, 100), and mean change in CDLQI from baseline
- Timepoint: 12 weeks
- 4 trials included in the network CADMUS, 20030211, A2311 and CAIN457A2310)
- A fixed effect model was used because of the size of the network and convergence issues

Trial	Secukinumab	Etanercept	Ustekinumab	Placebo
20030211		✓		✓
CADMUS			✓	✓
A2310	✓			✓
A2311	✓			✓



ERG

- Company did not include M04-717 (adalimumab) study – not connectable to the network
- ERG acknowledges that it is difficult to included into the NMA since there are no common treatment arms to link with the other three studies.
- NMA methodology was appropriate

NICE

Abbreviations: CDLQI: Children's Dermatology Life Quality Index; NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index; NMA: network meta-analysis. Source: company submission, figure 16 p.94

NMA results: PASI 50, 75

Similar benefit compared with ustekinumab

- [redacted]

Forest plot of the NMA results for the fixed-effects model comparing PASI 50 between secukinumab low dose and each comparator

Forest plot of the NMA results for the fixed-effects model comparing PASI 75 between secukinumab low dose and each comparator

Lead team:

- **Could include the adalimumab versus methotrexate data if also include methotrexate versus placebo studies in the network**

Source: company submission figures 17&18 p. 97&98. Abbreviations**:** NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

NMA results: CDLQI

Similar quality of life compared with ustekinumab

Forest plot of the NMA results for the fixed-effects model comparing mean change in CDLQI between secukinumab low dose and each comparator

Source: company submission figure 22 p. 101. Abbreviations: CDLQI, Children's Dermatology Life Quality Index; NMA: network meta-analysis

Adalimumab

Company

- Presented no comparative clinical data for adalimumab.
- Could not be connected to the evidence network due to the lack of adalimumab trial data on children and/or young people
- Included a scenario in which adalimumab is assumed to have equivalent efficacy to ustekinumab in response to clarification

ERG

- Paucity of data for adalimumab in the paediatric population – Adult adalimumab data were used in TA455
- Company scenario is a simplification but is consistent with conclusions for TA455

  "*the results for PASI 75 showed that the effectiveness of ustekinumab and adalimumab were similar, and that ustekinumab and adalimumab were more effective than etanercept*"
- Preferred to use a naïve indirect comparison from study M04-717 (Adalimumab vs. Methotrexate)

Conclusions in TA455

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people (2017)

Network meta analysis

- Not possible to connect the interventions and comparators together using direct evidence from children and young people alone because the trials did not use a common comparator.
  - Assessment group's preferred analysis included all available adult data.
- Assessment group adjusted for differences in population response rates and placebo response rates because they differed between trials and between children and adults.
  - Committee agreed that all available adult evidence should be included in the network, and that it was appropriate to adjust the data for population characteristics and placebo response rates.
- PASI 75 results showed that the effectiveness of ustekinumab and adalimumab were similar
- The committee was concerned that using adult data could potentially bias the effect estimates, but agreed that this was mitigated by the assessment group having adjusted for population and placebo effects
- In addition, the committee concluded that ustekinumab and adalimumab had broadly similar effectiveness

PASI 75 responses used in the economic model

Equal efficacy of ustekinumab and adalimumab suggested as in previous appraisals

PASI 75 responses	Secukinumab			Etanercept	Ustekinumab	Adalimumab
	<25 kg	25-50kg	≥50kg			
Company preferred	xxxx	xxxx	xxxx	64.6%	87.1%	-
Company base case (with adalimumab included)	xxxx	xxxx	xxxx	64.6%	87.1%	87.1%[A]
ERG preferred	xxxx	xxxx	xxxx	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.

[B] Taken from a naïve indirect comparison of adalimumab from study M04-717 which was not placebo controlled and therefore may provide inconsistent results

Lead team:

- **In the absence of direct or indirect evidence, the lead team considered it reasonable to assume equal efficacy of adalimumab to ustekinumab.**
- **Does the committee consider this a reasonable approach?**

NICE Source: ERG report Table 24

Company NMA taken from ID2692 Bimekizumab

- [redacted]
- [redacted]

Forest plot of probabilities of achieving at least given PASI response at 10–16 weeks

Source: company submission figure 17 p. 87. **Abbreviations:** NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

FTA clinical effectiveness conclusions

Lead team:

- Overall, secukinumab is likely to offer similar or greater health benefits compared with etanercept and ustekinumab
- Uncertainty remains in children and young adults for comparison to adalimumab

NICE

*Adalimumab not used as a comparator in clinical efficacy comparisons.

Cost comparison

Company cost-comparison model

Resource use assumed to be equivalent

- Healthcare resource costs assumed to be similar to other biologics and excluded from the cost comparison
  - Similar monitoring
  - Comparable safety profile
  - Similar treatment administration
- **Therefore company model considers only acquisition costs**

ERG:

- Unlikely to be a differences in monitoring costs and it is reasonable to assume similar healthcare resource use across the comparators.
- Assumption of no differences in AE costs between treatment arms to be reasonable and is also consistent with the approach taken in TA455.

Abbreviations: AE: adverse events; TA: technology appraisal

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Company cost-comparison model

ERG has concerns with time horizon, withdrawal and subsequent treatment

- 5-year time horizon
- 12 to 16-week initial phase (aligned with licenses)
- PASI 75 response rate after initial phase taken from company NMA
- Patients receiving secukinumab who weigh ≥50kg that achieve PASI 50-74 transition to high dose secukinumab and are reassessed for PASI-75 response at week 24
- Non-responders after the initial phase are assumed to discontinue treatment
- Discontinuation rate from the second year on assumed to be 20% per year
- Patients who discontinue treatment for any reason are assumed to have no further treatment acquisition costs – unlikely given treatment pathway

ERG:

- Preference for a time horizon of 12 years from age 6-17 to capture all relevant costs
- Model assumes no treatment costs incurred following treatment discontinuation.
  - Does not reflect clinical practice and means treatments with lower PASI-75 response rates are more likely to be cost saving.
- Uniform 20% withdrawal rate may be an overestimation for secukinumab and ustekinumab which tend to have lower withdrawal rates than etanercept or adalimumab

Abbreviations: NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

Cost comparison results

Confidential discounts in place and included in the results:

- Secukinumab
- Etanercept
- Ustekinumab
- Adalimumab

Results are reported in PART 2 slides because of confidential agreements information

Scenario's considered

- Increased time horizon
- Source of adalimumab response
- Equalising response
- Differing withdrawal rates

Innovation

Consultee comments:

- **Psoriasis and Psoriatic Arthritis Alliance:** Not particularly, given other similar agents are also available in this age group.
- **Novartis:** Secukinumab offers a novel mechanism of action for the treatment of plaque psoriasis in children and adolescents.
- **Novartis:** Secukinumab can be considered a step-change in the management of paediatric psoriasis

Equality

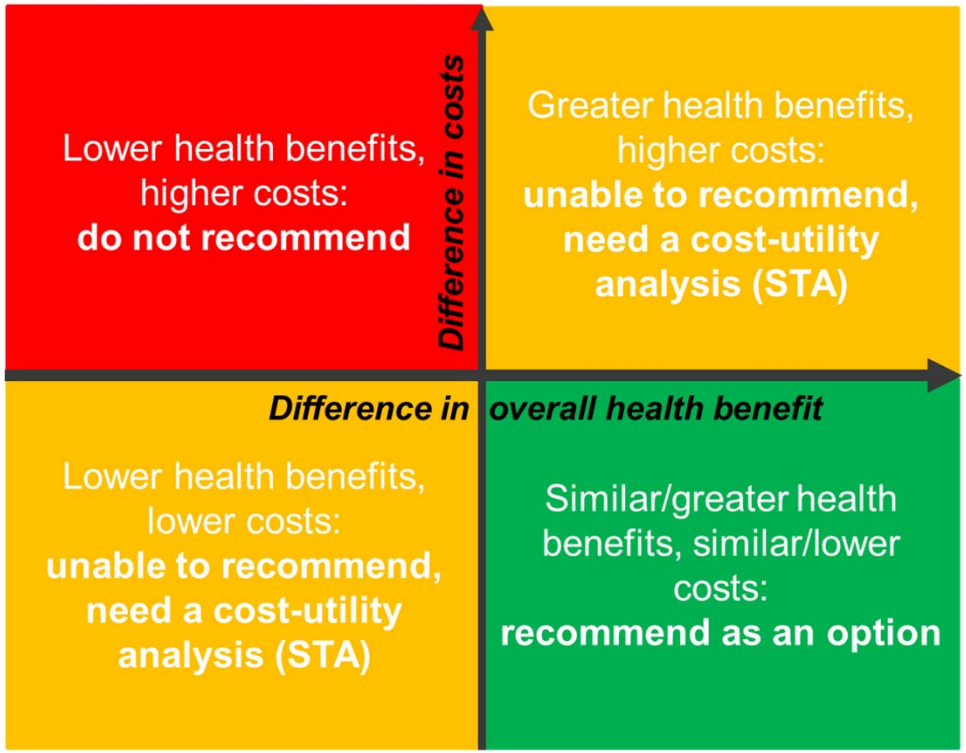
Consultee comments:

- PASI may underestimate disease severity in people with darker skin as redness may be less evident (a component of PASI)
- DLQI will underestimate impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression

NICE

Sources: British Association of Dermatologists [BAD], Psoriasis and Psoriatic Arthritis Alliance [PAPAA], Psoriasis Association.

Potential recommendations: cost comparison



What is the committee view on:

- the choice of comparators
- Specifically the inclusion/exclusion of adalimumab
- the similarity of health benefits and safety of secukinumab and comparators
- the similarity of costs of secukinumab and comparators
- is it reasonable to recommend secukinumab in the same way as TA455?